Liliana Carina Pereira Baptista

MEDICATION, EXERCISE AND QUALITY OF LIFE IN OLDER ADULTS

Doctoral Thesis in Sport Sciences, in the branch of Physical Activity and Health,
supervised by Prof. Doctor Raul Agostinho Simões Martins
and submitted to the Faculty of Sport Sciences and Physical Education of the University of Coimbra

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Universidade de Coimbra

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To my brother Carlos Manuel (in *memorian*)

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Looking back on my student and professional "*yellow brick road*"... I see a long course, filled with challenges, difficulties, uncertainties, growth, learning, knowledge, dedication, companionship, friendship, self-improvement, satisfaction, joy, but also and particularly, a sense of personal fulfillment with the attainment of this pre-established goal. Nevertheless, a study of this nature, in spite of its individual character, implies the cooperation, understanding and stimulation of several people, without which it would not be possible. In this way, I would like to express my full gratitude and appreciation here, to all those who directly or indirectly contributed to make this thesis an achievable task, but most important… a reality.

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ABSTRACT

Ageing and longevity, increase the risk of development/ aggravation of adverse health conditions that may lead to the increase of medication use and health care expenditure, loss of independence and physical disability, negative mood states and impaired health-related quality of life (HRQoL) and ultimately, to mortality. Exercise and/or some pharmacological therapies may counteract these negative effects. Therefore, the main goal of this thesis is to analyse the effect of a long-term multicomponent exercise training (MEX) and/ or pharmacological treatment plans in older adults (> 60 years old) with several chronic conditions namely hypertension, diabetes and dyslipidemia in terms of: *i*) medication [antidiabetic-metformin (MET); antihypertensive- angiotensin converting enzyme inhibitors (ACEi), calcium channel blockers, thiazide related diurectics and β-blockers; antidyslipidemic- statins (ST)]; *ii*) physical fitness using the *Senior Fitness Test battery*; *iii*) anthropometric profile [body mass (BM), waist circumference (WC), body mass index (BMI), waist-to-hip ratio(WHR)]; *iv*) hemodynamic and lipid profile [systolic (SBP) and diastolic blood pressure (DBP), total cholesterol, low density lipoprotein, high density lipoprotein, glycemia, glicosolated hemoglobin]; *v*) mood states using the *Profile of Mood States – Short Form* (POMS) and; *vi*) HRQoL using the *Short Form Health Survey 36* (SF-36).

This longitudinal un-randomized cohort study included a sample of 1473 comorbid older adults - age (66.5±5.9); comorbidity (2.2±1.6) - of the local community of Santa Maria da Feira, Aveiro, Portugal. Participants underwent one of 2 conditions: MEX participants (*n* = 1221; age [67.1±6.9]; medications [2.2±1.6]) underwent a 3 days/week, 60 minutes multicomponent exercise training, throughout 24 month intervention; and control groups maintained standard care (CO; *n* = 252; age [63.8±3.3]; medications [1.8± 1.6]).

After the 24-month intervention, the MET group unchanged cardiorespiratory fitness (CRF) and HRQoL, while increased WC, WHR, SBP and tension mood state. The ACEi monotherapy worsened CRF and HRQoL, but also the upper/lower body strength and flexibility, anthropometric profile, and SBP. The ST monotherapy decreased all functional status outcomes, including CRF, upper/lower body strength and flexibility and

also HRQoL. Moreover, this group augmented anthropometric and hemodynamic profile, but improved total cholesterol and bodily pain.

Reversely, MEX participants decreased BM, WC, BMI, SBP, DBP, triglycerides, glycaemia, depression, tension and anger mood states, and improved all physical fitness components, particularly upper/lower body strength and CRF, vigor mood state, and physical and mental HRQoL in older adults with T2D, hypertension and dyslipidemia.

Overall, the present data showed that: *i*) long-term MEX was the most effective treatment plan, decreasing multifactorial cardiovascular risk factors (CVR) and negative mood states, and improving functional status and positive mood states like vigor, physical and mental HRQoL, independently of the disease, antihypertensive medication or mode of therapy; *ii*) isolated pharmacological medications showed a negative evolution, worsening several CVR factors, decreasing functional status, augmenting negative mood states (tension and anger), and aggravating/unchanging HRQoL according to the disease; and *iii*) the combined groups (MEX+ MET; MEX+ ACEis; MEX+ TDs; MEX+ CCBs; MEX+ βBs; MEX+ ST) revealed an intermediated pattern between the improvements of isolated MEX and the decreases of isolated pharmacological treatments, suggesting that MEX might counterbalance the potential negative effects of the pharmachological therapies. Thus, MEX should be highly adopted/ prescribed in the early stages of T2D, hypertension and dyslipidemia as the most effective first-line non-pharmacological therapy to manage these chronic conditions. Secondly, for those that need pharmacological treatments due to the severity or cumulative risk factors, a multicomponent exercise program should be prescribed to counterbalance the negative effects that ageing and pharmacological treatments may have in terms of CVR factors, functional independence, mood states, medication consumption and HRQoL.

Keywords: Exercise; Metformin; Angiotensin converting enzyme inhibitors; Thiazide diuretics; Calcium channel blockers; β-blockers; Health related quality of life; Cardiovascular risk factors; Functional Status; Mood states; Older adults.

RESUMO

O envelhecimento e a longevidade aumentam o risco do desenvolvimento/ agravamento de diversas patologias crónicas que podem levar ao incremento do consumo de medicamentos e da despesa com cuidados de saúde, perda de independência e incapacidade física, a estados de humor negativos e diminuição da qualidade de vida relacionada à saúde (QVRS) e podem mesmo, em última instância, levar à mortalidade. O exercício físico e/ou alguns grupos farmacológicos poderão contrariar esses efeitos negativos. Assim, o objetivo principal desta tese é analisar o efeito longitudinal de um programa de exercício físico multicomponente (MEX) e/ou alguns grupos farmacológicos em idosos (> 60 anos) com hipertensão, diabetes e dislipidemia em termos de: *i*) medicamentos [antidiabéticos-metformina (MET); antihypertensores- inibidores da enzima de conversão da angiotensina (ACEi), bloqueadores dos canais de cálcio, diuréticos e β-bloqueadores; antidyslipidémicos- estatinas (ST)]; *ii*) aptidão física através da bateria do *Senior Fitness Test*; *iii*) perfil antropométrico [massa corporal (MC), circunferência da cintura (CC), índice de massa corporal (IMC), relação cintura- anca (RCA)]; *iv*) perfil hemodinâmico e lipídico [pressão arterial sistólica (PAS) e diastólica (PAD), colesterol total, lipoproteína de baixa e alta densidade, glicemia e hemoglobina glicosada]; *v*) estados de humor através do *Profile of Mood States – Short Form* (POMS); *vi*) QVRS através do *Short Form Health Survey 36* (SF-36).

Este estudo de coorte longitudinal não aleatorizado incluiu uma amostra de 1473 idosos com comorbidades - idade (66,5 ± 5,9); comorbidade (2,2 ± 1,6) - da comunidade de Santa Maria da Feira, Aveiro, Portugal. Os participantes foram divididos de acordo com duas condições: os participantes dos MEX (n = 1221; idade [67,1 ± 6,9]; medicações [2,2 ± 1,6]) foram submetidos a um programa de exercício físico multicomponente 3 vezes/semana, com duração de 60 minutos durante 24 meses; e os grupos de controlo mantiveram cuidados "standard" (CO; n = 252; idade [63,8 ± 3,3]; medicamentos [1,8 ± 1,6]).

Após 24 meses, o grupo sob MET manteve a aptidão cardiorrespiratória (CRF) e QVRS, aumentou a CC, a RCA, a PAS e a tensão. Os ACEi agravaram CRF e QVRS, mas também a força e flexibilidade, o perfil antropométrico e a PAS. As ST diminuiram o estado funcional, incluindo CRF, a força e flexibilidade superior/ inferior do corpo, e

também QVRS. Contudo, este grupo melhorou o colesterol total e a dor corporal. Por outro lado, o grupo com MEX diminuiu a MC, CC, IMC, PAS e PAD, triglicerídeos, glicemia, depressão, tensão e raiva, melhorou todos os componentes da aptidão física, particularmente a força superior e inferior e a CRF, aumentou o vigor e a QVRS física e mental na diabetes tipo 2, hipertensão e dislipidemia.

Analiticamente, os dados mostraram que: *i*) O MEX foi o plano de tratamento mais eficaz, diminuindo os factores de risco cardiovasculares (RCV), os estados de humor negativos, melhorando o estado funcional e incrementando estados de humor positivos como o vigor, e a QVRS física e mental, independentemente da patologia, da medicação anti-hipertensiva ou modo de terapia; *ii*) os tratamentos farmacológicos agravaram vários fatores de RCV, diminuiram o estado funcional, aumentaram os estados de humor negativos (tensão e raiva) e decresceram/ não alteraram a QVRS de acordo com a patologia; *iii*) mostrou-se também que as terapias combinadas (MEX+MET, MEX+ACEis, MEX+TDs, MEX+CCBs, MEX+βBs, MEX+ST) revelaram um padrão intermédio, entre as melhorias do MEX e os decréscimos dos grupos farmacológicos, sugerindo que o MEX parece contrabalançar os efeitos negativos que o envelhecimento e os tratamentos farmacológicos parecem ter. Assim, o MEX deve ser adotado/ prescrito em estágios iniciais da diabetes tipo 2, hipertensão e dislipidemia, como a terapia mais eficaz para a manutenção destas patologias. Mostrou-se também, que para os idosos que devido à severidade ou multiplicidade dos fatores de risco necessitam do tratamento farmacológico, deve ser prescrito, conjuntamente, um programa de exercício multicomponente para contrabalançar os efeitos negativos que o envelhecimento e as terapias farmacológicas parecem ter nos fatores de RCV, na independência funcional, nos estados de humor, no consumo de medicamentos e na QVRS.

Palavras-chave: Exercício Físico; Metformina; Inibidores da enzima conversora de angiotensina; Diuréticos; Bloqueadores dos canais de cálcio; β- bloqueadores; Qualidade de vida relacionado à saúde; Factores de risco cardiovascular; Estado funcional; Estados de humor; Idosos.

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LIST OF ABREVIATIONS

A

ACEis- Angiotensin converting enzyme inhibitors

ANCOVA- Analysis of covariance

ATP- Adenosine Triphosphate

B

βBs- β- blockers

BM- Body mass

BMI- Body mass index

C

CCBs- Calcium channel blockers

CRF- Cardiorrespiratory fitness

CVD- Cardiovascular Disease

D

DBP- Diastolic blood pressure

F

FPG- Fasting plasma glucose

G

GH- General health

H

HbA1c- Glycated hemoglobin

HDL- High density lipoprotein cholestreol

HRQoL- Health related quality of life

L

LDL- Low density lipoprotein cholesterol

M

MCS- Mental component score

MEX- Multicomponent exercise training

MET- Metformin

MH- Mental health

N

NHS- National Healthcare System

O

OGTT- Oral glucose tolerance test

P

PCS- Physical component score

PF- Physical Functioning

Q

QoL- Quality of life

R

RE- Role emotional

RP- Role physical

S

SBP- Systolic blood pressure

SF- Social functioning

SFT- Senior Fitness Test

ST-Statins

T

TC- Total Cholesterol

TDs- Thyaziade diurectics

TG- triglycerides

TMD- Total mood disturbance

T2D- Type 2 diabetes

TSF-36- Total SF-36

V

VO_2- Peak oxygen volume

W

WC- Waist circumference

WHO- World Health Organization

WHR- Waist-to-hip ratio

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1. INTRODUCTION

1.1. Rationale, Objectives and Thesis Outline

"The world´s population is aging"- this is one of the most significant twenty-first century epidemiological social transformation, with implications in nearly all sectors of society, including labor and economic markers, demands for goods and services, such as housing, transportation and social insurance protection, on family structures and intergeracional ties as well as, on society organizational structures (UN, 2015; World Health Organization, 2014). In fact, according to the data of the *World Population Prospect* (UN, 2015), the number of people aged 60 years and over, increased substantially in the recent years and it is projected to grow even faster in the upcoming decades, being between 2015 and 2030 nearly 56%, from 901 million to 1.4 million people.

This exponential growth is of such magnitude that in 2050 it is projected to be more than double the number of 2015, reaching to 2.1 billion people (UN, 2015). Furthermore, the group of the "oldest-old", meaning the individuals aged 80 years or over, wil grow even faster than the average of any other age group, having in 2015, 125 million people and being projected for 2050, almost the triple- 434 million individuals over the age of 80 (UN, 2015),

Ageing and longevity, these two basic principles of the geriatric epidemiology conducted by the biological changes (associated with accumulated cell damage, that with time decrease immunologic, cardiovascular and skeletal-muscle systems) diminishes body´s repairmen capacities and increases the risk of developing collateral adverse health conditions (Arthur C.Guyton & Hall, 2014; Bell & Saraf, 2016; Buford, 2016). These chronic conditions, particularly the non-communicable diseases- cardiovascular diseases that include hypertension and dyslipidemia, are a major concern due to the increased risk of collateral health effects including falls/fractures (Berlowitz et al., 2016), neuropsychiatric disorders and cognitive decline (Hajjar, Wharton, Mack, Levey, & Goldstein, 2016; Marventano et al., 2014), hospitalization, adverse surgical outcomes

(Dumurgier et al., 2009; Studenski, Perera, & Patel, 2011) loss of independence and increased physical disability (Buford, 2016; Rich et al., 2016). In fact, it seems that as life expectancy increases those extra years gained to the last generation, instead of being lived in good health, are lived with extended periods of disability and illness (UN, 2015).

According to the latest data, at birth, in 2013 the average world life expectancy was of 71 years of life. Unfortunately, it was only accounted 62 years of healthy life expectancy, implying that approximately 9 years of healthy life were lost due to disability (UN, 2015). Furthermore, at the age of 65 years more than 60% of adults suffer from 2 or more chronic conditions and more than 25% have 4 or more morbidities (Bell & Saraf, 2016) being that, these alarming numbers increase each decade, resulting in more than 50% of individuals aged 80 years or over suffering from 4 or more chronic conditions (Bell & Saraf, 2016). Apart from decreasing functional ability, chronic conditions may ultimately, lead to mortality (Buford, 2016; Rich et al., 2016). Indeed, the latest data of the *Global status report of non-communicable diseases,* reported a total of 56 million deaths occurred worldwide (Bell & Saraf, 2016; UN, 2015; World Health Organization, 2014), of which 38 million deaths were due to the non-communicable diseases, 46% to cardiovascular diseases, 22% cancers, 11% of obstructive pulmonary disease and 4% diabetes (World Health Organization, 2014). Worringly, these diseases econonmic cost are also an important issue once in 2012, in the European Union, the cardiovascular diseases estimated cost was almost 196 billion euros, 54% of which were due to direct health care costs (Melanie Nichols, Nick Townsend, 2012). Thus, this biological ageing degradation ensemble with the changes in social roles and the shifts in the close relationship ties (including loss of wife/husband and retirement) added with the accumulated behavior exposure to various external health risks, including physical inactivity, unhealthy diet, tobacco and alcohol use originates a vastly heterogenic older population and increases the prevalence of both, comorbidity and multimorbidity (Bell & Saraf, 2016; UN, 2015), creating an virtuous cycle that may impair the quality of the life in this age group (Rich et al., 2016) and simultaneously worsen the individual economic condition and health care systems.

Portugal, despite is small geographic area, is not an exception of this global ageing concern. In 2015, there were 10.341.3 million Portuguese's, 2.1 million were aged 65 years or above, of which 1 million were over 75 years old, 260,000 were over 85, and more than

4,000 were above 100 years (Ministério da Saúde, 2015). Moreover, in 2015, Portugal was the fifth country worldwide with the biggest percentage of individuals aged above 60 years (27.1%), only exceeded by Finland, Germany, Italy and Japan (UN, 2015), with an ageing index of 146; meaning that for 100 individuals under 15 years, there were approximately 146 older individuals (> 65 years) (Carrilho & Craveiro, 2014) and in only 2 years this index augmented 10% (2013 ageing index was of 136) (Carrilho & Craveiro, 2014). Concurrently, in 2014 healthy life expectancy at age 65 was of 6.9 years for men and 5.6 years for women, numbers below the European average of 8.6 in both sexes (Direcção Geral de Saúde, 2016).

In terms of mortality, the portuguese leading causes of death in 2015, were cardiovascular diseases (33%), followed by malignant tumors (27%), respiratory system diseases (13%) and ultimately, endocrine, nutritional and metabolic diseases (6%) (Direcção Geral de Saúde, 2016). The major risk factors which lead to the total years of healthy life loss by the Portuguese population were: inadequate eating habits (16%), hypertension (13%), smoking (12%), high body mass index (12%), fasting plasma glucose (10.2%), alcohol and drug consumption (8.7%), high total cholesterol (5.5%) and low physical activity levels (3.8%) (Direcção Geral de Saúde, 2016). But, for those above 65 years, these numbers were more concerning, once that 71% of this age group had hypertension, 47% was pre-obese and 22% was obese, 79% had high total cholesterol and almost 87% and 80% of Portuguese women and man, respectively, were inactive (American College of Sports Medicine, 2014; Direcção Geral de Saúde, 2016).

In terms of medication consumption, the growth in the number of packages has been constant over the last few years in Portugal, highlighting that in the period between 2011 and 2014 there was an increase of 8.7%, meaning that, in 2014, 13.169.601 packages of medicines were more consumed than in 2011 (Ministério da Saúde, 2015). The antihypertensive and anti-dyslipidemic medication accounted with an increase of 4% and 3%, respectively (Direcção Geral de Saúde, 2015).

Older adults treatments efficacy in some chronic conditions, on the other hand is not completely understood, once clinical trials, systematic reviews and meta-analysis frequently exclude older adults due to the concerns about safety and/or confounding effects (Buford, 2016; Cruz-Jentoft, Carpena-Ruiz, Montero-Errasquín, Sánchez-Castellano, & Sánchez-García, 2013). Moreover, studies with exclusively older adults are still scarce

and/or inconsistent, because or used wide range age samples, mixing adults of all ages, with different physical cardiovascular profiles, or include tight exclusion criteria's like comorbidity, polypharmacy, or other poorly justified exclusion criteria that limits the heterogenic community of older individuals, hampering the applicability of their results in the general population (Cruz-Jentoft et al., 2013).

On on hand, this improved longevity and ageing, considered as a demographic success history, led by the changes in fertility and mortality, economic and social development, advances in public health, medical, technologies and improvements in living conditions (UN, 2015) allowed that more people lived longer, and in many cases, healthier than there preceding generation. On the other hand, these facts, negatively pressure organizational structures, particularly the health care systems, demanding for more care, services and technologies to prevent and treat diseases and chronic conditions, that are prevalent among this population group (UN, 2015; World Health Organization, 2014). Faced with this reality, it is imperative to find solutions to minimize health system expenditure and at the same time contribute to the long-term development of action plans, specifically targeted to older persons, to combat ageism, to promote health and well-being, controlling behavioral risk factors and creating conditions and incentives for healthy lifestyles (Direcção Geral de Saúde, 2016; UN, 2015; World Health Organisation, 2016).

Nowadays, the realization of studies directed to this problematic is so crucial and will allow a deeper understanding, providing clinicians, exercise specialists and other interested parties, with more accurate and precise methods and knowledge to act preventively, curatively and/or managing disease approaches, through the promotion of an active, successful, healthier and with more quality of life ageing. The challenge today is not only the *amount*, meaning how many years we live, but fundamentally *the way* we live, that is the *quality* of those years once a 'successful' ageing largely depends on the relationship between positive health, autonomy and independence in the elderly (Gotshall, 2009). Thus, based on these premises, we intend with the present investigation to describe and to characterize the relationship between medication, exercise, physical fitness and quality of life of noninstitutionalized older adults with comorbidities. This study will analyze the effects of long-term multicomponent exercise training and/or pharmacological treatment plans, in several chronic conditions namely hypertension, diabetes and dyslipidemia, in individuals that engage in a 3 days/week, 60 minutes multicomponent

exercise training program versus participants without intervention- only standard care throughout a 24 month intervention. Variables include medication (antidiabetic-metformin; antihypertensive- angiotensin converting enzyme inhibitors, calcium channel blockers, thiazide related diurectics and β- blockers; antidyslipidemic- statins); physical fitness (upper/lower body strength, upper/lower body flexibility, agility/dynamic balance, cardiorespiratory fitness); anthropometric (body mass, waist circumference, body mass index, waist-to-hip ratio); hemodynamic and lipid profile (systolic and diastolic blood pressure, total cholesterol, low density lipoprotein, high density lipoprotein, glycemia, glicosolated hemoglobin); mood states (depression, anger, tension, vigor, confusion, fatigue and total mood disturbance); and health related quality of life.

More specifically, this thesis is based on the following objectives:

i) To determine the effect of long-term multicomponent exercise training on health related quality of life and cardiovascular risk factors (anthropometric, hemodynamic and cardiorespiratory fitness) in older adults with type 2 diabetes and comorbidities. **Study I**- Baptista, L.C. et al. (2017). Effects of Long-Term Multicomponent Exercise on Health-Related Quality of Life in Older Adults With Type 2 Diabetes: Evidence From a Cohort Study, *Quality of Life Research*, 26(8):2117-2127. DOI 10.1007/s11136-017-1543-3.

ii) To analyse the effect of 3 types of treatment (exercise, metformin and combined exercise plus metformin) on cardiovascular risk factors (anthropometric, hemodynamic, lipid and glycemic profile and cardiorespiratory fitness) in older adults with type 2 diabetes and comorbities. **Study II**- Baptista, L.C. et al. (2017). Back to basic with active lifestyles: exercise is more effective than metformin to reduce cardiovascular risk in older adults with type 2 diabetes, *Biology of Sport.*

iii) To analyze the effect of 3 types of treatment (exercise, metformin and combined exercise plus metformin) on the health related quality of life and mood states in older adults with type 2 diabetes and comorbities. **Study III-** Baptista, L.C. et al (2017). Exercise but not metformin improves health-related quality of life and mood states in older adults with type 2 diabetes; *European Journal Sport Science*, 17(6):794-804. DOI: 10.1080/17461391.2017.1310933;

iv) To determine the effect of 3 types of antihypertensive treatment (exercise, angiotensin converting enzyme inhibitors (ACEi) and combined exercise plus ACEi) on functional status, cardiovascular risk factors and physical health related quality of life in hypertensive older adults with comorbidities. **Study IV-** Baptista, L. C. (2017). Exercise training improves functional status in hypertensive older adults under angiotensin converting enzymes inhibitors medication, *Experimental Gerontology*. DOI: 10.1016/j.exger.2017.06.013; [Epub ahead of print]

v) To determine the effect of 2 types of antihypertensive treatment combined with exercise training (monotherapy with ACEi and combined therapy ACEi plus other antihypertensive treatment) on functional status, cardiovascular risk factors and physical health related quality of life in hypertensive older adults with comorbidities. **Study V-** Baptista, L. C. (2017). Antihypertensive monotherapy or combined therapy: which is more effective on functional status?, *Clinical and Experimental Hypertension.*

vi) To determine the effect of 3 types of antihypertensive treatment (thiazide diurectics, calcium channel blockers and β- blockers) combined with exercise training on functional status, cardiovascular risk factors and physical health related quality of life in hypertensive older adults with comorbidities. **Study VI-** Baptista, L. C. (2017). Functional status improves in hypertensive older adults: the effects of antihypertensive therapy combined with multicomponent exercise training. *Endocrine.*

vii) To determine the effect of 3 types of antidyslipidemic treatment (exercise, statins (ST) and combined- exercise plus ST) on functional status, cardiovascular risk factors and physical health related quality of life in dyslipidemic older adults with comorbidities. **Study VII-** Baptista, L. C. (2017). Statin combined with exercise training is more effective to improve functional status in dyslipidemic older adults with comorbidities than each isolated therapy: the longitudinal effect of statins and exercise. *Journals of Gerontology - Series A Biological Sciences and Medical Sciences.*

viii) To analyze the effect of different types of treatment (exercise, metformin (MET), angiotensin converting enzyme inhibitors (ACEi), statins (ST) and combined exercise plus pharmacological therapies) on medication number, cardiovascular risk factors,

cardiorespiratory fitness and health related quality of life in older adults with comorbidities. **Study VIII-** Baptista, L. C. (2017).

This thesis is presented in original manuscripts format with a similar general structure, and it is organized in 6 chapters.

Chapter 1- Introduction- exposes the global contextualization with the rationale and relevance of the present thesis.

Chapter 2- Theoretical background- presents a general descriptive theoretical review of the different concepts and contributions of the main authors within the framework of the ageing, medication, exercise and quality of life in the elderly.

Chapter 3- Methods- provides a brief description of the materials and methods, as well as the samples and studies characteristics.

Chapter 4- Results- includes all the manuscripts published or submitted. The manuscripts have a common structure with minor modifications according to the style of the journal where they were submitted for publication. Each manuscript addresses to a specific component of the overall purpose of the study.

Chapter 5- Discussion- comprises the general discussion, reflecting the findings of the various studies with previous theoretical context and their implications.

Finally, Chapter 6 summarizes the main findings and conclusions of the thesis highlighting the clinical implications and recommendations to future researches in this area.

2. THEORETICAL BACKGROUND

2.1. The Ageing Process

While in many ways, the improvement of longevity and ageing should be considered a demographic success history, driven by the changes in fertility and mortality, economic and social development, advances in public health, medical and technological improvement in living conditions (UN, 2015), on the other side, this ageing phenomenon is not yet completely understood, begining with their own conceptual definition (Anton et al., 2015).

The analysis of the literature reveals that there is no global standard conceptualization to define the ageing process once ageing is not a static phenomenon, but rather the culminating point and the extension of a continuous process (Farinatti, 2008), it is also a multidimensional phenomenon, encompassing mechanisms of catabolism and anabolism triggered or interrupted at different times and rhythms for each human being (Bell & Saraf, 2016). Moreover, ageing *per se* involves many endogenous and exogenous variables (genetics, lifestyle, chronic diseases, environmental and behavioral factors, among others) that synergistically interact with each other and significantly influence the way we reach a certain age (Bell & Saraf, 2016).

According to several authors (Berger, 1989; Mazo, Lopes, & Benedetti, 2001), the concept of ageing seems to be closely related to the concept of age (Mazo et al., 2001) even though, with different meanings and relevant differences. While to Mazo and collegues (Mazo et al., 2001) ageing is delimitated by a *chronological* landmark and stratified into three stages: the *middle age*, between 45 and 60 years, where the first signs of ageing are found and where there is a tendency or predisposition for the disease; the gradual *senescence*, then, between 60 and 70 years, characterized by the onset of morbid processes typical of age; and finally, *senility or old age*, which occurs between 70 years old forward, where most of the problems, that require medical, social and rehabilitative care, occur (Mazo et al., 2001). In Portugal, due to the retirement criteria and based only in this definition, men and women above 65 years of age are considered older adults (Carrilho & Craveiro, 2014). To Berger (Berger, 1989) the concept of ageing is defined according to

several age meanings, beginning with the *chronological* age used for statistical purposes and translates a set of information expressed by numerical scales, in which people are grouped according to their birth date, that is, life time; the *biological* age is classified as the biological condition of the organs, tissues and systems of the organism when compared with normative and standardized values; the *psychological* age referring to the capacity of adaptation, to relationships and self-image, that can be considered the sum of experiences and mental maturation which a person has been exposed throughout life; the *social* age that depends, to a large extent, on social structures, on the longevity of a given society and on the role society attributes to the people they connote as elderly; and lastly the *functional* age, that, in turn, represents an attempt to relate the biological, psychological and social ages with each other.

However, in our perspective, the ageing process can not be defined only by the age factor, although the categorization of the population into groups according to age is necessary for certain purposes (eg. statistical purposes). Nevertheless, this chronological perspective reduces the heterogenic holistic individual ageing process to a rigid numerical scale and diminishes all the exogenous and endogenous factors that allow us to distinguish two individuals of the same chronological age. Indeed, if we look to our community, we observe individuals with the same chronological age with completely different levels of ageing. While some are healthy, active and live independently in the community, others are in the opposite pole, with comorbidities and chronic diseases, frailty and dependent of family or institution care. Thus, Spirduso and colleagues (Spirduso, Francis, & MacRae, 2005) argued that the concept of ageing cannot be considered only by the time dimension, as an rigid landmark for all the individuals, once in terms of the biological perspective the organism does not age uniformly between individuals of the same species and even in the same organism, because some systems are older than others. Furthermore, life-course functional trajectories for body functions (e.g. muscle) or structures (e.g. bone mass), are used as a dynamic way of studying lifetime influences on health and disease risk and confirm that there is much variation between individuals in the patterns, rate of decline and the age at onset of decline (Margolick & Ferrucci, 2015), which seems to support this perspective. Therefore, according with this biological perspective, ageing is a process or group of processes that occur in living organisms over time, generating loss of adaptability, functional damage and eventually death, being a logical extension of the physiological

processes of growth and development and cause, lastly, the collapse of homeostasis (Spirduso et al., 2005). It is expressed by the progressive decrease in viability, and an increase in vulnerability of the body, with a decline in vital functions, limitations in cardiorespiratory, musculoskeletal and other bodily processes (Spirduso et al., 2005).

Up to now to date, the ageing process has not been possible to define due to the amount of definitions and theories (like the biologic theories of ageing, some of them supported on genetic factors, and the others focused on the stochastic mechanisms) (Mota, Figueiredo, & Duarte, 2004) that are not the focus of our thesis, and traduces in considerable variations in health status, levels of independence, autonomy and social participation among older people with the same age (*Estratégia Nacional para o envelhecimento activo e saudável 2017-2025*, 2017), we believe that ageing encompasses: the biological processes contributing to ageing per se; the socio-economic and environmental exposures across life which modulate ageing and the risk of age-related frailty, disability and disease; and the possibility to modulate the ageing trajectory through development of healthy interventions (Lara et al., 2015).

2.2. The Ageing Phenotype

Apart from the definition of ageing, there is a general consensus that an ageing phenotype exists. Certain anatomical, physiological, psychological and social changes that occur universally in humans are possible to be identified and can be used to operationally define the ageing phenotype distinguishing among young, old, and very old people (Fabbri et al., 2015; Lara et al., 2015). Moreover, the biological measures of ageing allow us to characterize and quantify important functions which are subject to decline at faster, or slower rates during individual human aging (Lara et al., 2015).

As previously mentioned, ageing affects all cells, organs, tissues and the majority of body systems (Lara et al., 2015) but, due to the amount and the complexity of such mechanisms, we will describe the most significant changes which are important to the aetiology of the chronic diseases being analyzed in this thesis (hypertension, dyslipidemia,

diabetes and functional status decline) beginning with a brief description of the micro-changes (cellular and molecular) and than the macro-changes.

Ageing-related changes can be clustered into several domains: molecular homeostatic regulation, hormonal changes, cerebral and neuropheripheral function, bone tissue, cardiovascular and pulmonary system, cognitive function, body composition, psychological and social changes (Arthur C.Guyton & Hall, 2014; Fabbri et al., 2015; Margolick & Ferrucci, 2015)

Several interconnected cellular and molecular mechanisms have been proposed as common determinants of ageing, resulting in loss of homeostasis across different tissues and organs (Fabbri et al., 2015). These determinants include genomic instability, telomere attrition, epigenetic alterations, protein-homeostasis loss, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem-cell exhaustion, and altered intercellular communication that together or independently reduce the efficiency of cellular maintenance, repair, and turnover mechanisms, and ultimately result in the accumulation of lipids and damaged biomolecules and organelles (Anton et al., 2015; Arthur C.Guyton & Hall, 2014).

During ageing process, the ability to resolve *inflammation* becomes impaired leading to sustained tissue infiltration of leukocytes and chronic release of pro-inflammatory cytokines and chemokines (Anton et al., 2015; Buford, 2016). As a result, we switch the life-long protection against infection and injury for long-term risk of chronic inflammation and disease. Even though, factors such as obesity and insulin resistance, smoking and changes in circulating sex hormone concentrations are associated with age-related inflammation, the increase in inflammatory mediators are thought to derive most directly from decreases in the efficiency of the immune system, *immuno-senescence* (Buford, 2016).

Immuno-senescence is characterized by thymus atrophy, reductions in neutrophil function, naïve T cell number, cytotoxic capacity of natural killer cells, and lowered β-cell antibody production in response to antigen (Arthur C.Guyton & Hall, 2014; Buford, 2016). The inflammatory biomarkers most consistently associated with ageing are elevated circulating concentrations of interleukin-6, C-reactive protein, and tumor necrosis factor alpha (Anton et al., 2015; Buford, 2016). These markers increase during ageing process even in the absence of acute infection and have been associated with the prevalence of a

wide-range of age-related co-morbidities (cardiovascular disease, insulin resistance and diabetes, osteoporosis, cognitive decline and dementia, frailty and disability, and cancer) (Anton et al., 2015; Buford, 2016).

Chronic elevations in inflammatory mediators during late life contribute to a deleterious chronic overproduction of reactive oxygen species, coupled with aged-related declines in nitric oxide production and bioavailability, contribut to an imbalance between the production and breakdown of reactive oxygen species, the *oxidative stress*, which leads to the damage of cellular proteins and organelles (Buford, 2016). Furthermore, inflammation/oxidative stress is linked to the vascular dysfunction and, the relationships among these three biological mechanisms have been termed the "*Vascular Health Triad*" which has been implicated in ageing process (Buford, 2016).

In response to ageing, the endothelium releases other vasoactive substances such as endothelin-1, angiotensin II, and COX- derived prostanoid and superoxide anions which contribute to impaired endothelium-dependent vasodilation, contrary to an healthy endothelium that exerts anti-inflammatory effects such as nitric oxide (Arthur C.Guyton & Hall, 2014). When nitric oxide is released, it causes smooth muscle relaxation and subsequent vasodilation. However, nitric oxide also tends to react with oxidants to form the potent free radical peroxynitrite which removes nitric oxide from the endothelium thereby reducing the vasodilatory capacity of the vessel (Arthur C.Guyton & Hall, 2014).

Endothelial dysfunction develops in response to these changes and contributes directly to increased systemic vascular resistance, and therefore increased blood pressure, due to an imbalance between vasodilatory and vasocontrictory substances, that in turn also contributes to further exacerbating inflammation and oxidative stress, creating an even larger vicious cycle (Buford, 2016). Pro-inflammatory endogenous factors include adiposity (specially visceral adiposity), and oxidative stress, among others (Anton et al., 2015). These age-related dysregulation of immune function may have direct adverse consequences on physical function, promote disability by causing fatigue, loss of muscle strength, impaired mobility, and slow walking speed (Anton et al., 2015).

There is evidence that *hormonal dysregulation* during ageing also has multiple impacts on physiological systems including the muscle, brain, and immune system (Arthur C.Guyton & Hall, 2014). In general, hormones are secreted from specific tissues in the body and the brain and transported in the blood to influence metabolic functions at close or

distant sites. This dysregulation includes an age-related decrease in some trophic hormones such as the gonadal steroids, estrogen and testosterone which have been implicated in the muscle and obesity (may reduce risk for osteoporosis, cardiovascular disease, and Alzheimer's disease); age-related increase in stress-related hormones such as cortisol (high levels of cortisol have been shown to exert neurotoxic effects on muscles and the brain contributing to age-related impairments); and age-related changes in neuropeptides such as oxytocin (with beneficial effects on socio-affective functioning) (Anton et al., 2015; Arthur C.Guyton & Hall, 2014).

M*itochondrial dysfunction* seems to have a key role in the pathogenesis of several age-related comorbidities. Abnormalities in mitochondrial enzyme activity, lowers mitochondrial protein synthesis rates, oxidative capacity, and adenosine triphosphate (ATP) synthesis (Anton et al., 2015) which is associated with muscle energy balance. Additionally, reactive oxygen species contributes to mitochondrial damage once the mitochondrial genome is particularly susceptible to free radical (oxidant) damage because of its close proximity to reactive oxygen species generation and the lack of protective histones (Anton et al., 2015; Arthur C.Guyton & Hall, 2014). Impairments in autophagy can result in the accumulation of damaged mitochondria, reductions in the bioenergetic status of the cell, and in myocyte apoptosis that in turn may be related with decreased muscle strength (Anton et al., 2015; Arthur C.Guyton & Hall, 2014). Moreover, these impairments can further exacerbate the production of reactive oxygen species leading to a vicious cycle (Anton et al., 2015).

In terms of body composition, ageing increases the variation in the *amounts and distribution of muscle and body fat* (Donini et al., 2012). In numerical data, by the age of 70 years, subjects have an additional 25-40% increase in fat mass and 30-40% decrease in fat-free mass (Donini et al., 2012). The decrease of fat-free mass as part of the ageing process can produce an obesity characterized by a high percentage of body fat but a stable or low body weight (Donini et al., 2012). Consequently, elderly adults have a greater proportion of fat than younger adults with the same body mass index (BMI) (Donini et al., 2012).

Body fat distribution also changes with an increased centralization of fatness from the limbs to the trunk (central obesity) while total fat remains constant, and there is an additional increase in fatty infiltration of muscle tissues (Donini et al., 2012). As a result of

these changes and in conjunction with chronic disease and developing frailty, some elderly can develop a condition defined as *sarcopenic obesity,* with significantly high prevalence of physical impairment and disability as well as a high prevalence of metabolic syndrome and co-morbidity (Donini et al., 2012).

Ageing also decreases height, justified by changes in posture, increased interdiscal compression and structural alterations of the osteoporotic vertebrae, and weight gain in both sexes up to 65 years of age and, although body weight stabilizes or declines in the last years of life, body composition continues to modify (Donini et al., 2012).

The initial onset and progression of functional decline is typically associated with the progressive loss of skeletal muscle mass, age-related loss of muscle mass and quality, *sarcopenia*, is primarily due to the progressive atrophy and loss of type II muscle fibers and motor neuronsmuscle fibers, protein synthesis, and mitochondrial function (Buford, 2016). Even in healthy people, muscle strength and power begins to decline around age 25 years, particularly in the lower extremities (Concannon, Grierson, & Harrast, 2012). The process accelerates after the age 65 years, when a typical person already has lost 25% of youth strength, and by the 80 years of age, up to 50% of peak skeletal muscle mass (Concannon et al., 2012). These changes disproportionally contribute to deficits in total strength, strength per unit of cross-sectional muscle area, power, as well as the lower capacity for hypertrophy and fatigue (Buford, 2016). These factors, in addition to the consequences on muscular function, also lead to a decrease in balance and joint mobility (Concannon et al., 2012). Age-related decreases in androgens and other growth factors may contribute to this process with selective loss of type II muscle fibers, less synchronization of motor units, and deteriorating muscle quality and myosin function (Concannon et al., 2012). These changes appear to be even more pronounced in obese individuals, as previously mentioned, once the combination of muscle loss and fat gain may act synergistically, and the excess of adiposity may lead to an increase production of reactive oxygen species and inflammatory cytokines, damaging mitochondria and adversely affecting cellular quality control processes, which can further accelerate the process of functional decline in older adults (Anton et al., 2015).

In terms of *bone tissue,* ageing decreases mass, density and architecture of the bone tissue, which favors the development of osteoporosis, degeneration of the cartilage and

joint capsule and reduction of the synovial fluid, causing a higher prevalence of osteoarthrosis (Arthur C.Guyton & Hall, 2014).

Cerebral and peripheral neurodegeneration also occur with advancing age, cerebral gray matter (primarily consisting of neuronal cell bodies) atrophy and gray matter volume have been linked to a variety of movement deficits including gait disturbances, such as slow speed, shorter steps and longer double support time (Anton et al., 2015). Additionally, cerebral white matter, myelinated axons, is also affected by ageing with an increase in demyelination and/or dilated perivascular spaces (Anton et al., 2015). On the peripheral neurodegenaration impairments occur in both motor and sensory nerve function. Motor neuron degeneration is evidenced by a decline in the conduction velocity and in the amplitude of the maximum evoked compound muscle action potential because of the increased rates of apoptosis of the large diameter, fast conducting motor neurons that innervate powerful type II muscle fibers, affecting functional capacity (Arthur C.Guyton & Hall, 2014). The sensory nervous system is associated with an impaired somatosensation. A variety of factors can contribute to decline of nerve health in older adults including chronic inflammation, oxidative stress, diabetes, chronic infections, prolonged smoking, prolonged alcohol use, and prolonged vitamin deficiency (Anton et al., 2015).

In the *cardiovascular system*, ageing produces significant functional modifications in the myocardium, which include decline in the peak systolic volume and cardiac contractility, increased peripheral vascular resistance with subsquent increase in blood pressure and in ventricular wall thickness, incomplete relaxation during diastolic filling, increased final diastolic volume with a reduction in the maximum systolic volume, all of which negatively affect stroke volume, ejection fraction, and cardiac output (Concannon et al., 2012). However, one of the most important changes in cardiovascular system to exercise training is the decline in peak oxygen uptake (VO^2max), which is related with cardiovascular disease (Anton et al., 2015). Moreover, the decrease in maximum heart rate and the increase in oxygen flow reduce the adaptability and exercise recovery (Concannon et al., 2012).

Ageing changes the *pulmonary system* decreasing vital capacity, increasing residual volume, anatomical dead space and ventilation during exercise; decrease mobility of the chest wall and decrease lung oxygen diffusion capacity (Concannon et al., 2012).

In terms of *cognitive changes*, ageing aggravates loss of memory and (in some cases) subsequent onset of dementia, decreased perceptual ability, and increased brain dysfunction (Buford, 2016). Additionally, there is a change in the number of neurons that slows the time reaction and information processing, besides causing a deterioration of the reflex arcs and lower impulse transmission affecting the capacity of motor coordination and cognitive capacity, namely the concentration and the short-term memory (Llano et al, 2004).

Finally, apart from these physiological changes during old age, the elderly suffer from changes in their daily lives that compel them to play new roles but also present them new problems and new challenges, particularly in *psychological and social* terms (Llano, Manz, & Oliveira, 2004). The reduction of social contacts, decreased pace of life, increased free-time, lack of initiative, feeling of unproductiveness, frustration, feeling of dependency, weak family integration, decreased income and social marginalization aggravated by the deterioration of health status and functionality, raising of depressive states, low self-esteem, isolation, inactivity, the feeling of depauperation and passivity, a decrease in their self-efficacy and increase in regressive attitudes towards society (Llano et al., 2004).

To sum up, the ageing process is determined by this biological degradation, that combined with the changes in social roles and the shifts in the close relationship ties (including loss of spouse/husband and retirement) added to the accumulated behavior exposure to various external health risks, including physical inactivity, unhealthy diet, tobacco and alcohol use, originates a vastly heterogenic older population and increases the prevalence of both, comorbidity and multimorbidity (Bell & Saraf, 2016; UN, 2015). Under these circumstances, an in-depth understanding of the several chronic conditions is fundamental to illustrate the holistic vison of the ageing process and prevalent comorbidties.

2.3. Ageing, Common Pathologies and Functional Changes

It has long been known that ageing, both in cellular and organismal levels, contributes to the development and progression of many chronic diseases (Anton et al., 2015), particularly cardiovascular disease (CVD) (World Health Organization, 2014). The importance of age as we previously observed, as one of the acknowledged CVD risk factors is to a certain extent, reflected in the cardiovascular SCORE risk charts, which are used in clinical practice in most of the European countries (Catapano et al., 2016; Piepoli et al., 2016). Furthermore, the identification of the ageing cardiovascular risk factors was a decisive step for the development of a preventive action policy, decreasing the development of CVD, but also reducing the related morbidity and mortality (Piepoli et al., 2016). About 80% of CVD is mainly caused by the accumulated behavior exposure to various external health risks (World Health Organization, 2014). In fact, by the age of 65, more than 60% of adults suffer from 2 or more chronic conditions and more than 25% have 4 or more morbidities, with increments in each decade, resulting in more than 50% of individuals with 80 years or more, suffering from 4 or more chronic conditions (Bell & Saraf, 2016).

The causes of CVD are multifactorial – while some are partly or completely modifiable: smoking, alcohol, obesity, lack of physical activity, dietary habits, elevated blood pressure, type 2 diabetes, dyslipidemias, others are non-modifiable: age, gender, ethnicity, family history of heart disease (Mazalin Protulipac, Sonicki, & Reiner, 2015).

Dyslipidemia, together with hypertension, smoking, diabetes mellitus, abdominal obesity, and physical inactivity are the leading CVD risk factors in all age groups, and the risk is believed to be multiplied in the elderly (World Health Organization, 2014)

In Portugal, 71% of adults above 65 years have hypertension, 47% are pre-obese, 22% are obese and 79% have high total cholesterol (Direcção Geral de Saúde, 2016). So, an effort to try to understand the aetiology, consequences and treatment plans will help to develop strategies in order to prevent or delay the burden of CVD multimorbidity (Fabbri et al., 2015), once disease mechanisms seem to be affected by some of the same pillars that have been associated with ageing- inflammation, oxidative stress and endothelial dysfunction (Buford, 2016; Hodes et al., 2016; Lara et al., 2015).

Briefly, concerning the intrinsic importance to our research we will focus in the 3 most prevalent chronic ageing conditions and risk factors for the development of CVD: diabetes, hypertension, dyslipidemia and also functional status decline. The role of physical inactivity is highlighted in section 2.5.

2.3.1. **Diabetes**

The highly prevalent nature of diabetes in ageing populations is characterized by the multifactorial complexity of the disease, the increased risk of medical comorbidities, the early development of functional decline, the risk of frailty (Colagiuri et al., 2014) and the requirement of continuous medical care (American Diabetes Association, 2016).

Diabetes can be defined on any of the following criteria: fasting plasma glucose (FPG) ≥ 7.0 mmol/l (126 mg/dl) or, 75 g oral glucose tolerance test (OGTT) with FPG ≥ 7.0 mmol/l (126 mg/dl) and/or 2 hour plasma glucose ≥ 11.1 mmol/l (200 mg/dl) or, glycated hemoglobin (HbA1c) ≥ 6.5% (48 mmol/mol), or random plasma glucose ≥ 11.1 mmol/l (200 mg/dl) in the presence of classical diabetes symptoms (American Diabetes Association, 2016; Colagiuri et al., 2014).

According to the American Diabetes Association (American Diabetes Association, 2016), diabetes can be classified into 4 categories; *i*) type 1 diabetes caused by β-cell destruction, usually leading to absolute insulin deficiency; *ii*) type 2 diabetes caused by progressive loss of insulin secretion on the background of insulin resistance; *iii*) gestacional diabetes diagnosed in the second or third trimester of pregnancy, not being clearly overt diabetes; *iv*) and, specific types of diabetes due to other causes, e.g., monogenic diabetes syndromes (such as neonatal diabetes and maturity-onset diabetes of the young), diseases of the exocrine pancreas (such as cystic fibrosis), and drug- or chemical-induced diabetes (such as with glucocorticoid use, in the treatment of HIV/AIDS or after organ transplantation) (American Diabetes Association, 2016).

In this study we will focus on the most prevalent among older adults: type 2 diabetes (T2D).

T2D has a long asymptomatic preclinical phase which frequently goes undetected and complications are commonly present at the time of diagnosis (Colagiuri et al., 2014). Individuals with T2D are on average at double the risk of CVD (Piepoli et al., 2016).

Metabolic alteration of diabetes causes arterial dysfunction affecting endothelium function, smooth muscle cells and platelets, and the cardiovascular complications of diabetic patients can be divided into microvascular - renal, ophthalmic and neurological, and macrovascular - coronary, cerebrovascular and peripheral arterial (Colagiuri et al., 2014).

The risk of developing T2D increases with age, obesity, lack of physical activity and occurs more frequently in women with prior gestacional diabetes, in those with hypertension or dyslipidemia, in certain racial/ethnic subgroups (African American, American Indian, Hispanic/Latino, and Asian American), and it is often associated with a strong genetic predisposition (American Diabetes Association, 2016).

Recent international guidelines highlight the role of lifestyle modifications along with pharmacological treatment to improve health, and to maintain an HbA1c below 7.0% (53 mmol/mol) (American Diabetes Association, 2016; Aschner et al., 2014; Colagiuri et al., 2014). A patient-centered treatment approach is highlighted by international recommendations, including patient preferences, cost, and potential side effects of each class, effects on body weight, and hypoglycemia risk (American Diabetes Association, 2016; Colagiuri et al., 2014).

Diabetes treatment plan should innitiate with lifestyle changes, which may include educational lifestyle counseling, increasing physical activity goal to 150 min/week minimum, and 7% weight loss for those who are obese (American Diabetes Association, 2016; Colagiuri et al., 2014) (Figure 2.1). When lifestyle changes do not achieve or maintain glycemic goals, metformin (MET) monotherapy is usually recommended at, or soon after, diagnosis, unless there are contraindications or intolerance (American Diabetes Association, 2016; Colagiuri et al., 2014). MET, the focus of our research in diabetes, is generally considered the first pharmacological anti-hyperglicemic oral choice medication, once presents favourable effects on weight, low risk of hypoglycaemia, and low cost (Aschner et al., 2014). However, some gastro-intestinal intolerance and renal function impairment can be problematic in many older adults (Aschner et al., 2014).

Dual combination therapy is usually considered by physicians when HbA1c is ≥ 9% (75 mmol/mol), with the combination of MET with another agent usally, a sulfonylurea. Alternatives include the addition of an α-glucosidase inhibitor, DPP-4 inhibitor or thiazolidinedione (Aschner et al., 2014).

Insulin treatment is considered when blood glucose is above 300– 350 mg/dL (16.7–19.4 mmol/L) and/or when HbA1c is superior to 10–12% (86–108 mmol/mol), as part of any combination regimen when hyperglycemia is severe, especially if other symptoms are present or any catabolic features (weight loss, ketosis) (American Diabetes Association, 2016; Colagiuri et al., 2014).

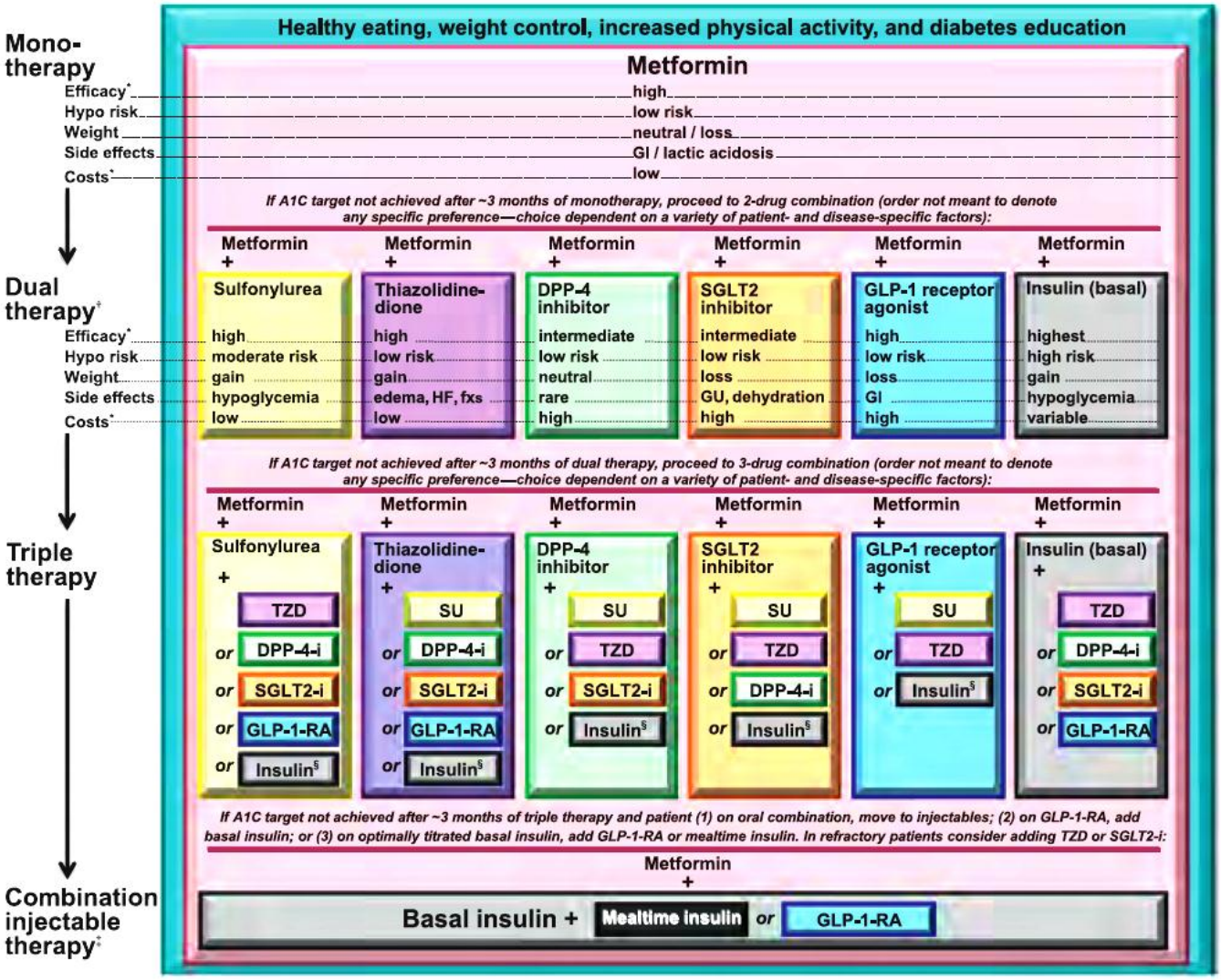

Figure 2.1- Hypoglycemic treatment in type 2 diabetes- general recommendations- Adapted from (American Diabetes Association, 2016). DPP-4-i- DPP-4 inhibitor; fxs- fractures; GI- gastro-intestinal; GLP-1-RA- GLP-1 receptor agonist; GU- genitourinary; HF- heart failure; Hypo-hypoglycemia; SGLT2-i- SGLT2 inhibitor; SU- sulfonylurea; TZD- thiazolidinedione.

2.3.2 **Hypertension**

Hypertension is a highly prevalent multi-dimensional condition with multiple health risks, particularly among older adults (Buford, 2016; Touyz & Dominiczak, 2016).

Traditional discussions of hypertension have largely focused on the risks for CVD and associated events in which heart disease, stroke, and renal failure are the leading causes of death (Touyz & Dominiczak, 2016). However, hypertension also lead to a considerable number of collateral effects, including risks for dementia, falls/fractures and physical disability (Buford, 2016).

Blood pressure encompasses systolic blood pressure (SBP), which corresponds to cardiac ventricular systole (phase in which the heart is pumping blood through the arterial system) and diastolic blood pressure (DBP) representing the ventricular diastole (phase in which the heart relaxes and the flow returns to the heart) (Arthur C.Guyton & Hall, 2014) .

Blood pressure is determined from one of the most fundamental equations of vascular physiology, that is, the result of cardiac output by peripheral vascular resistance (Arthur C.Guyton & Hall, 2014). In practical terms, a person's blood pressure depends on the volume of blood, the rate of circulation and especially, the diameter of the vessels (Arthur C.Guyton & Hall, 2014).

Although hypertension disease is relatively easy to prevent, simple to diagnose, and relatively inexpensive to treat, in reality, in the elderly this rationale is misleading and not well understood, once the large number of clinical trials, systematic reviews and meta-analyes addressed to the proper treatment frequently exclude older adults (Buford, 2016). Moreover, the altered drug metabolism, the multiple concomitant medications and co-morbidities, as well as increased blood pressure variability and orthostatic hypotension make it difficult to obtain definitive evidence of proper treatment guidelines among hypertensive older adults (Mancia et al., 2013). Thus, to date, blood pressure thresholds at which treatment should be initiated and the target goals at which blood pressure should be maintained in older adults still remain a topic of much discussion and debate. While the *European Society of Hypertension* and the *European Society of Cardiology* set hypertension definition as values ≥140 mmHg for SBP and/or ≥90 mmHg for DBP, and established a progressive risk scale to guide physicians on when and how to treat (Mancia et al., 2013), the *Seventh Joint National Committee* update suggested liberalizing the SBP

goal to 150 mmHg for those without diabetes or chronic kidney disease (P. James, Oparil, BL, & Al, 2014). However, recent evidences support the importance of minimum SBP goal under 140/90 mmHg for adults under 80 years of age (Pflederer, Estacio, & Krantz, 2016).

In terms of treatment, guidelines support once again the initiation of management plans with lifestyle changes (including caloric restriction and the increase of physical activity) along with pharmacological antihypertensive treatment with different classes of agents: thiazide related-diuretics (TDs), β-blockers (βBs), calcium channel blockers (CCBs), angiotensin converting enzyme inhibitors (ACEi) and/ or with angiotensin receptor blockers, according to the presence or not of other comorbidities and blood pressure levels (P. James et al., 2014; Mancia et al., 2013). The rationale of anti-hypertensive treatment is described in Figure 2.2.

Other RF, assimptomatic OD or disease	Blood Pressure (mmHg)			
	High normal SBP 130-139 or DBP 85-89	Grade 1 SBP 140- 159 or DBP 90-99	Grade 2 SBP 160-179 or DBP 100-109	Grade 3 SBP ≥ 180 or DBP ≥ 110
No other RF	-No BP intervention	-Lifestyle changes for several months; -Then add BP drugs targeting < 140/90	-Lifestyle changes for several weeks; -Then add BP drugs targeting < 140/90	-Lifestyle changes; -Immediate BP drugs targeting < 140/90
1-2 RF	-Lifestyle changes; -No BP intervention	-Lifestyle changes for several weeks; -Then add BP drugs targeting < 140/90	-Lifestyle changes for several weeks; -Then add BP drugs targeting < 140/90	-Lifestyle changes; -Immediate BP drugs targeting < 140/90
≥ 3 RF	-Lifestyle changes; -No BP intervention	-Lifestyle changes for several weeks; -Then add BP drugs targeting < 140/90	-Lifestyle changes; -BP drugs targeting < 140/90	-Lifestyle changes; -Immediate BP drugs targeting < 140/90
OD, CKD stage 3 or Diabetes	-Lifestyle changes; -No BP intervention	-Lifestyle changes; -BP drugs targeting < 140/90	-Lifestyle changes; - BP drugs targeting < 140/90	-Lifestyle changes; -Immediate BP drugs targeting < 140/90
Simptomatic CVD, CKD stage ≥ 4 or Diabetes with OD/RFs	-Lifestyle changes; -No BP intervention	-Lifestyle changes; -BP drugs targeting < 140/90	-Lifestyle changes; -BP drugs targeting < 140/90	-Lifestyle changes; -Immediate BP drugs targeting < 140/90

Figure 2.2- Innition of lifestyle changes and antihypertensive drug treatment- Adapted from (Mancia et al., 2013). BP- Blood Pressure; CKD- Chronic kidney disease; CVD- Cardiovascular disease; DBP- Diastolic blood pressure; OD- Organ damage; RF- Risk factor; SBP- Systolic blood pressure.

Some treatment strategies and choice of medicines should attain some recommendations: *i*) TDs, βBs, CCBs, ACEi and angiotensin receptor blockers are all suitable and recommended for the initiation and maintainance of antihypertensive treatment, either as monotherapy or in some combinations with each other; *ii*) some agents should be considered as the preferencial choice in specific conditions (e.g. organ damage); *iii*) initiation with 2 drugs combination should be considered in individuals with marked high blood pressure or at high cardiovascular risk (Mancia et al., 2013).

The antihypertensive drugs have similar protective effects exerted on the target organs in treating hypertension (the heart, blood vessels and kidney), but imply, nevertheless, differences in the action mechanisms once some agents act as direct vasodilators, while others may have indirect effects (Digne-malcolm, Frise, & Dorrington, 2016).

2.3.3. **Dyslipidemia**

Dyslipidemia can be defined as a disorder of lipid metabolism with repercussions on the serum levels of lipoproteins in the blood circulation, as well as on the concentrations of their different components, with a positive association of CVD between total cholesterol (TC) as well as low density lipoprotein cholesterol (LDL), once most cholesterol is normally carried in LDL form (Piepoli et al., 2016).

Blood lipids are essentially cholesterol and triglycerides (TG), and are presented in two main forms: low density lipoproteins (LDL) and high density lipoprotein (HDL) (Arthur C.Guyton & Hall, 2014). In a simplistic way, it can be stated that LDL promotes the accumulation of cholesterol in various organs and tissues, while HDL removes excess cholesterol from the cells and promotes its transport to the liver (Arthur C.Guyton & Hall, 2014).

The guidelines of the *European Society of Cardiology* (Piepoli et al., 2016) and the *European Society of Cardiology and European Atherosclerosis Society* (Catapano et al., 2016), estabblished target values to the lipid profile to prevent cardiovascular risk. Their approach is primarily aimed at reducing LDL but it is also addressed to improve plasma TG and HDL levels, as described: *i*) patients at a very high total cardiovascular risk, the

goal is an LDL under 1.8 mmol/L (70 mg/dL) with at least a 50% reduction from baseline if between 1.8 and 3.5 mmol/L (70 and 135 mg/dL); *ii*) subjects at high total cardiovascular risk, the goal is an LDL level under 2.6 mmol/L (100 mg/dL) with at least a 50% reduction from baseline if between 2.6 and 5.1 mmol/L (100 and 200 mg/dL); *iii*) in people at moderate total cardiovascular risk, the LDL goal is under 3 mmol/L (<115 mg/ dL) (Catapano et al., 2016; Piepoli et al., 2016). Moreover, although the cardiovascular disease risk is increased if fasting TG are above 1.7 mmol/L (150 mg/dL) the use of drugs to lower TG may only be considered in high-risk subjects when TG are higher than 2.3 mmol/L (200 mg/dL) and cannot be lowered by lifestyle measures. The target goal to TG is recommended to be lower than 1.7 mmol/L (150 mg/dL) (Catapano et al., 2016; Piepoli et al., 2016).

Low levels of HDL under 1.0mmol/L (<40mg/dL) in men and under 1.2mmol/L – (<45mg/ dL) in women constitute a strong, independent and inverse predictor of the risk of premature development of atherosclerosis (Catapano et al., 2016) once HDL has protective effect that derive primarily from its role as a mediator of reverse cholesterol transport, protecting against oxidation of LDL (Arthur C.Guyton & Hall, 2014). Furthermore, the increase in cardiovascular risk relative to low HDL levels is especially dramatic over the range of 0.65 to 1.17 mmol/L (25 to 45 mg/dL), whereby maintaining HDL levels above this value is desirable (Catapano et al., 2016; Piepoli et al., 2016).

In terms of treatment, the first recommended approach is the innitiation of therapeutic lifestyle changes, including weight reduction, exercise, smoking cessation and moderate alcohol consumption, but, international guidelines also recommend the introduction of one pharmacological therapy to decrease both dyslipidaemia and hypertriglyceridaemia (Catapano et al., 2016; Piepoli et al., 2016).

The currently available lipid-lowering drugs include inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase (statins), fibrates, bile acid sequestrants (anion exchange resins), niacin (nicotinic acid), selective cholesterol absorption inhibitors (e.g. ezetimibe) and, protein convertase subtilisin/ kexin type 9 (PCSK9) inhibitors (Catapano et al., 2016; Piepoli et al., 2016).

Statins (ST), our focus of anti- dislipidemic treatment, are among the most studied drugs in CVD morbidity and mortality in both primary and secondary prevention, in both genders and in all age groups (Catapano et al., 2016; Piepoli et al., 2016). Although the

reduction of LDL is the major effect of statins, they also reduce TG by 30–50% and may increase HDL by 5–10% (Catapano et al., 2016). ST reduce the synthesis of cholesterol in the liver by competitively inhibiting HMG-CoA reductase activity (Catapano et al., 2016). The reduction in intracellular cholesterol concentration induces an increased expression of LDL receptor on the surface of the hepatocytes, which results in increased uptake of LDL from the blood and a decreased plasma concentration of LDL and TG (Catapano et al., 2016). The response to all ST therapies varies among individuals, drugs and dose, therefore monitoring the effect on LDL levels is recommended. (Piepoli et al., 2016)

The combination of moderately elevated TG, LDL and low concentrations of HDL is a common trait in patients with T2D, abdominal obesity, insulin resistance and in those who are physically inactive so, a lifestyle intervention, including dietary changes with weight loss, and increased physical activity, contribute to reducing the overall cardiovascular risk through direct influence on other risk factors, (e.g.hypertension, inflammation or impaired insulin sensitivity) (Catapano et al., 2016; Piepoli et al., 2016).

2.3.4. **Functional status decline**

Although, functional status decline is not a disease itself but rather a chronic ageing condition, being able to perform self-care functional tasks in everyday life is fundamental for older adults (Marventano et al., 2014). Functional status is the cornerstone of geriatric care and serves as an indicator of well-being (Peron, Gray, & Hanlon, 2011) once the health status of a person can be described in terms of body functions and structures, activities, and participation in life situations (Peron et al., 2011). Functional efficiency is the ability to be independent in fulfilling the basic needs of everyday life (Muszalik, Dijkstra, Kędziora-Kornatowska, Zielińska-Więczkowska, & Kornatowski, 2011).

As age increases, a certain reduction in the ability to perform daily activities is considered natural. However, the presence of individual diseases, such as arthritis and arthrosis, CVD, hypertension and diabetes, as well as the total number of chronic conditions, is independently associated with lower functional status (Marventano et al., 2014). Moreover, specific combinations of diseases (CVD and hypertension) may have not only additive effects, but also synergistic ones (Marventano et al., 2014).

The decline in function increases health care use, worsens quality of life, threatens independence and increases the risk of mortality (Buford, 2016; Marventano et al., 2014; Muszalik et al., 2011; Peron et al., 2011). Thus, functional status has been recognized as a relevant and important treatment outcome in the elderly population.

Althougth to now, there are no specific guidelines or target goals to define who is in risk of functional decline or not, special measures have been used to monitorize older adults. According to Peron and colleagues (Peron et al., 2011) there are 2 ways to measure functional status:

- self- or caregiver-reported measures including: (1) basic activities of daily life like bathing, dressing, getting around the house, toileting, feeding, grooming (2) instrumental activities of daily life, such as using the telephone, paying bills, taking medications, preparing light meals, doing laundry, shopping, housekeeping, mode of transportation, ability to handle finances) and (3) mobility (e.g. walking one-half mile, walking up and down stairs, doing heavy work around the house)(Peron et al., 2011); one instrument that derivate from these measures is the 36-Item Short Form Health Survey (SF-36).
- performance based measures include: gait, walking speed and distance, among others, which can be measured by the Senior Fitness Test battery (R.E. Rikli & Jones, 1999). This battery predicts the level of capacity needed to maintain physical independence into later life according to age (Roberta E. Rikli & Jones, 2013).

Risk factors for functional status decline include advanced age, low income, poor self-rated health, presence of comorbidities or certain medical conditions (eg, arthritis, cognitive impairment, hypertension, depression), lifestyle habits (eg, lack of physical activity, current or past smoking, excessive alcohol consumption), and medication use (Peron et al., 2011).

In terms of treatment plans, to date, exercise training is the only consistent intervention to demonstrate beneficial effects on functional decline among older adults (Ip et al., 2013; C. K. Liu et al., 2014; Pahor et al., 2006; Rejeski et al., 2009). However, these benefits are not observed in all individuals and the change in performance is quite variable. A variety of participant-specific factors may limit gains in functional performance including: obesity (Manini et al., 2010), hypertension and medication use (Buford et al.,

2012; Sumukadas et al., 2014), each with independent influences on the responsiveness of the participants to train. These results seem to suggest that exercise may be necessary, but insufficient, for preserving function status and disability among many older adults (Buford et al., 2012).

Recently, pharmachological interventions also have been suggested as therapeutic strategie for enhancing physical function and mobility in older adults. For example, it has been suggested that MET could potentially improve function and reduce frailty risk in older adults with T2D (Wang, Lorenzo, & Espinoza, 2014) once, even though, the underlying biological mechanisms of MET remain to be fully elucidated, it makes sense that one of the major proposed mechanism of MET is to activate the enzyme AMP-activated protein kinase, a key sensor of cellular energy status (Anton et al., 2015), decreasing insulin levels, reducing insulin/insulin-like growth factor-1 (IGF-1) signaling, inhibiting mTOR and mitochondrial complex I in the electron transport chain, reducing endogenous production of reactive oxygen species, that in turn will help in ageing, body composition and function status mechanisms (Christy S. Carter et al., 2012; De Cabo, Carmona-Gutierrez, Bernier, Hall, & Madeo, 2014).

Moreover, in hypertensive older adults, a growing interest has highlighted the potential utility of ACEi as therapeutic agents to prevent functional decline. Buford and colleagues (Buford et al., 2012) reported that older adults (age > 70) who took ACEi displayed significant improvements in function status in response to a 12-month exercise program compared to non ACEi users. However, evidence from studies evaluating the effects of mono-modal pharmacologic strategies on physical function have been mixed at best (Christy S. Carter et al., 2012; Sumukadas et al., 2014), and others also suggested that the strategy of combining potentially beneficial medications with chronic exercise may be more effective than the intervention alone once exercise could stimulate adaptations to pharmaceuticals that are not observed in response to the drug alone (Buford, 2016). Another example could be the case of statins´users due to the main adverse effect-muscular pain and myalgia (Piepoli et al., 2016) that, with exercise, could decrease this effect.

Despite these treatments, no pharmachological treatment has proven, to date, to be effective in attenuating age-related functional decline (Simon et al., 2015) but their potential use to improve functional status in older adults could have significant clinical

impact since such regimens typically require minimal effort from the patient, an important issue to be considered once “effort” may act as a primary barrier to lifestyle changes (Simon et al., 2015) and thus, should be analyzed in-depth.

In short, although we present CVD diseases as isolated conditions, many older adults are affected by multiple chronic conditions (Bell & Saraf, 2016; Fabbri et al., 2015). Thus, studying multimorbidity will help to understand the biology of ageing and, at the same time, understanding the underpinnings of ageing may help to develop strategies to prevent or delay the CVD burden of multimorbidity (Fabbri et al., 2015).

2.4. Ageing and Medication

Health systems are increasingly large and more complex, with health care expenditure never having been as high, consuming an increasing share of national income, contributing decisively to the increasing in total health expenditure, medication costs (Barros & Nunes, 2011).

In Portugal the policy of medicines has been subject to great evolution in recent years, according to the political ideologies and the economic situation that Portugal goes through (Barros & Nunes, 2011).

According to the latest data (INFARMED I.P., 2014), medicine retail price and national healthcare expenditure have been decreasing since 2010, contrarily with the preceding years, which accounted with increasing medication costs in National Healthcare System (NHS). Unfortunately, the cost of medication users did not follow the same path because since 2011 the users co-payment has been increasing due to the augment of the number of prescriptions and packages of medicines and also to the decreasing of reimbursement levels (Table 2.1). These consequences reflect the commitment made in the Memorandum of Understanding with the *Troika*, in 2011, not only to "reduce public drug costs to 1.25% of gross domestic product (GDP) by the end of 2012 and to around 1% of GDP by 2013" but also to introduce new policies, including the Protocol-Brake, the increasing of generic medicines, and the review/reduction of the reimbursement levels.

The growth in the number of packages and consequently medicines has been constant over the last years. Indeed, between 2011 and 2014, there was an increase of 8.7%, revealing that, in 2014, additional 13.169.601 packages of medicines were dispensed.

Table 2.1- National Health System market- medicines dispense between 2010-2014. Adapted (INFARMED I.P., 2014)

Medicines	2010	2011	2012	2013	2014
Retail Price (€)	2.346.661.610	2.124.571.962	1.855.642.761	1.849.703.511	1.873.043.848
National Healthcare Expenditure (€)	1.639.275.468	1.325.999.501	1.173.075.462	1.160.219.375	1.170.352.630
User Co-payment (€)	707.386.142	798.572.460	682.567.299	689.484.136	702.691.219
Packages (n.º)	139.907.224	139.850.812	140.017.420	149.086.465	153.020.413
Prescriptions (n.º)	67.045.254	68.300.221	70.190.287	76.920.243	72.916.263
Reimbursement (%)	69,9	62,4	63,2	62,7	62,5
User co-payment (%)	30,1	37,6	36,6	37,3	37,5

In 2014, the major 3 pharmacotherapeutic contributors, responsible for 68,13% of the NHS expenditure were the cardiovascular system (24,76%), central nervous system (22,39%) and the endocrine system (20,98%) (INFARMED I.P., 2014). If we examine the 2 pharmacotherapeutic groups, cardiovascular and endocrine systems, we observed that antihypertensive, antidislipidemic and antidiabetic medication accounted with the largest NHS expenditure, packages and medication consumption, revealing the concerning prevalence of these diseases among Portuguese population (Table 2.2). In fact, the antihypertensive and antidislipidemic medication increased 4% and 3%, respectively between 2010 and 2014 (Direcção Geral de Saúde, 2015).

In economic and sociodemografic terms, this issue is extremely concerning once older adults are among the biggest consumers of medicines and the increasing effects of ageing and longevity, will put additional pressure on an already compromised healthcare system (Barros & Nunes, 2011). Indeed, the use of prescription medication among older adults has increased dramatically. In Portugal, in 2014, the proportion of elderly who consumed medicines was approximately 90.5%, almost the double comparatively with the remaining population groups 45.4% (Instituto Nacional de Estatística, 2016).

In a Canadian study, 17% of older adults living in the community were identified as multiple medication users, taking on average more than five prescription medications. The

group of users from 75 to 84 years of age, was more likely to be multiple prescription medication users than their younger counterparts, on the 65 to 74 year age group (16% compared with 11%) (Ramage-Morin, 2009). Additionally, the use of more than 5 medications has tripled to nearly 40% (Charlesworth, Smit, Lee, Alramadhan, & Odden, 2015a), increasing the concerns to polypharmacy and the need of more cost-effective treatment plans (American Diabetes Association, 2016; Aschner et al., 2014; Catapano et al., 2016; P. A. James et al., 2013; Mancia et al., 2013; Piepoli et al., 2016; Weber et al., 2014)

Table 2.2- Pharmacotherapeutic groups and sub-groups retail price, expenditure and packages consumed in 2014. Adapted (INFARMED I.P., 2014)

Pharmacotherapeutic group	Pharmacotherapeutic Sub-group	Retail Price (€)	NHS (€)	Packages (n.º)
Cardiovascular System	Cardiotonics	840.003	652.770	381.812
	Antiarrhytmics	7.685.303	5.963.348	713.397
	Sympathomimetics	54.202	23.842	16.127
	Antihypertensives	322.901.417	197.804.959	27.818.150
	Vasodilators	34.969.291	22.605.726	2.817.953
	Venotropic agents	1.608.896	710.077	77.914
	Antidislipidemics	162.469.000	62.060.844	10.623.881
Endocrine System	Hypothalamus and Pituitary Hormones	4.276.285	3.692.238	146.424
	Corticosteroids	6.960.763	2.912.320	1.134.233
	Thyroid	6.596.909	4.612.884	1.676.370
	Insulins, Oral Antidiabetics and Glucagon	242.645.787	222.009.727	10.040.190
	Sex hormones	13.526.451	7.943.977	1.521.732
	Gonadotropins and Ovulation Stimulants	6.417.660	4.359.233	47.010
	Hormone Antagonists	133.859	49.794	9.967

On the other hand, in an interesting qualitative study in older adults, associating the quantity of medications with the perception of their health status, results showed that the less prescription medications consumed, the healthier participants believe they were (Holroyd, Vegsund, Stephenson, & Beuthin, 2012). Reversely, highest prescription medications use was associated with a less healthy state (Holroyd et al., 2012).

However, prescribing medications in older adults is not a simple process and requires additional knowledge of age-associated changes in pharmacokinetics and pharmacodynamics once multiple conditions increase the likelihood of experiencing harmfull drug effects and the benefits of many medications, even those that presume

unquestionable benefit, are uncertain in older adults with multimorbidity (Ramage-Morin, 2009)

Age changes pharmacokinetics, reducing medication absorption, which may result of atrophic gastritis, reduced gastric motility and secretions and reduced intraluminal surface area (Singh & Bajorek, 2015). Moreover, the distribution volume of a medicine depends on body composition, plasma protein profile, changes in liver size, liver blood flow and in phase I reactions (e.g. oxidation, reduction) which are particularly affected in older people (McLean & Couteur, 2004; Singh & Bajorek, 2015). Furthermore, the decline of glomerular filtration rate is one of the most important age-associated pharmacokinetic change (McLean & Couteur, 2004). Some researchers have argued that some diseases, such as hypertension, chronic heart failure, diabetes can significantly affect renal function (Singh & Bajorek, 2015) and renal hemodynamics in older people (McLean & Couteur, 2004).

The pharmacodynamic behaviour of a medicine is also affected by age- associated physiological changes including altered receptor number, receptor affinity, homeostatic reserve, altered neurotransmitters and/or receptors, hormonal changes and impaired glucose metabolism (Bowie & Slattum, 2007). The altered sensitivity of β-adrenergic receptor is a classic example of pharmacodynamics change in the elderly presenting a decreased response to β-agonists and an increased response to β-blockers (Singh & Bajorek, 2015).

In terms of the adverse effects, medication has several age side-effects that should also be acknowledged. However, due to the amount of medicines, we will only report the ones focused on our study.

MET has been associated with gastrointestinal side effects, vitamin B_{12} deficiency being contraindicated in older adults with chronic kidney disease, acidosis, hypoxia and dehydration (American Diabetes Association, 2016). Addittionally, MET has been shown to, slightly but significantly, reduce oxygen consumption and could have also blunted the effect of exercise (Cadeddu et al., 2014).

ACEi are well tolerated, but their main side effects are cough (most common in women and in patients of Asian and African background) and hyperkalemia, which may occur more frequently at higher doses; TDs increase metabolic-hypokalemia,

hyperglycemia and hyperuricemia; CCBs may cause peripheral edema; and, βBs may reduce sexual function, fatigue, and reduced exercise tolerance (Weber et al., 2014).

ST are a concern due to the potential to increase myalgia with or without chronic kidney elevation, myopathy and the rare but serious rhabdomyolysis (Catapano et al., 2016). Unfortunately, it seems, while these treatments present negative interactions that may lead to dementia, falls/fractures and physical disability (Buford, 2016), the literature still supports the belief that medications are a dangerous, yet *necessary*, element in the overall care and management of the top prevalent and persistent illnesses among older adult population (Ramage-Morin, 2009) highlighting the need of more research to confirm this rationale.

2.5. Exercise and Inactive Ageing

The concept of exercise is often used indistinctly without any clarity and it is sometimes confused with concepts of physical activity and physical fitness but, these terms are not synonymous. Moreover, the concepts of inactivity and sedentary behaviour are also used interchangeably in the literature but they are independent entities with different operational functionalities (Mark S Tremblay et al., 2017). In the present thesis, we chose to first delimitate these different conceptual entities in order to elucidate the target of our intervention.

Physical activity refers to any voluntary movement produced by the skeletal muscles, translating into energy expenditure, encompassing every day-to-day activity (e.g. locomotion, gardening, domestic activities, work movements, among others) reflecting the total energy expenditure (Caspersen, Powell, & Christenson, 1985). *Exercise* is a subcategory of physical activity that is planned, structured and repetitive, performed with the intention to improve or maintain one or more elements of physical fitness described by the FITT formula, meaning the Frequency, Intensity, Time (duration) and Type of activity (American College of Sports Medicine, 2014) being the main focus of our intervention.

The *physical fitness* refers to a set of characteristics possessed or acquired by an individual, related to the ability to perform physical activity (Caspersen et al., 1985) and it

is the basis of the realization of daily activities in a safe and autonomous way without revealing fatigue, such as food, hygiene care, dressing, walking or even recreational activities (R.E. Rikli & Jones, 1999). These characteristics can be separated into the health-related and skill-related components of physical fitness (American College of Sports Medicine, 2014; Caspersen et al., 1985). Due to our study population, it is more important to stress the dimensions of physical fitness related to health as the main determinant of independence and quality of life, like cardiorrespiratory fitness, muscular strength, agility/dynamic balance and flexibility (R.E. Rikli & Jones, 1999).

The concept of *inactivity* refers to an insufficient level of physical activity according to the physical activity recommendations (Mark S Tremblay et al., 2017); that is, not achieving 150 min of moderate-to-vigorous intensity of physical activity, or 75 min of vigorous intensity of physical activity per week or an equivalent combination of moderate- and vigorous-intensity activity (American College of Sports Medicine, 2014). *Sedentary behavior*, on the other hand, is defined as any waking behaviour characterized by an energy expenditure under 1.5 metabolic equivalents, while in a sitting, reclining or lying posture (Mark S Tremblay et al., 2017).

This conceptual delimitation is important once older adults are the most inactive and sedentary age group (Wullems, Verschueren, Degens, Morse, & Onambélé, 2016). Indeed, inactivity is the fourth-leading risk factor for all global deaths and its contribution to all-cause mortality amounts to over 500,000 deaths per year, deaths that could be averted through enabling and encouraging people to engage lifestyles that achieve the recommended levels of physical activity (Centre for Economics and Business Research., 2015). Furthermore, health benefits can be achivied with comparatively smaller levels of physical activity. In fact, it was demonstrated that the transition from a sedentary life to some degree of activity presented highest benefits (Eijsvogels, Molossi, Lee, Emery, & Thompson, 2016).

Worringly, the *World Health Organization* estimates that a quarter of European adults are inactive (Centre for Economics and Business Research., 2015) but these numbers are more concerning to Portuguese adults, once 52% reported never exercising and only 17% achieved the recommended physical activity levels (Melanie Nichols, Nick Townsend, 2012). Nevertheless, for those aged 65 or over, these numbers are even more pronounced, since almost 87% and 80% of Portuguese women and man, respectively,

refered to be inactive according to the latest data (Direcção Geral de Saúde, 2016). This epidemiological data raise new concerns due to the increased risk inactive people have to develop cancer, T2D, heart disease and suffer from premature death (World Health Organization, 2014). Alongside this alarming numbers, inactivity imposes an economic cost of 80.4 billion euros per year to the 28- European Union, through direct costs of the major non-communicable diseases, and indirect costs with related mood and anxiety disorders (Centre for Economics and Business Research., 2015).

Unfortunately, older adults also accumulate one other deleterious risk factor- high amounts of sedentary behaviour. In fact, older adults, apart from inactivity, also engage in approximately 16 types of sedentary behaviours daily, with TV viewing, reading, eating meals, computer use and transportation being the most common (E. K. Lenz, 2014). It has been estimated with an accelerometer-derived, an average of 8.5–9.6 hours a day in sitting time, representing 65–80 % of their waking time (Wullems et al., 2016). Moreover, this sedentary behaviour patterns increase with age, resulting in old-older adults being more sedentary than younger-older adults (Harvey, Chastin, & Skelton, 2015). Additionally, not only the amount of sedentary behaviours increase, but also the decline in total daily physical activity accelerates after retirement (~65 years old)(Wullems et al., 2016). In fact, the pattern of physical activity appears to be lower and of less intensity, making light-intensity physical activity, the most common type of physical activity within the oldest age groups (Wullems et al., 2016).

This detrimental association between inactivity, sedentary behaviour and aggravation of several health outcomes, has been reported. In cardio metabolic terms, it has been proposed that reduced energy expenditure and muscle contractions, not only lead to reduced insulin sensitivity and increased pro-inflammatory cytokines (Mark Stephen Tremblay, Colley, Saunders, Healy, & Owen, 2010), but also decreased lipoprotein lipase activity and muscle glucose transporter protein content (Gianoudis, Bailey, & Daly, 2015; Mark Stephen Tremblay et al., 2010). The increase in visceral and intermuscular fat stimulates the release of pro-inflammatory cytokines and decreases the anti-inflammatory markers from adipose tissue, making a catabolic effect on muscle tissue and impairing muscle protein synthesis (Gianoudis et al., 2015). Moreover, shear rate, superficial femoral artery, brachial artery diameter decrease, endothelial cell damage and blood pressure increase were also associated with the increase of sedentary behaviour (Thosar, Bielko,

Mather, Johnston, & Wallace, 2015) which have been positively associated with sarcopenia, dyslipidaemia, obesity, hypertension and glucose intolerance (E. K. Lenz, 2014).

Inactivity and sedentary behaviour also affect skeletal-muscle system once it is thought to change the balance between bone resorption and deposition, mainly by a rapid increase in bone resorption without concomitant changes in bone formation, resulting in reduced bone mineral content and increasing the risk of osteoporosis (Mark Stephen Tremblay et al., 2010). Additionally, sedentary behavior was related to lower total body and leg lean mass, which were associated with an increased risk of sarcopenia and limited physical function, increased number of falls/ fractures and physical disability (Buford, 2016), independently of physical activity or other potential confounding factor (Gianoudis et al., 2015). Furthermore, in terms of quality of life, it has been suggested a link between sedentary behaviours, health, and well-being, independently of physical activity (Harvey et al., 2015). The number of sitting hours was inversely related to the scale scores of physical functioning, physical role, bodily pain, vitality, social functioning and mental health (Balboa-Castillo, León-Muñoz, Graciani, Rodríguez-Artalejo, & Guallar-Castillón, 2011).

Collectively, this information seems to suggest that, not only small changes from inactivity and sedentarism to physical activity may lead to a reduction in the risk of chronic diseases and mortality (Pedersen & Saltin, 2015; Wullems et al., 2016), but also might preserve functional status and performance in terms of daily functioning tasks and independent living (Santos et al., 2012). Nevertheless, regular moderate to vigorous physical activity still seems more important in the prevention and treatment of chronic diseases, even in older adults (Dunstan, Howard, Healy, & Owen, 2012; Pedersen & Saltin, 2015; Warburton & Bredin, 2016).

There is a consistency of findings across studies and a range of outcome measures related to functional independence, regular aerobic activity and short-term exercise programs confering a reduced risk of functional limitations and disability in older age (Paterson & Warburton, 2010; Warburton & Bredin, 2016). Although a precise characterization of a minimal or effective physical activity dose to maintain functional independence is difficult, it appears that moderate to higher levels of activity, particularly exercise programs, seem to be more effective for significant outcomes (Warburton & Bredin, 2016). Therefore, both physical activity and sedentary behaviours should be

targetted, but more studies are needed particularly in long-term exercise prevention programs in order to decrease these patterns, because even though, interventions might be successful in the short-term, future research should examine the long-term effects of exercise programs interventions (Wullems et al., 2016).

2.6. Quality of Life and "Active Ageing"

Health is a multi-dimensional concept, closely related to the concept of quality of life (QoL), capturing how people feel and how they function, from the individual to the cellular level (Kuh, Karunananthan, Bergman, & Cooper, 2014). It can be seen as the ability to adapt and self-manage, based on resilience to cope, maintain and restore one's integrity, equilibrium and sense of wellbeing in three areas: biologically, in terms of physiological resilience; mentally, in terms of capacity to cope; and socially, in terms of the capacity to fulfill potential obligations, to manage independent living and social participation (Kuh et al., 2014). Health and disease, these antagonic concepts, reflect the ability of an organism to respond adaptatively to environmental challenges (Kuh et al., 2014).

In a historical perspective, many evolving classifications defined health, diseases and disease risk using, a constellation of signs, symptoms and by extension QoL.

Many of the initial definitions of health and disease were in line with the *biomedical model*, which conceptualized health and disease, largely based on the presence or absence of chronic disease conditions and reduction of the disease risk factors (Anton et al., 2015). Within this model, individuals were typically classified into distinct dichotomous categories of healthy or diseased, such that successful or healthy ageing was represented by good health, independence and high levels of cognitive and physical functioning (Anton et al., 2015). Nevertheless, this model did not recognize the role of lifestyle and/or psychosocial factors as contributers to good or poor health, and so, a more dynamic concept of health across life was needed (Anton et al., 2015). In parallel, there was a growing need to evaluate treatments in terms of medical efficacy and also in terms of patients' perceptions on everyday life improvement. Due to the increasing recognition of the complex interplay among biological, psychological, and social factors affecting an

individual's health status and disease risk, a new model emerged in order to understand the development of disease- the *biopsychosocial model* (Engel, 1977). This model views the individual's health not as a dichotomous classification of healthy or diseased but rather as occurring along a spectrum, across multiple dimensions (Engel, 1977).

In 1997, the World Health Organization (WHO) defined health as "*a state of complete physical, mental and social well-being, not merely the absence of disease*" and introduced an estimation of well-being as well as a the measurement of health and the effects of health care through the use of QoL (The Whoqol Group, 1998). QoL was than defined as the individual's perception care of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns (The Whoqol Group, 1998). In global terms, this vision includes psychological state, level of a person's independence, social life and personal beliefs (The Whoqol Group, 1998).

This definition served as a reference to the formulation of health policies and programs, with positive connotations and with several dimensions, regardless of the presence of diseases, to promote the health status of individuals and communities (Anton et al., 2015) like the "*Sucessful Ageing*", and more recently "*Active Ageing*". The "Sucessful Ageing" model, is more applied by the American geriatric community and the model of "Active Ageing" is more emphasized in the European countries (Paúl, Ribeiro, & Teixeira, 2012).

"Succesfull ageing" results from a combination of three components: avoiding disease and disability, high cognitive and physical function, and engagement with life (Rowe & Kahn, 1997). Recent successful ageing models continue to support the multidimensional nature of this construct and have incorporated both objective and subjective dimensions in their definitions (Pruchno, Wilson-Genderson, & Cartwright, 2010). For example, Pruchno and colleagues (2010) have proposed a two-factor model, incorporating both objective (i.e., functional abilities, pain and diagnosed health conditions) and subjective criteria (i.e., perceptions of quality of life and successful ageing). However, this model is problematic as it encourages unattainable ideals of success and inappropriate ideas of failure; it takes little account of the variation in environmental challenges that individuals face; it appears to promote the idea that older people should act like younger people for as long as possible; and it also questions whether functional

decline is inevitable (Kuh et al., 2014; Martin et al., 2015). Moreover, in light of this model, measures used in studies of healthy ageing commonly use criteria that distinguish the least healthy individuals rather than identifying those in the best of health, and often do not investigate variability across the whole spectrum (Kuh et al., 2014). For these reasons, the "Active Ageing" model seems more suitable to our conceptual delimitation and goal, referring it to "*the process of optimizing opportunities for health, participation, and security in order to enhance quality of life as people age*"(WHO, 2002).

The concept of active ageing is based on three pillars mentioned in the definition: participation, health, and security (WHO, 2002). According to the WHO document on active ageing, the key aspects are (1) autonomy which is the perceived ability to control, cope with and make personal decisions about how one lives on a day-to-day basis, according to one's own rules and preferences; (2) independence, the ability to perform functions related to daily life, that is, the capacity of living independently in the community with no and/or little help from others; (3) and QoL, that is "an individual's perception of his or her position in life in the context of the culture and value system where they live and in relation to their goals, expectations, standards and concerns" (WHO, 2002). This proposed model encompasses six groups of determinants, each one including several aspects: (1) health and social services (promoting health and preventing disease; health services; continuous care; mental health care); (2) behavioral (smoking; physical activity; food intake; oral health; alcohol; medication); (3) personal (biology, genetics and psychological factors); (4) physical environment (friendly environment; safety houses; falls; absence of pollution); (5) social (social support; violence and abuse; education); (6) economic (wage; social security; work), embedded in cultural and gender context, with recommendations for health policy for old people, to be implemented through national health plans all over the world (WHO, 2002). This model is a broad ranging concept, incorporating, in a complex way, the person's physical health, psychological state, level of independence, social relationships, personal beliefs and relationship, to salient features in the environment, once as people get older, their QoL is largely determined by their ability to maintain autonomy, independence and healthy life expectancy, which is how long people can expect to live without disabilities (Paúl et al., 2012).

When explicitly exploring the concept of active ageing, Bowling (2008) reported that the most common perceptions of active ageing were having/maintaining physical

health and functioning (43%), leisure and social activities (34%), mental functioning and activity (18%) and social relationships and contacts (15%). The predictors of positive self-rated active ageing were optimum health and QoL (Bowling, 2008) highlighting the role of health related quality of life (HRQoL).

HRQoL is generally conceptualized as a multidimensional construct and a global indicator of health resulting from the individual's perception of the impact that diseases exert on different spheres of life (physical, mental, social and functional health)(Balboa-Castillo et al., 2011). Among older adults, HRQoL it is thought to be one of the most important factors for assessing the health status and an important outcome measure that is being increasingly used to evaluate outcomes in clinical studies of elderly patients with chronic diseases (Kim, Lee, & Kim, 2012). Several studies have reported an association between number of chronic medical conditions and HRQoL, with more diseases being related to lower physical, social and psychological functioning (Marengoni et al., 2011). However, the association between multimorbidity patterns and HRQoL has not been fully investigated among elderly people. In other words, it is not clear if there are prominent diseases that affect HRQoL.

Diminished HRQoL in older adults have been related with lower exercise training, age, gender, lower education, living alone, longer disease duration, treatment type, number of medications, comorbidities, disease complications, or obesity (Al Hayek, Robert, Al Saeed, Alzaid, & Al Sabaan, 2014; Balboa-Castillo et al., 2011; Baptista, Machado-Rodrigues, & Martins, 2017; Charlesworth et al., 2015a; Holroyd et al., 2012; Javanbakht, Abolhasani, Mashayekhi, Baradaran, & Jahangiri noudeh, 2012; Kim et al., 2012; Maddigan, Feeny, Majumdar, Farris, & Johnson, 2006; V. Myers & McVay, 2013; Papadopoulos, Kontodimopoulos, Frydas, Ikonomakis, & Niakas, 2007; Wee, Cheung, Li, Fong, & Thumboo, 2005).

Much research has been conducted to evaluate the effects of exercise on HRQoL. However, most of these studies have used cross-sectional and observational designs, and the evidence from randomized controlled trials is both limited and inconsistent, particularly in the mental component (Awick et al., 2015; Cadeddu et al., 2014; Florez et al., 2012; Kelley, Kelley, Hootman, & Jones, 2009; Marrero et al., 2014; V. Myers & McVay, 2013). Furthermore, those studies which have examined exercise training effects on HRQoL in a pre-post treatment design used different patient groups as subjects and different time

lengths (between 3 to 12 months)(Awick et al., 2015; Imayama, Alfano, et al., 2011; Kelley et al., 2009), different exercise types and volumes (Awick et al., 2015; Imayama, Alfano, et al., 2011; V. Myers & McVay, 2013; Nicolucci et al., 2012) and only a few studies have concentrated in comparing different types of treatment (Cadeddu et al., 2014; Florez et al., 2012). Collectively, these facts highlight the need to assess HRQoL as part of large-scale and long-term studies, incorporating standard care as a control group and examine the changes of HRQoL components over time in different types of treatments in older adults with comorbidities once that the amount, pattern and some treatment types have been associated with impaired HRQoL (Fabbri et al., 2015; Kim et al., 2012).

2.7. Ageing, Medication, Exercise, and Health-Related Quality of Life

The beneficial effects of exercise on several aspects of health are nowadays well known and generally accepted. In healthy older adults, exercise and a physically active lifestyle are known to positively contribute to the prevention of 26 different diseases: psychiatric diseases (depression, anxiety, stress, schizophrenia); neurological diseases (dementia, Parkinson's disease, multiple sclerosis); metabolic diseases (obesity, hyperlipidemia, metabolic syndrome, polycystic ovarian syndrome, T2D, type 1 diabetes); cardiovascular diseases (hypertension, coronary heart disease, heart failure, cerebral apoplexy, and claudication intermittent); pulmonary diseases (chronic obstructive pulmonary disease, asthma, cystic fibrosis); musculo-skeletal disorders (osteoarthritis, osteoporosis, back pain, rheumatoid arthritis); and cancer (Pedersen & Saltin, 2015).

Higher levels of exercise are related to lower rates of CVD among people over 60 years old. In this way, when compared, individuals with high amounts/ intensity of exercise training reduced approximately 30–35 % CVD risk compared with moderate amounts/ intensity of exercise, and this decreased approximately 20–25 % CVD risk compared with individuals with low amounts/ intensity of exercise training (Shiroma & Lee, 2010). Moreover, regular exercise training has been indicated as a lifestyle intervention to improve almost all risk factors that are involved with CVD (Fig. 2.3) (Halloway, Wilbur, Schoeny, Semanik, & Marquez, 2016). The underlying mechanisms

related to the benefits of exercise include multiple alterations in the myocardium, skeletalmuscle, and vascular system associated with changes in inflammation and endothelial function, as previously seen (Anton et al., 2015).

Regular exercise training improves the CVD risk profile by reducing LDL, triglycerides and increasing HDL, lowering blood pressure, improving glucose metabolism and insulin sensitivity, reducing body weight and reducing inflammatory markers (Eijsvogels et al., 2016; Mann, Beedie, & Jimenez, 2014; Seron, Lanas, Pardo Hernandez, & Bonfill Cosp, 2014)

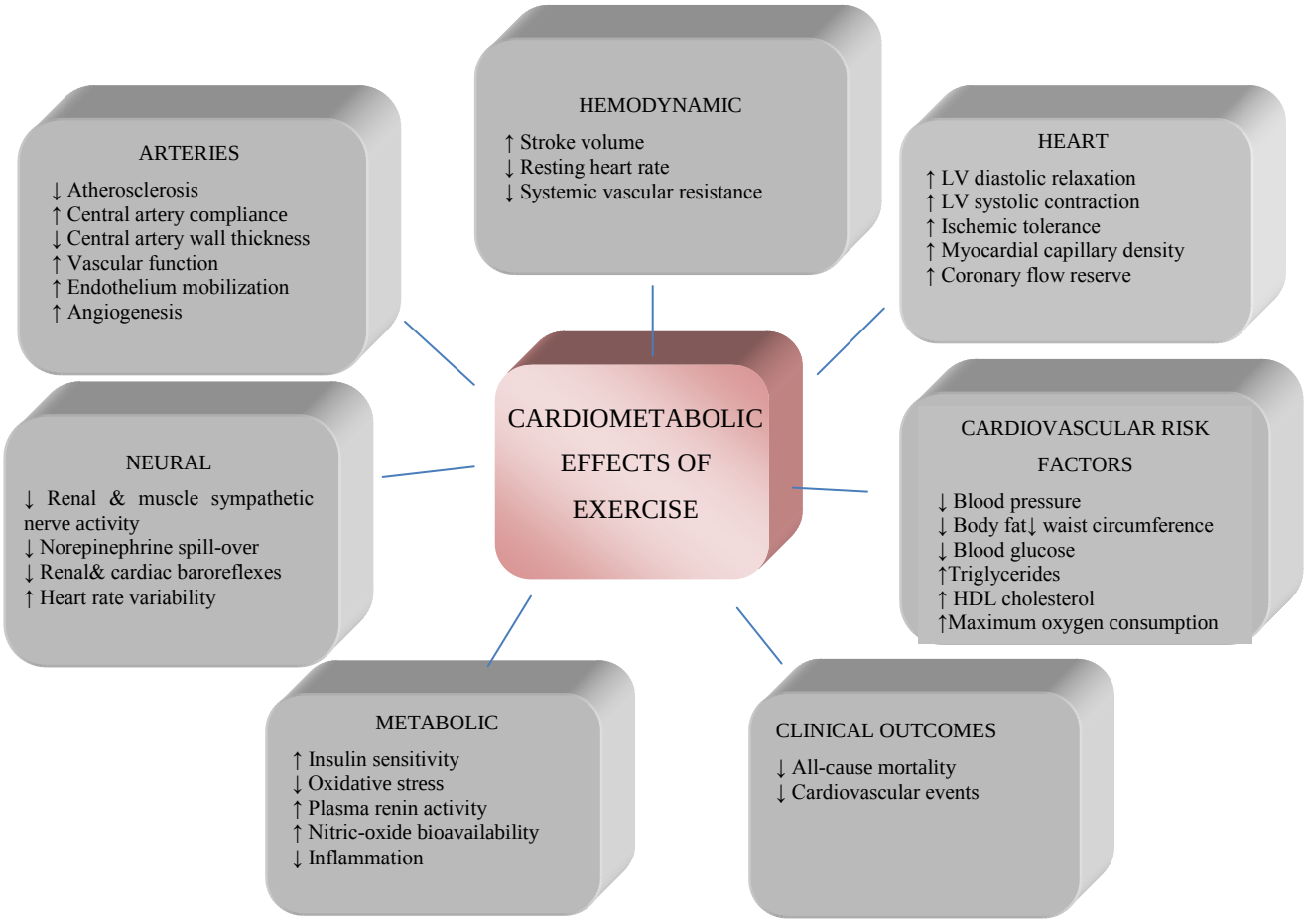

Figure 2.3- Summary of the cardiometabolic beneficial effects of regular exercise. ↑increase or improvement; ↓decrease or improvement. Adapted from (Sharman, La Gerche, & Coombes, 2015)

In T2D, chronic exercise as been suggested as an effective treatment, resulting in stabilization of plasma glucose in the acute phase and improvements in body composition,

insulin resistance and HbA1c (O'Hagan, De Vito, & Boreham, 2013). However, in the elderly population, engagement in exercise is suboptimal, due to the tendency of expert bodies and physicians to prioritize the roles of diet and medication over exercise in their treatment plans (O'Hagan et al., 2013) but also to the participants own intrinsic barriers to an "active" treatment plan (Ambrose & Golightly, 2015).

On one hand, T2D international organizations (Aschner et al., 2014; Inzucchi et al., 2012) recommend a stepwise management plan approach based on lifestyle modification with change on nutritional and exercise habits as the first step, but they differ in the introduction of a first-line pharmacologic hypoglycemic drug in an early stage of the disease, usually with MET. On the other hand, randomized controlled trials have shown that intensive lifestyle may decrease the rate of diabetes onset in adults at high risk of developing T2D (Diabetes Prevention Program Research Group, 2009; Griffin et al., 2011; Pan et al., 1997; The Look AHEAD Research Group, 2010) and reducing cardiovascular risk (American Diabetes Association, 2016). However, it has also been suggested that pharmacological therapies alone, or in combination with diet and exercise could be even more effective (Schellenberg, Dryden, Vandermeer, Ha, & Korownyk, 2013; Stevens et al., 2015; Thompson et al., 2014). Nevertheless, pharmacologic treatments rise new issues regarding adverse side effects and drug-disease interactions (Abdelhafiz & Sinclair, 2015; American Diabetes Association, 2016; Bell & Saraf, 2016; Richman & Schub, 2015). Furthermore, it has been reported that greater reductions in morbidity and mortality in T2D could come from the result of the management of other cardiovascular risk factors, especially hypertension and lipid profile, rather than the solely independent tight glycemic control (American Diabetes Association, 2016).

In terms of HRQoL, exercise was also associated with improvements in T2D (V. Myers & McVay, 2013). However, in older adults there is a gap in studies measuring the isolated effects of exercise and pharmachological treatments like MET, or the combination of both in HRQoL (Imayama, Plotnikoff, Courneya, & Johnson, 2011; V. Myers & McVay, 2013; Nicolucci et al., 2012; Wadden, 2014). Evidence from experimental studies (V. Myers & McVay, 2013; Nicolucci et al., 2012) in older adults is both limited and inconsistent, conflicting on whether exercise interventions can improve mental HRQoL, but also the MET effect (Cadeddu et al., 2014; Florez et al., 2012; Marrero et al., 2014) once that the existing evidence included lifestyle change with weight-loss and exercise

training (Florez et al., 2012; Green, Fox, & Grandy, 2011; Marrero et al., 2014; Wadden, 2014), or measured different modes (V. Myers & McVay, 2013) or volumes of exercise (Nicolucci et al., 2012), or used different time-lengths between 6 months (Marrero et al., 2014), 9 months(V. Myers & McVay, 2013), 12 months (Imayama, Plotnikoff, et al., 2011; Nicolucci et al., 2012) up to 9.6 years (Wadden, 2014), but also used different stages of the disease (Cadeddu et al., 2014; Florez et al., 2012; Marrero et al., 2014). Therefore, it seems crucial, to understand the relative value of exercise training and/or drug treatment in the elderly, due to the incongruent lack of evidence previously demonstrated (Thompson et al., 2014).

In hypertensive older adults, exercise has also proven to be effective in managing blood pressure (Veronique A Cornelissen, Buys, & Smart, 2013). In fact, this meta-analysis of randomized controlled trials has shown that aerobic training reduces resting SBP and DBP by 3.0-2.4 mmHg overall, and even by 6.9-4.9 mmHg in hypertensive participants (Veronique A. Cornelissen & Smart, 2013). Among older sedentary men in stage 1 or 2 of hypertension, the reduction in blood pressure load from an acute exercise bout (45 minutes) was immediately apparent and persisted for 24 hours (Sharman et al., 2015). However, as previously observed, older adults with hypertension represent a specific high risk group for accelerated rates of functional decline and associated cardiovascular events (Buford et al., 2015), comparatively with normotensive individuals of the same ages (Dumurgier, Elbaz, Dufouil, Tavernier, & Tzourio, 2010).

Up to now, only exercise interventions have shown promising results in functional decline (Liu et al., 2014; Pahor et al., 2006), although in the last decade, pharmacological interventions with ACEi have been associated with clinical benefits on cardiovascular outcomes (Simon et al., 2015) and on physical function (Buford et al., 2012). Neverteless, this issue still remains controversial. In fact, while some studies have found improvements in physical function (George & Verghese, 2016; Hutcheon, Gillespie, Crombie, Struthers, & McMurdo, 2002; Kurklinsky & Levy, 2013; Sumukadas, Witham, Struthers, & McMurdo, 2007), others failed to obtain any gains (Matteo Cesari, Pedone, Antonelli Incalzi, & Pahor, 2010; Spira et al., 2016; Zi, Carmichael, & Lye, 2003), and others even found a negative association between ACEi use and physical performance and muscle strength (Gray et al., 2012). Furthermore, inconsistent results were also reported in the literature with different antihypertensive drugs, which include positive associations

between functional status with the use of βBs (Belenkov et al., 2003; Drescher, Konishi, Ebner, & Springer, 2016; Morley, 2016; Pötsch et al., 2014; Zhubrina et al., 2009), and TDs (Shih, Lin, Wang, & Lin, 2014), and negative associations with the use of CCBs, and TDs (Rosenberg et al., 2008). These results suggests that the efficacy of antihypertensive medication as a therapeutic option for physical function may vary considerably according to selected circumstances (Sica, 2011), drugs and/or specific population characteristics.

More recently, it has been suggested that the benefits in functional status may only occur when pharmacological drugs are combined with exercise training, particularly ACEis (Buford et al., 2012; Christy S. Carter et al., 2012), even though, contradictory evidence from a randomized control trial exist (Sumukadas et al., 2014).

Hypertensive people may also experience adverse effects on HRQoL due to the burden of hypertension itself/hypertension complication, the treatment (pharmacological and/or non-pharmacological) and the so called labeling effect following diagnosis (Tsai et al., 2004) being also associated with headache, dizziness, and tiredness (Mancia et al., 2013). In a recent general population-based study, the patients with known hypertension presented lower scores on four SF-36 sub-scales, including physical function, vitality, mental health and general health compared with scores of general population (Mena-Martin et al., 2003). Additionally, patients with known hypertension reported more bodily pain than those with unknown hypertension, whereas there were no differences between patients with unknown hypertension and the nomotensive subjects (Mena-Martin et al., 2003).

On one hand, exercise training seems to improve HRQoL in hypertensive patients (Cuevas Fernandez, Marco Garcia, Rodriguez Alvarez, Iglesias Giron, & Aguirre-Jaime, 2007; Tsai et al., 2004), particularly in 3 domains of HRQoL (bodily pain, general health, and role function/emotional). On the other hand, long-term pharmacological antihypertensive treatment does not seem to negatively impact HRQoL, although some specific drug classes may do so. Indeed, benefits seem to be similar among hypertensive treated patients with TDs, βBs, CCBs, and ACEis, but βBs seem to increased depressive symptoms (Aronow et al., 2011). Moreover, in one randomized control trial the improvements with pharmacological treatment only occurred in the physical component summary score, but it did not occur in the mental component of the SF-36 questionnaire (Kurklinsky & Levy, 2013). Collectively, the existing data, suggests potential differences

in adverse and beneficial effects among drug classes, needing a more in-depth understanding.

Evidence from several large observational studies that examined the effect of ST, exercise and function showed contraditory results. In the Osteoporotic Fractures in Men Study the ST use, especially the initiation, led to decreased physical activity and increased sedentary behavior (Lee et al., 2014); in The Women's Health Initiative study, no association between ST use and the rate of functional decline was showed (Gray et al., 2012); but in the Three City cohort sub-study, Dumurgier and colleagues found a 25% slower decline in walking speed among older adults taking ST (Dumurgier, Singh-Manoux, Tavernier, Tzourio, & Elbaz, 2014). Moreover, ST use and muscular exercise performance in older adults also present contradictory inconsistent results (Bahls et al., 2017; Henderson et al., 2016; Panayiotou et al., 2013; Parker Beth A, Capizzi Jeffrey A, Grimaldi Adam S, Clarkson Priscilla M, 2013; Riechman, Andrews, Maclean, & Sheather, 2007). While, Parker and colleagues found that 6-months high-dose atorvastatin did not decrease the average muscle strength or exercise performance in healthy subjects and showed that ST raised muscle complains through increased average creatine kinase that produced mild muscle injury even among asymptomatic subjects (Parker Beth A, Capizzi Jeffrey A, Grimaldi Adam S, Clarkson Priscilla M, 2013), Panayiotou and colleagues contrarily, observed that ST use did not increase muscle damage following exercise in older men (Panayiotou et al., 2013).

Bahls and colleagues found that ST use was associated with lower cardiopulmonary exercise capacity (VO^2 peak), even though this effect seemed to be sex specific, once ST medication seem to impaired exercise capacity on males but not on females (Bahls et al., 2017). Additionally, Riechman and colleagues found that older adults using ST had a greater response to resistance training (Riechman et al., 2007), but, contradictory evidence was also shown, in the Effect of Statins on Skeletal Muscle Function and Performance study, once no difference in muscle strength or exercise capacity was found after 6-months of high-dose ST treatment versus placebo (Parker Beth A, Capizzi Jeffrey A, Grimaldi Adam S, Clarkson Priscilla M, 2013).

Although ST have been associated with adverse effects on muscle, data from the LIFE Study showed that ST users and nonusers both benefited from an exercise intervention (Henderson et al., 2016). This paradoxal relationship increase the need to

further assess the evidence of this association, as well as clarifing the mechanisms in which these effects are mediate, once both, ST therapy and exercise are a pre-requisite for the treatment of dyslipidemia (Catapano et al., 2016). Furthermore, these results highlight, not only the need of long-term research to analyze the effects of ST treatment on muscular and exercise performance, (Parker Beth A, Capizzi Jeffrey A, Grimaldi Adam S, Clarkson Priscilla M, 2013) but also the sex specific effects.

One important issue regarding treatments efficacy is the presence of comorbidity or multimorbidity, since an inverse relationship between increasing multimorbidity, HRQoL and disability is well-documented in literature (Fabbri et al., 2015). The evidence shows that physical health is more affected than mental health by the presence of multiple diseases. In fact, patients with multimorbidity are more likely to be functionally impaired or disabled, with increasing risk of immobility and functional dependency, according to the increasing number of chronic diseases (Marengoni et al., 2011; Marventano et al., 2014). Interestingly, some studies reported that even one newly diagnosed chronic condition is associated with nearly twice the likelihood of functional dependency onset during 12, 24 and 36 months of follow-up (Wolff, Boult, Boyd, & Anderson, 2005). Furthermore, older adults affected by multiple chronic diseases are more likely to receive multiple drugs, to face difficulties with therapeutic compliance and greater vulnerability to adverse events, to suffer more psychological distress and depression, to be admitted more often in a hospital and to face longer hospital stays (Fabbri et al., 2015). However, evidence from a randomized control trial showed that lifestyle interventions with exercise training resulted in fewer hospitalizations, fewer medications and an average annual savings of almost $600 per participant comparatively to a standard care group over the course of 10 years (Espeland et al., 2014). Thus, the management of multimorbid older adults does not necessarily correspond to the optimal treatment of each of their individual chronic disease because undesirable combinations of drugs elevate the risk of adverse drug reactions and the risks grow as the number of medications increases to an individual patient (Fabbri et al., 2015). Whilst, the potential benefit of a medication must be weighted against possible risks arising from its use (Singh & Bajorek, 2015).

In patients with multimorbidity, therapeutic and adverse effects are likely different from those with a single disorder highlithing the need to continue developing, not only our collective understanding of interactions between medications but also with exercise in

comorbid older adults, so the risk-benefit assessment could be effective (Buford, 2016; Singh & Bajorek, 2015) once standard care for individual chronic diseases, frequently leads to increased risk for drug–drug interactions, drug–disease interactions, therapeutic competition, poor adherence to treatment, adverse drug events, hospitalization and mortality, related not only with the number of medications, but also with the regimen complexity, impairing the efficacy of treatment but also the users quality of life (Bell & Saraf, 2016; Charlesworth et al., 2015a; Colagiuri et al., 2014; Singh & Bajorek, 2015). Moreover, more research is needed to gain further insights into the long-term effects of these interventions alone and/or combined and clarify their long-term applicability once it has been suggested that the combination of pharmacological and exercise therapy may be more effective than each treatment alone (Sica, 2011). Furthermore, it has been suggested that a supervised resistance exercise or multicomponent/combined exercise programs should be recommended, particularly for frail or sedentary community-dwelling older people (Cruz-Jentoft et al., 2014). In a retrospective cohort study, exercise training participants had similar total healthcare costs during the first year but, during the second year, adjusted total costs were lower than for non exercise training users, highlighting the important role of the long-term exercise commitment in physical health and in health costs (Ackermann et al., 2008). Additionally, clinical trials assessing controlled exercise programmes on several cardiovascular risk are warranted (Seron et al., 2014), once it has been suggested that a moderate reduction in various risk factors may be more effective than a major reduction in only one of them (Véronique A. Cornelissen & Fagard, 2005; Sharman et al., 2015).

It seems that there is a pervasive lack of evidence to guide clinical decision making in older adults population, particularly in individuals with morbidity, as well as a paucity of data on the impact of diagnostic and therapeutic interventions on key outcomes that are particularly important to older patients, such as HRQoL, physical function, cardiovascular risk factors and therapeutic treatments (Rich et al., 2016) (Fig. 2.4). So, it is our intention to address our efforsts to try to answer these questions that are not yet completely understood.

After looking into the literature, we hypothesize that the combination of both, exercise training (non-pharmacological therapy) and pharmacological treatments (antihyperglycemic, antihypertensive and anti-dislipidemic) would promote more benefits

in all the cardiovascular risk factors, functional status, medication consumption and HRQoL outcomes analyzed than each treatment alone due to the combined pleiotropic effect of exercise with the pharmacological therapies (Sica, 2011).

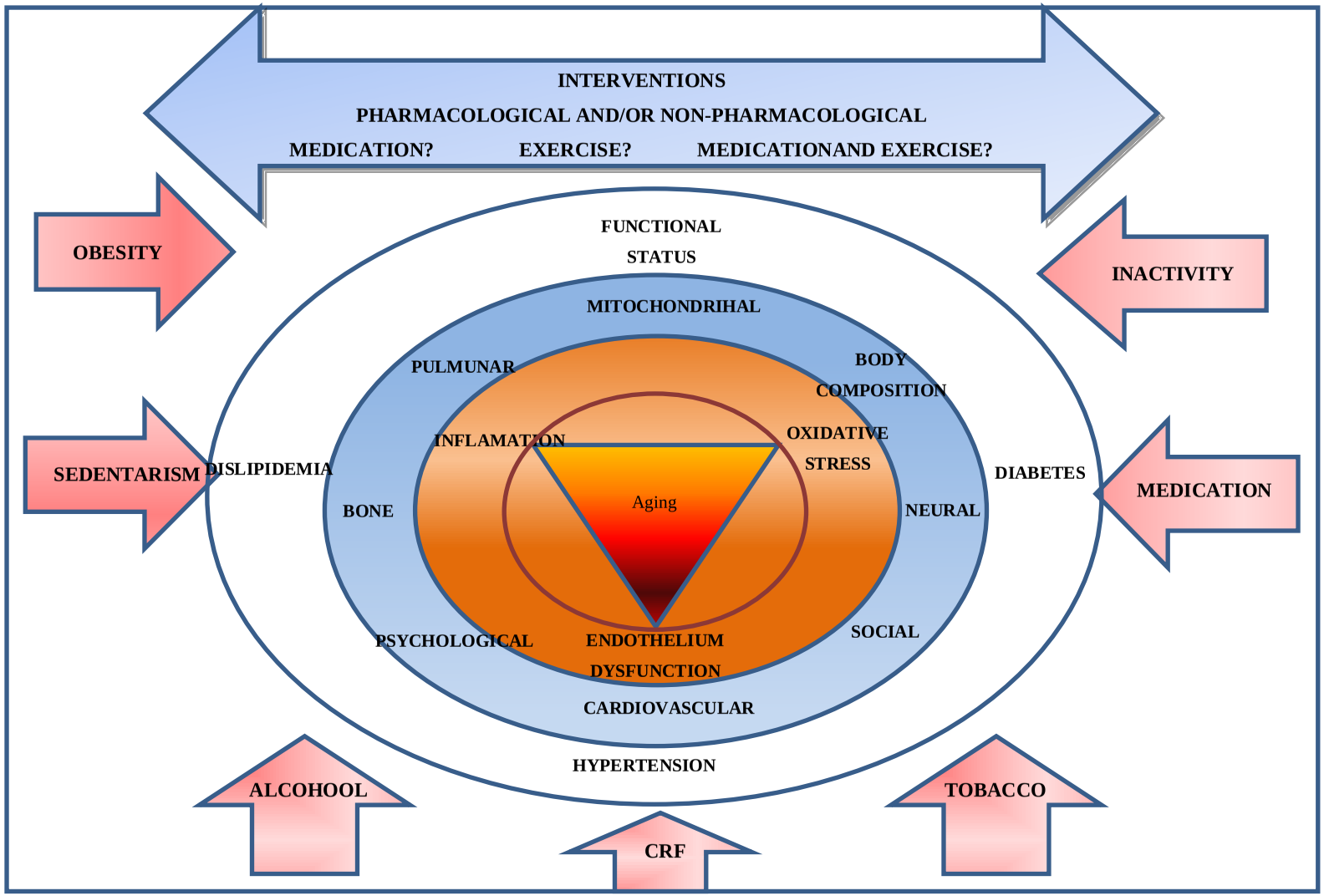

Figure 2.4- The conceptual model illustrates important factors that can affect aging process and ultimately maintenance of HRQoL and independence in older adults. This figure is not intended to be exhaustive but rather to highlight key biological mechanisms, cardiovascular risk factors, and disease conditions that can contribute to decrease aging in older adults, as well as promising interventions to attenuate age- related declines. CRF- cardiorespiratory fitness.

3. GENERAL METHODS

After theoretical framework and revision of the different concepts within the scope of the constructs related to the characterization of medication, exercise and health related quality of life in the elderly, the presentation of the general methodological processes begins. It is the intention of this chapter to state the experimental design adopted, involving the selected variables, the characteristics of the sample and the procedures related to the administration of the tests, namely in what concerns the instruments and equipments, protocols used, the evaluators team and procedures prior to testing. We also intend to specifically define the preparation of the participants, the chronological evaluations and data collection. This chapter ends with a description of the general procedures regarding the statistical analysis and how the quality of the data was controlled. Moreover, a detailed description concerning variables assessment, samples characteristics and methodological procedures are given in each paper of the following pages.

3.1. Study design and sampling

This thesis and all the studies included in it were funded by a Portuguese grant supported by the Portuguese Foundation for Science and Technology (SFRH/BD/90221/2012). The methods and procedures were approved by national ethic committees (Data Protection Authority-CNPD; Health Administration from North Ethics Committee-ARS/Norte), Institutional Scientific Board of the University of Coimbra and local institution (Santa Maria da Feira City Hall) and were conducted in accordance to the ethical procedures of the Declaration of Helsinki by the World Medical Association (World Health Organisation, 2013) for experimental human studies as described in the following pages.

The baseline interviews, clinical examination and the follow up testing occurred between September 2013 and September 2015 and were performed by the same order at the baseline and at the end of the follow-up.

The 8 studies had a non-randomized longitudinal study design and were addressed to analyze the effects of long-term multicomponent exercise on several variables. This project involved a total sample of 1473 inactive community-dwelling adults aged 60 and over, of the local community of Santa Maria da Feira, Aveiro, Portugal (Table 3.1). At baseline, it was given the opportunity to all participants engage in the local community multicomponent exercise program named "Movimento e bem-estar", however, 252 participants' preferred to maintain only the standard care (control group). All the others accepted to participate in the exercise program (experimental group).

Table 3.1. Summary of the total sample characteristics (*N*=1473)

Variables	**Total** (*N*=1473)	**MEX** (*n*= 1221)	**CO** (*n*= 252)
Sex, Female (%)	75	79	67 **
Age, (years)	66.5 (7.9)	67.1 (7.9)	63.8 (3.3)**
Comorbidities, (n)	2.2 (1.6)	2.1 (1.6)	2.3 (1.5)
Medication, (n)	2.0 (1.6)	2.2 (1.6)	1.8 (1.6)**
Medication annual cost, (€)	286.0 (285,5)	287.5 (288.8)	277.2 (264.2)
Waist circumference, (cm)	90.8 (10.0)	91.0 (9.8)	90.2 (10.9)
Body mass index, (kg/m^2)	28.6 (4.2)	28.7 (4.3)	28.3 (4.0)
CRF- 6-min walk test, (m)	449.7 (110.7)	450.2 (119.9)	447.7 (65.9)

Data are expressed as mean (SD). MEX- Multicomponent exercise group- Experimental Group. CO- Control group- standard care. CRF- Cardiorespiratory fitness. ** Differences between groups (p <0.001)

In The Table 3.2 summarizes the basic characteristics of the samples of each study, regarding participants pathology, sample size within each group and variables studied.

The inclusion criteria for the definition of the participants' pathologies were: *i)* Diabetes according to the criteria of the *International Diabetes Federation* (Aschner et al., 2014): self-report of clinical history of the pathology confirmed by the primary care physician and/or pharmacological treatment; or HbA1c ≥ 6,5%/ 48 mmol/mol; or FPG ≥ 126 mg/dl (7.0 mmol/l); 75 g OGTT with fasting plasma glucose ≥126 mg/dl (7.0 mmol/l) and/or 2 hour plasma glucose ≥ 200 mg/dl (11.1 mmol/l); *ii)* Hypertension was defined according with *European Society of Hypertension* and of the *European Society of Cardiology* (Mancia et al., 2013): self-reported diagnosis of the pathology confirmed by the health professional and/or pharmacological treatment; or blood pressure values above 140 mmHg for SBP and/or 90 mmHg for DBP; *iii*) Dyslipidemia was defined according to the *European Society of Cardiology* and *European Atherosclerosis Society* (Catapano et al., 2016): previous clinical diagnosis confirmed by the health professional and/or

pharmacological treatment; and/or LDL cholesterol ≥ 115 mg/dl (3.0 mmol/l); or HDL cholesterol values ≤ 40 mg/dl in men and 45 mg/dl in women; and/or triglycerides ≥ 150 mg/dl (1.7 mmol/l).

Table 3.2. Summary of the basic sample characteristics of each study

Study	Pathology	Sample Size	Sample Group Characteristics/ Size	Variables
I	T2D	279	Multicomponent exercise training group- 241 Control group- 38	HRQoL; Hemodynamic profile; Anthropometry; CRF.
II	T2D	284	Multicomponent exercise training group- 59 Metformin therapy group- 30 Multicomponent exercise training and metformin group- 195	Hemodynamic profile; Anthropometry; CRF.
III	T2D	284	Multicomponent exercise training group- 59 Metformin therapy group- 30 Multicomponent exercise training and metformin group- 195	HRQoL; Mood States; Anthropometry; Blood biochemistry.
IV	Hypertension	418	Multicomponent exercise training group- 116 Angiotensin converting enzyme inhibitors therapy group- 70 Multicomponent exercise training and angiotensin converting enzyme inhibitors therapy group- 232	Hemodynamic profile; Anthropometry; Physical HRQoL; Functional Status
V	Hypertension	96	Thyazide- related diuretics and multicomponent exercise training group- 33 Calcium channel blockers and multicomponent exercise training group- 23 Beta- blockers and multicomponent exercise training group- 40	Hemodynamic profile; Anthropometry; Physical HRQoL; Functional Status
VI	Hypertension	440	Mono- dose angiotensin converting enzyme inhibitors and multicomponent exercise training group- 232 Combined therapy and multicomponent exercise training group- 208	Hemodynamic profile; Anthropometry; Physical HRQoL; Functional Status
VII	Dyslipidemia	981	Multicomponent exercise training- 298 Statins- 178 Multicomponent exercise training and Statins- 505	Hemodynamic profile; Anthropometry; Physical HRQoL; Functional Status
VIII	Total Sample	1473	Multicomponent exercise training- 1221 Control group- standard care- 252	Hemodynamic profile; Anthropometry; HRQoL; CRF; Medication number and cost

HRQoL- Health related quality of life; CRF- Cardiorespiratory fitness; T2D- Type 2 diabetes

Exclusion criteria included: (a) unstable angina; (b) uncontrolled symptomatic heart failure; (c) uncontrolled cardiac dysrhythmias; (d) symptomatic aortic stenosis; (e) participants who were not under regular supervision of the treating physician during the period of the study evaluation; (f) known cancer or limited life expectancy, acute emergencies; (g) Parkinson's disease; (h) Alzheimer's disease; (i) dementia or mild/severe cognitive impairment; (j) severe visual impairment; (k) further reasons that made it impossible or highly problematic to participate and come to the follow-up visits, completing baseline and follow-up testing (programme log ≥ 80 %)

3.2. Variables and instruments

The evaluation protocol for this thesis included 5 dimensions: the first set of information was of anthropometric nature, the second set was related to physical fitness, the third set of information on the hemodynamic profile and medication consumption, the fourth dimension was on the HRQoL domains and lastly, mood states.

3.2.1- Anthropometry

A set of simple and composed anthropometric variables were selected to characterize the participants' morphology. The simple anthropometric variables included BM, height, waist and hip circumferences. Based on these simple anthropometric variables, it was possible to obtain compose measures regarding the degree of adiposity and the pattern of distribution of subcutaneous fat (American College of Sports Medicine, 2014), with the use of BMI and WHR.

The anthropometric data collection was performed by trained nurses and followed the standard procedures of the American College of Sports Medicine Manual (American College of Sports Medicine, 2014) in a reserved space. Anthropometric data was registered in a specific sheet created for this purpose (Appendix 1). For each simple anthropometric variable, two measurements were performed and the mean value of both registered.

Stature was measured using a standard stadiometer to 0.1 cm in the upright position, with the participant´s back square against the wall and eyes looking straight ahead, at the maximum air volume inspiration. BM was measured by a calibrated digital balance-beam scale (SECA 770, Germany) with a precision nearest 100 grams, with participants in light clothing and barefooted. WC was measured at the midpoint between the lowest rib and the top of the iliac crest at minimal respiration and hip circumference was taken in a horizontal plan along pubic symphysis using a Hoechstmass-Rollfix® fiberglass measuring tape, with the metric scale accuracy of 0.1 centimeters. BMI and WHR were calculated according to standard methods (American College of Sports Medicine, 2014).

3.2.2- Physical fitness

Physical fitness was assessed with a performance based measure (Peron et al., 2011), the *Senior Fitness Test battery* (R.E. Rikli & Jones, 1999) designed to determine the physiological parameters that support physical mobility and functionality in the elderly. The theoretical basis of this battery is well described, the application process is detailed and simple to perform and the variety and assurance are sufficiently documented (Roberta E. Rikli & Jones, 2013). Additionally, the strong psychometric properties (validity and test-retest reliability between 0.80 and 0.98), (Roberta E. Rikli & Jones, 2013) ease and the safe use of a wide range of physical abilities, the continuous scale that allows a gradual assessment of changes over time (improvement or decline) (Roberta E. Rikli & Jones, 2013) seemed well suited to the primary end-point of this research. This battery test includes a set of 6 tests, allowing the evaluation of strength, flexibility, aerobic endurance, speed, agility and dynamic balance, as described in table 3.3

Physical fitness data collection was performed by experienced exercise professionals according to the standard procedures (R.E. Rikli & Jones, 1999) and the data was registered in a specific sheet (Appendix 1). For the data collection it was used a hand weight with 2.2 kg for women and 3.6 kg for men, chairs, digital chronometers with resolution of 0.001s (onstart, 710, Geonaute) and fiberglass measuring tape (Hoechstmass-Rollfix®), with the metric scale accuracy of 0.1 centimeters..

Table 3.3. Functional physical fitness parameters, tests and description. Adapted from (Jones, J., Rikli, 2002)

Parameters	Test	Description
Upper body strength	30s Arm-Curl	Number of biceps curl in 30 s.
Lower body strength	30s Chair-Stand	Number of full stands in 30 s with arms folded across chest.
Upper body flexibility	Back Scratch	Distance between the middle fingers, with one hand reaching over the shoulder and one up in the middle of the back.
Lower body flexibility	Chair sit-and-reach	Distance between extended fingers and tip of toe, with one leg extended.
Agility/dynamic balance	8 foot-up-and-go	Number of seconds required to get up from the seated position, walk 2,44 m, turn, and return to the seated position.
Aerobic endurance	6 min-walk	Number of walked meters in 6 minutes in a course of 50 m.

3.2.3- Hemodynamic profile and medication consumption

Hemodynamic data provided information on a set of parameters grouped by: blood pressure, lipid and glycemic profile. Medication consumption was analyzed according to the type and class of medication, annual drug expenditure, as well as the dose- drugs consumed in accordance with *"Prontuário Terapêutico"*, manual developed by the INFARMED (Caramona et al., 2012).

Medication type, class and dosage were assessed by detailed questionnaire (Appendix 1) with visual confirmation of prescription drugs recorded by the study staff and all the data was registered in the health history questionnaire (Appendix 1).

Resting blood pressure was measured three times, by trained nurses, using a sphygmomanometer (Aneroid Sphygmomanometer-HICO HM 1001, Germany) and stethoscope (Nurse Type Professional Stethoscope-HICO HM-3005, Germany) in the seated position, after 5 minutes rest; the measurements were performed with 2 minute intervals (American College of Sports Medicine, 2014). The mean of the measurements was used for systolic and diastolic blood pressure. Trained nurses also collected venous blood in the morning after 12 hours fasting. Glycaemia, triglycerides, LDL- cholesterol, HDL- cholesterol and TC were determined by standard methods (American College of Sports Medicine, 2014) by an accredited laboratory.

3.2.4- Health related quality of life

Self-reported perception of the HRQoL was assessed by the study staff (experienced exercise specialists) using the *Medical Outcomes Study 36-item Short-form Health Study questionnaire* (SF-36), adapted and validated for the Portuguese population (Ferreira, 1998). This instrument, with high internal consistency and reliability (between 0.80 and 0.86) (Ferreira, 1998), was developed to measure generic health status and HRQoL (Anderson, Laubscher, & Burns, 1996), through the evaluation of eight health-related subscales: Physical Functioning (PF), Role-Physical limitations (RP), Bodily Pain, General Health (GH), Vitality (V), Social Functioning (SF), Role-Emotional limitations (RE) and Mental Health (MH). Two summary scores also derived from SF-36 and grouped as Physical Component Score (PCS) and Mental Component Score (MCS). A Total SF-36 Score was calculated aswell. The standardized summary scores for physical and mental components were calculated using the methods set out by Ware and colleagues (Ware. Jr, 2000) and separately used as outcome measures. The scores range from 0 to 100, with higher scores indicating better functional health and well-being.

3.2.5- Mood States

Mood states profile was assessed by the study staff (experienced exercise specialists) using the *Profile of Mood States Short-form questionnaire* (POMS-SF), validated and adapted to the Portuguese population with a substantial internal consistency and reliability (between 0.81 and 0.92) (Cruz & Mota, 1997). The POMS-SF is a 22-item version of the standard 65-item form (McNair, Lorr, & Droppleman, 1971) being expressed into a Likert scale (0-4). This self-report questionnaire describes the feelings/mood states that participants have felt in the past week. Scores fit into 6 categories: tension-anxiety, depression, anger-hostility, vigor, fatigue and confusion. The global score, Total Mood Disturbance (TMD) is computed by subtracting the positive category (vigor) from the sum of the five negative dimensions (tension, depression, fatigue, anger and confusion) adding a constant (+100) in order to eliminate negative scores (Cruz & Mota, 1997), with higher values indicating worst mood profile.

3.3. Procedures prior to test administration

The procedures of the tests evaluation required a meticulous planning, given the large number of variables to be determined and the sample size, to monetize the various resources, namely the temporal, human and the economic resources, but also to assure the accuracy, objectivity and feasibility of the outcome results (American College of Sports Medicine, 2014). Given this rationale, a set of procedures was developed prior to test evaluation, regarding the authorizations from several national institutions for the implementation of the research, prior preparation of the participants and evaluators and lastly, the scheduling and sequencing of data collection as described in the following pages.

3.3.1- Institutions authorizations

The first procedure was the approval of national institutions/organisms to the study development, respecting international and national ethical principles, namely the national ethics committees (Data Protection Authority-CNPD; Health Administration from North Ethics Committee-ARS/Norte), Institutional Scientific Board of the University of Coimbra and the local institution (Santa Maria da Feira City Hall), (Appendix 2).

3.3.2- Participants preparation

Participants´preparation included the methods of inclusion, procedures prior to testing and safety procedures. Participants were either referred to the study by their primary care physician or self-referred from flyers distributed at community centers, media advertisements or word of mouth.

After the recruitment period, participants were invited to a preliminary meeting in which they were informed about the nature, benefits and risks of the study (Appendix 2). At this meeting, potential adverse effects were explained and participants were encouraged to notify study staff immediately if they experienced any abnormal symptom with medication, personnel disease or exercise training. Posteriorly, study staff was instructed to

notify the coordinator to contact physicians that ultimately, decided the appropriate course of action. Due to this safety procedure, it was also requested that participants maintained regular supervision with their primary care physician, who had full discretion to manage pathology regimen, doing all the necessary dose or drug changes prescription in order to maintain a medically supervised symptom-limited.

Each participant received a brief written description of the tests and questionnaires to be performed, a schedule of measurements and documents to be delivered, as well as written recommendations about proper clothing (light sport cloth), avoidance of vigorous physical activities prior to testing, etc (Appendix 2) . Moreover, participants also received a notification to maintain the nutritional and physical activity pattern prior to investigation.

All participants that agreed to participate in this project, gave their written informed consent, consistent with Helsinki Declaration (World Health Organisation, 2013) (Appendix 2).

3.3.3- Evaluators preparation

The technicians team was composed by: *i*) experienced nurses who were responsible not only for collecting the hemodynamic and anthropometric data but also for the visual confirmation of medication consumption; and *ii*) by experienced exercise specialists who were responsible for the physical fitness tests data collection and for completing the health, mood states and HRQoL questionnaires, only when needed, in case of illiterate participants. To assure the accuracy, objectivity and feasibility of the data collection all the evaluators received one theoretical and one practical session prior to testing, regarding the various measurement procedures. For all the measurements considered to be affected by tester technique, the same investigator took the measurements at baseline and at the end of the study and were periodically supervised by the Research Coordinator to minimize any systematic error associated with variation in measurement techniques (American College of Sports Medicine, 2014).

The Research Coordinator was responsible for the contacts, scheduling of activities, requisition of materials, lecturing the theoretical and practical training sessions, but also, data acquisition.

3.3.4- Schedule and sequence of data collection

Baseline interviews and clinical examination occurred between September 2013 with follow-up until September 2015. All evaluation procedures were performed in the same order at baseline and at the end of the follow-up, after 24 months. The scheduling and sequence of data collection was in accordance with the following criteria:

- Day 1- Health, mood states and HRQoL questionnaires (experienced exercise specialists).

- Day 2- Hemodynamic and anthropometric profile (trained nurses); physical fitness- *Senior Fitness Tests batterry* (experienced exercise specialists). This test battery was performed in the form of a circuit organized to minimize the effects of localized fatigue. An initial warm-up was conducted by an experienced exercise specialist, and then, participants were divided into groups and sent to one of the stations (upper strength, lower strength, superior flexibility, lower flexibility and speed, agility and dynamic balance). The evaluation of the cardiovascular endurance was performed at the end of all parameters. To minimize intraday variability, temperature effects and biological rhythms, this battery test was performed between 8am and 10am.

3.4. Statistical Analyses

Data analysis was performed using Statistical Package for the Social Sciences for Windows (IBM-SPSS, Inc. Chicago, IL, USA), software version 24. Statistical tests were 2-tailed and significance was set at 5%.

Different statistical procedures were performed according to the aims of each study (Table 3.4). In brief, the statistical treatment was preceded by an exploratory data analysis, with the objective of ascertaining the normality of the distribution in each variable measured, as well as the presence of outliers through the "box plot" diagram. Abnormal values were deleted from the analysis. Afterwards, descriptive statistic data was performed using measures of frequency, central tendency and dispersion (mean and standard deviation). Inductive statistics allowed us to draw conclusions, based on the elements

observed (through confidence intervals and parametric and non-parametric statistical tests). Longitudinal differences between groups were performed using the independent Students T-Test, univariate analysis of variance (ANOVA), univariate analysis of covariance (ANCOVA), controlling for important covariates, and a two- way ANOVA for repeated measures followed by *post-hoc* tests. In some studies, responsiveness to change was also used to measure differences between groups after the intervention, by the estimation of the minimum important difference (MID), standard error of measurement (SEM), reliability and the magnitude of the results by the Hedges´s *g* (Hedges & Olkin, 1985) effect size.

Finally, the strength of variables association was performed using Pearson's bivariate correlation, also linear regression model and multinominal logistic regression models, according to the type of variable used between HRQoL, medication, mood states, anthropometry, hemodynamic and functional status variables.

Table 3.4. Summary of the statistical procedures in each study

Analyses	Study							
	I	II	III	IV	V	VI	VII	VIII
Kolmogorov- Smirnov Test	■	■	■	■		■	■	■
Shapiro-Wilks Test					■			
Skewedness Coefficient					■			
Levene´s Test	■	■	■	■	■	■	■	■
Floor and Ceiling Analysis	■		■					
Independent Student T-Test	■					■		
One- Way ANOVA		■	■	■	■		■	■
Two- Way ANOVA repeated measures	■	■		■	■	■	■	■
ANCOVA	■	■	■	■	■	■	■	■
Hedges g	■	■	■	■	■	■	■	■
SEM	■		■					
MID	■		■					
Pearson´s bivariate correlation			■					
Linear Regression Model								■
Multinominal Logistic Regression								■

ANOVA- Analysis of variance; ANCOVA- Analysis of covariance; SEM- Standard error measurement; MID- Minimum importance difference.

4. RESULTS

4.1. Study I- Effects of Long-Term Multicomponent Exercise on Health-Related Quality of Life in Older Adults with Type 2 Diabetes: Evidence From a Cohort Study

Effects of Long-Term Multicomponent Exercise on Health-Related Quality of Life in Older Adults with Type 2 Diabetes: Evidence From a Cohort Study

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4.1.1. Abstract

Objetive – To establish the effect of a long-term multicomponent exercise (LTMEX) intervention (24 months) on health-related quality of life (HRQoL) in older adults with type 2 diabetes (T2D).

Methods – This longitudinal retrospective cohort study analyze the effects of a supervised LTMEX program on HRQoL in older adults with T2D (n = 279). Participants underwent one of 2 conditions: LTMEX (n = 241) trained three times per week; and unchanged lifestyle – the control group (CO; n = 38). Participants completed baseline, and 2-year follow-up evaluations including the Short Form Health Survey 36 (SF-36), anthropometric, hemodynamic components and cardiorespiratory fitness (VO2peak).

Results – LTMEX improves HRQoL, specifically physical functioning ($P < 0.001$), role-physical ($P < 0.05$), general health ($P < 0.05$), vitality ($P < 0.001$), physical component score ($P < 0.001$), mental component score ($P < 0.001$) and Total SF-36 ($P < 0.001$). LTMEX group also decreased body weight (BW; $P < 0.005$), waist circumference (WC; $P < 0.001$), waist-to-hip ratio (WHR; $P < 0.001$), and systolic blood pressure (SBP; $P < 0.001$), and increased VO2peak ($P < 0.001$). CO group increased WC ($P = 0.012$), BMI ($P = 0.024$), waist-to-hip ratio (WHR; $P = 0.003$) and SBP ($P < 0.001$), and decreased vitality ($P < 0.001$) and mental health ($P < 0.05$).

Conclusions – A LTMEX intervention improves physical and mental HRQoL in older adults with T2D, and also anthropometric, hemodynamic profile and cardiorespiratory fitness.

Keywords: diabetes, quality of life, exercise, older adults

4.1.2. Introduction

Quality of life (QoL) is a central concept in the management of diabetes (American Diabetes Association, 2016; Aschner et al., 2014; S. R. Colberg et al., 2010) The health-related quality of life (HRQoL), referring to the physical, psychological, and social domains of health that are influenced by a person's experiences, beliefs, expectations, and perceptions (Al Hayek et al., 2014), has been increasingly used as an outcome measure to monitor the burden of diabetes of population (Kirkman et al., 2012; Papadopoulos et al., 2007). Health care providers should strive to understand the physical, emotional, and social impacts of chronic diseases including diabetes (American Diabetes Association, 2016). Furthermore, the guidelines for treatment of diabetes have emphasized that one of the primary objectives should be the improvement in the HRQoL (American Diabetes Association, 2016). This implies that HRQoL assessment has the proven potential to identify ways in which treatments can be used to reduce the deleterious effects of diabetes (Speight, Reaney, & Barnard, 2009).

Previous studies, identified several determinants of diminished HRQoL in adults with type 2 diabetes (T2D), including age (Javanbakht et al., 2012)(Maddigan et al., 2006), being women (Al Hayek et al., 2014; Papadopoulos et al., 2007), lower education, not being married, longer diabetes duration, treatment type-insulin use, comorbidities or disease complications, obesity, and lower exercise training (ET) (Al Hayek et al., 2014; V. Myers & McVay, 2013; Wee et al., 2005). However, knowledge on HRQoL in older adults with T2D is scarce.

ET has positive impact on glycaemia control, lipemia, blood pressure, cardiovascular events, and mortality (American Diabetes Association, 2016; S. R. Colberg et al., 2010; Kirkman et al., 2012). Also, literature from cross-sectional and observational studies is quite consistent that more active adults have greater global QoL (Kirkman et al., 2012), however evidence from experimental studies is both limited and inconsistent (Imayama, Alfano, et al., 2011)(Bize, Johnson, & Plotnikoff, 2007). While regular ET may prevent or delay diabetes and its complications, most people with T2D are not engaged in regular exercising programs (S. R. Colberg et al., 2010), especially in older adults (Maddigan et al., 2006). A study comprising older adults reported a positive dose-response relationship between PA and HRQoL (Dondzila et al., 2015). Nevertheless, a meta-

analysis examining exercise intervention effects on HRQoL, as measured by the Short-Form (SF)-36, in community-dwelling older adults(Kelley et al., 2009) found significant effect only on physical functioning but little effect on other subscales of HRQoL. The authors observed that the length of interventions could be critical, because the majority lasted 3 months or less, while the longest intervention was only 6 months.

Other ET interventions showed beneficial effects on HRQoL in diabetic populations (Lambers, Van Laethem, Van Acker, & Calders, 2008; Lincoln, Shepherd, Johnson, & Castaneda-Sceppa, 2011) but many of these studies used small sample sizes, short follow-up periods, self-directed exercise interventions, rather than well-verified, supervised exercise interventions. Additionally, largest trials (V. Myers & McVay, 2013; Nicolucci et al., 2012; Reid et al., 2010; Wadden, 2014) have shown inconsistent results, conflicting on whether exercise training interventions improve mental HRQoL in individuals with T2D, probably due to the different methods to assess HRQoL, the wide age-range samples mixing adults of all ages, and varying in demographic, social, mental and physical characteristics.

Although well-designed randomized controlled exercise trials may help understand the exercise–HRQoL relationship in older adults (Kelley et al., 2009), it may be more appropriate to assess HRQoL as part of a longitudinal large-scale evaluation [8].

As it was observed by Dale and colleagues (Dale et al., 2013), in 4286 older women without obesity or pre-existing health conditions, over a 7-years period, those who undertake more PA were more likely to experience high HRQoL through time, reinforcing the importance of time-length in subjective HRQoL. However, in diabetic participants there is a lack on long-term evaluations, especially with older adults. Despite this, enhancement of HRQoL is considered a critical component of clinical management and public health services for older adults with T2D (American Diabetes Association, 2016).

Individuals with diabetes should be referred to an effective ongoing support lifestyle change program, targeting reduction of 5% of body weight (BW) and increase of PA to at least 150 min/week (American Diabetes Association, 2016; Marwick et al., 2009; O'Hagan et al., 2013; Wadden, 2014). However, studies are still inconsistent on the effect of exercise on HRQoL in older adults with T2D in long terms (> 12 month), or are not exclusively with older adults (Cruz-Jentoft et al., 2013). A very low percentage of 440 trials (1.4%) investigating treatment for T2D were specifically designed for older adults

(Cruz-Jentoft et al., 2013). Therefore, given the discrepancies found in the literature, and the lack of studies assessing exercise-HRQoL relationship in older adults with T2D, the aim of this study is to analyze the effect of a long-term exercise intervention (24 months) on HRQoL in older adults with T2D.

4.1.3. Methods

4.1.3.1. Participants

This retrospective cohort study is part of a larger investigation involving 1473 community-dwelling adults aged 60 and over, to study the effects of long-term multicomponent exercise (LTMEX) on several variables. Participants were either referred to the study by their physician or self-referred from flyers distributed at community centers, media advertisements or word of mouth.

4.1.3.2. Interventions and procedures

This study focuses specifically on the effects of LTMEX on subjective HRQoL in older adults with T2D. After the initial evaluation a sub-group of 279 physically independent participants (completed the Senior Fitness Test battery (R.E. Rikli & Jones, 1999) developed to measure physical capacity of older adults to perform normal activities) was identified fulfilling the criteria for diabetes defined by the International Diabetes Federation (IDF) (Aschner et al., 2014). Exclusion criteria included (a) uncontrolled hypertension; (b) severe autonomic neuropathy; (c) severe peripheral neuropathy or history of foot lesions; (d) unstable proliferative retinopathy, which could affect the ability to perform the LTMEX; (e) participants who were not under regular supervision of the treating physician for the period of the evaluation of the study; (f) with type-1 diabetes; (g) known cancer or limited life expectancy, acute emergencies; (h) Parkinson's disease; (i) Alzheimer's disease; (j) dementia; (k) severe visual impairment; and (l) participants with further reasons that made it impossible or highly problematic for the patient to participate and come to the follow-up visits completing baseline and follow-up testing (program log ≥

80 %). The final sub-group of 279 old adults with T2D that fulfilled all the criteria exposed was retained as participants and underwent one of 2 conditions: LTMEX group (n = 241); CO group (n = 38). The criteria for inclusion in the LTMEX group was regular exercise practice in a local program (3 sessions/week of 60 minutes/session), while the participants in CO had not engaged regularly in any formal exercise program during the follow-up.

After the recruitment period, the participants were invited to a preliminary meeting in which they were informed about the nature, benefits and risks of the study. In this meeting, participants completed the health history questionnaire and the Medical Outcomes Study 36-item Short-form Health Study questionnaire (SF-36). A second meeting was then scheduled for the assessment of anthropometric, hemodynamic components and aerobic fitness, in this order. Blood pressure, BW, waist and hip circumferences, and stature were assessed by trained nurses who were periodically supervised to minimize any systematic error associated with variation in measurement techniques, and to ensure the precision and accuracy of the evaluations (American College of Sports Medicine, 2014). Anthropometrics determinations were carried out in separate rooms, to ensure the participants' privacy. Self-reported questionnaires were used to collect data on demographic and lifestyle factors, medical outcomes, and HRQoL variables, which were completed by trained interviewers only when needed, in case of illiterate participant.

Baseline interviews and clinical examination occurred in September 2013 with follow-up LTMEX until September 2015. All evaluation procedures were performed in the same order at baseline and at the end of the follow-up, after 24 months. For all the measurements that were considered to be affected by tester technique, the same investigator took the measurements at baseline and at the end point.

Participants of the LTMEX group met three times a week for one hour over the 24-months intervention period to perform the exercise in local centers of Santa Maria da Feira. No ET intervention was conducted for the CO group. All participants received the same notification to maintain the same nutritional pattern prior to investigation.

All participants agreed to participate in this study and gave their written informed consent, consistent with Helsinki Declaration. All methods and procedures were approved by Institutional Scientific Board of the University of Coimbra, local institution (Santa Maria da Feira County) and national ethics committees Data Protection Authority-CNPD; Health Administration from North Ethics Committee-ARS/Norte).

4.1.3.3. Multicomponent exercise program

The exercise program consisted in three 60-min sessions/week supervised by professional trainers, on three non-consecutive days. Aerobic, resistance, balance and flexibility were trained accordingly to these items: 5 to 10 minutes of warm-up, 20 to 30 minutes of aerobic, 15 to 20 minutes of resistance training, 10 minutes of balance, 10 minutes of stretching, and 5 to 10 minutes of cool down exercises. Aerobic exercise started with participants in a standing position (e.g., walking in place with arm movements), and involved continuous movement of major muscles of the upper limb, performed alternately with movement of the lower limb. Time and intensity of aerobic exercise was increased from 20 minutes per session at 50%HRmax (maximum heart rate) to 30 minutes at 70%HRmax per session (American College of Sports Medicine, 2014).

Resistance training was conducted every Monday and Friday; on these 2 days, the aerobic session was shortened to approximately 20 minutes. Resistance training came from participants' own BW or with light free weights. Five to eight exercises involving the large muscle groups were performed, with one to three sets of 8 to 15 repetitions for each upper and lower body muscle group. Intensity was set at 50% to 70% 1-RM, with 90 to 120 seconds of rest between sets. Balance training was also based on functional tasks required by older adults such as alternate leg lifting, walking sideways, and throwing and catching ball. Prior to cool down, participants performed stretching exercises designed to improve flexibility of the major muscle groups; each stretch was sustained between 15 and 30 seconds to the point of tightness, and repeated three times.

Over the 24-months intervention, progression increased every 6 weeks through augments on duration, repetitions, resistance, and/or difficulty (e.g., transition from sitting to standing to complete exercises). Exercise modifications such as reduced duration, number of repetitions, or use of an exercise auxiliary were recommended as needed by the group instructor.

4.1.3.4. Outcome Measures

Subjective health-related quality of life

Self-perception of HRQoL was assessed using the SF-36 questionnaire, adapted and validated for the Portuguese population (Ferreira, 1998). This instrument with high internal consistency and reliability (Ferreira, 1998) was developed to measure generic health status and HRQoL, through the evaluation of eight health-related subscales: Physical Functioning (PF), Role-Physical limitations (RP), Bodily Pain (BP), General Health (GH), Vitality (V), Social Functioning (SF), Role-Emotional limitations (RE) and Mental Health (MH). Two summary norm-based can also derived from SF-36 and grouped as Physical Component Score (PCS) and Mental Component Score (MCS). A Total SF-36 Score was also calculated. The standardized summary scores for physical and mental components were calculated using the methods set out by Ware and colleagues (Ware. Jr, 2000) and separately used as outcome measures. The scores range from 0 to 100, with higher values indicating better functional health and well-being.

Anthropometrics

Stature was measured to 0.1 cm in the upright position, with the participant´s back square against the wall and eyes looking straight ahead, without shoes, and using a standard stadiometer. BW was measured barefoot and in light clothing by a calibrated digital balance-beam scale (SECA 770, Germany) with a precision nearest to 100 grams. Body mass index (BMI) was calculated dividing BW in kilograms by stature in meters squared. Circumferences were also measured to 0.1 cm. Waist circumference (WC) was measured at the midpoint between the lowest rib and the top of the iliac crest at minimal respiration, and hip circumference was taken in a horizontal plan along pubic symphysis. Waist-to-hip ratio (WHR) was calculated by dividing waist by hip.

Hemodynamics

Resting blood pressure was taken three times using a sphygmomanometer (Aneroid Sphygmomanometer-HICO HM 1001, Germany) and stethoscope (Nurse Type Professional Stethoscope-HICO HM-3005, Germany), in the seated position, after 5

minutes rest; the measurements were performed with 2 minutes intervals. The mean of the measurements was used for systolic (SBP) and diastolic blood pressure (DBP).

Trained nurses collected venous blood in the morning after 12 hours fasting. Glycaemia, triglycerides (TG), LDL-cholesterol (LDL-C), HDL-cholesterol (HDL-C) and total cholesterol (TC) were determined by standard methods by an accredited laboratory.

Health history

The participants´ health history was obtained by a questionnaire, and data included age, gender, education level, living situation, exercise practice, smoking status and the presence of several conditions like heart disease, hypertension, stroke, diabetes, dyslipidemia, osteoarthritis, pulmonary diseases, liver diseases, thyroid diseases, visual and audio problems, cancer, Parkinson's disease, Alzheimer disease, dementia or other comorbidities. Diabetes medication type and dosage were assessed by detailed questionnaire with visual confirmation of prescription drugs at which study staff recorded.

Cardiorespiratory Fitness

Cardiorespiratory fitness (CRF) was evaluated using the six-minute walk test (6MWT) performed on a flat 50-meter rectangular course, marked off in 5-meter segments (R.E. Rikli & Jones, 1999). To minimize intraday variability, temperature effects, and biological rhythms, the 6MWT was performed between 8 am and 10 am. Participants were told to avoid vigorous exercise in the 2 hours prior to testing, to wear comfortable clothes and appropriate walking shoes, and to continue with their usual medication. Recommended reasons for immediately stopping the 6MWT include the following: chest pain, intolerable dyspnea, leg cramps, staggering, diaphoresis, and pale or ashen appearance.

Safety

Numerous safety procedures were taken to ensure participants safety. Firstly, blood glucose monitoring was made before and after exercise training and was continuously measured and individually recorded by study staff. Notably, communication with participants' physician was the key factor to maintain safety. All participants had regular trimester consultations with their primary care physician that had full discretion to manage diabetes regimen, doing all the necessary dose or drug changes prescription in order to

maintain a medically supervised symptom-limited, to prevent hypoglycemia or other common symptoms associated with exercise like: shakiness, weakness, abnormal sweating, nervousness, anxiety, tingling of the mouth and fingers, hunger, headache, visual disturbances, mental dullness, confusion, amnesia, seizures, or coma. Exercise sessions were planned and adjusted according to the safety limits (American College of Sports Medicine, 2014), with moderate intensity (11-13 points on a rate of perceived exertion scale with 6-20 points) and controlled using Borg's scale (Borg, 1988).

Additionally, potential adverse effects were explained in the preliminary meeting and participants were encouraged to notify study staff immediately if they experienced any abnormal symptom with medication, glycaemia or exercise training.

Posteriorly, study staff was instructed to notify physicians that ultimately decided the appropriate course of action. Nevertheless, no aggravated adverse events were registered during the intervention period, except for soreness.

Statistical analysis

Statistical analysis included participants' demographic and clinical characteristics across the two sub-groups to determine any statistical differences at baseline. Baseline participant's characteristics were described using frequencies, means and standard deviations (SD) for the following variables: age, BW, WC, BMI, 6MWT, WHR, SBP, DBP, TC, HDL-C, LDL-C, TG, glycaemia, HbA1C and HRQoL domains. Additionally, an exploratory analysis of the data quality included the analyses of the reliability, floor and ceiling effects and responsiveness of the participants at baseline. The reliability in the study population was measured by the internal consistency.

To test internal consistency we used alpha Cronbach´s in the total sample (Cronbach´s alpha=0.943) and separately for the two groups: LTMEX (Cronbach´s alpha=0.944) and CO (Cronbach´s alpha=0.935)(Cohen, 1988).

Floor and ceiling effects were measured in the health scales of the SF-36 questionnaire at baseline, by the percentage of the participants who achieved the highest (100) or the lowest (0) scores, in total sample group and in the two sub-group samples.

To test responsiveness at baseline and after 24-months intervention, we calculated Hedges´s g effect size, providing a measure of the effect size weighted according to the

relative different sample size within our study population and the respective 95% confidence intervals (Hedges & Olkin, 1985).

Responsiveness to change was also used to measure differences between groups after the intervention in the HRQoL outcomes, by the estimation of the minimum important difference (MID) using the formula: MID= 1.96 x √2 x standard error of measurement (SEM) (Hedges & Olkin, 1985).

SEM was estimated for each group by the equation: SEM= SD x √(1-r), where r represents the reliability of the current study and was estimated by alpha Cronbach´s for each group (Crosby, Kolotkin, & Williams, 2003). Normality of distribution was verified for all continuous variables by Kolmogorov–Smirnov test.

Comparisons between groups at baseline were performed with T-Test Student. A two-way analyses of variance (ANOVA) for repeated measures was used to test the differences within groups. Analysis of covariance (ANCOVA) was used to measure differences between groups after 24-month intervention, adjusting to baseline score values, age and sex.

All analysis were performed using Statistical Package for the Social Sciences for Windows (IBM-SPSS, Inc. Chicago, IL, USA), software version 19, at the 95% level of significance.

4.1.4. Results

4.1.4.1. Sample characteristics

A total of 1473 older adults underwent the investigation. After applying the exclusion criteria, 279 eligible participants with diagnosed T2D were assigned to this study. Overall, 66% were women, with mean (±SD) HbA1C of 6.7 (1.0) %, the age was 70.6 (6.2) years, the BW was 78.0 (12.4) kg, and the WC was 95.9 (9.5) cm. Participants were then divided into one of two conditions: the LTMEX group (n = 241; 27% men); and CO group (n = 38; 58% men). After the 24-months exercise intervention, the trial was completed by 80% of the participants (n = 222): LTMEX group (n = 186; 31% men); and CO group (n = 36; 61% men) (Figure 4.1.1).

4.1.4.2. Baseline characteristics

Baseline characteristics and differences between groups in anthropometrics, CRF, hemodynamic, glycemic profile and HRQoL are presented in Table 4.1.1. Comparing with CO group, LTMEX group was older and had less BW, WC and WHR ($P < 0.05$). CRF, blood pressure, glycemic and lipid profile were similar in both groups ($P > 0.05$). At baseline, HRQoL was perceived by both LTMEX and CO groups as positive with higher values being observed on PF and SF, and lower values on GH. The two groups showed similar HRQoL ($P > 0.05$), except for RP that was higher in LTMEX group ($P < 0.05$). Completeness of data was 100%, there were no missing responses, but there were high ceiling effects on the SF and RE scales in both groups.

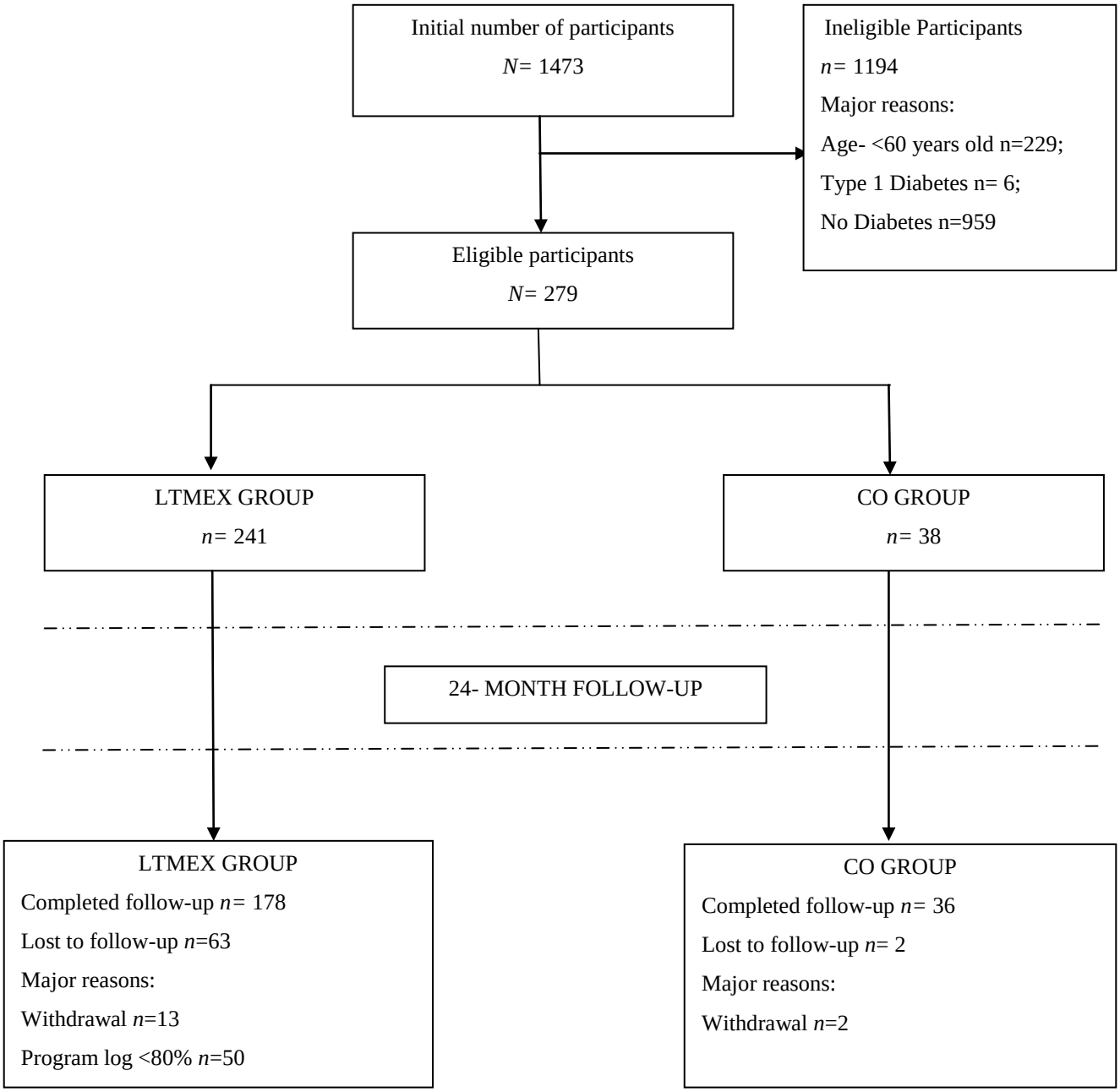

Figure 4.1.1. Cohort flux diagram

Table 4.1.1. – Descriptive baseline characteristics of participants (*N*=279)

Variables	Total (*N* = 279)	Floor-Ceiling Effect (%)	LTMEX Group (*n* = 241)	Floor/Ceiling Effect (%)	CO Group (*n* = 38)	Floor/Ceiling Effect (%)	Group Effect *P* Values	Effect Size	Confidence Interval (95%)
Female, n	193	-	167	-	16	-	0.003*	-	-
Age, years	70.6 (6.2)	-	71.1 (6.2)	-	67.9 (4.4)	-	<0.001**	0.534	0.189: 0.879
Body weight, kg	78.0 (12.4)	-	76.8 (13.5)	-	84.1 (12.7)	-	0.002*	0.545	0.200: 0.890
Waist circumference, cm	95.9 (9.5)	-	94.7 (9.9)	-	98.1 (10.6)	-	0.050*	0.340	0.003: 0.683
BMI, kg/m^2	30.5 (4.5)	-	30.0 (4.7)	-	30.5 (4.6)	-	0.508	0.107	0.236: 0.449
Waist-to-hip ratio	0.92 (0.07)	-	0.91 (0.07)	-	0.95 (0.09)	-	0.011*	0.548	0.003: 0.893
6-min walk distance, m	441 (97)	-	437 (114)	-	429(72)	-	0.579	0.073	-0.269: 0.415
Systolic BP, mmHg	140 (18)	-	141 (18)	-	136 (15)	-	0.107	0.284	-0.059: 0.627
Diastolic BP, mmHg	79 (10)	-	79 (11)	-	76 (9)	-	0.215	0.279	-0.064: 0.622
Total cholesterol, mg/dL	182 (36)	-	183 (36)	-	171 (25)	-	0.075	0.345	0.002: 0.689
HDL-cholesterol, mg/dL	50 (22)	-	49 (18)	-	46 (9)	-	0.235	0.178	-0.167: 0.518
LDL-cholesterol, mg/dL	108 (32)	-	109 (32)	-	99 (25)	-	0.110	0.321	-0.022: 0.664
Triglycerides, mg/dL	130 (62)	-	129 (58)	-	134 (66)	-	0.703	0.085	-0.427: 0.258
Glycaemia, mg/dL	129 (31)	-	128 (32)	-	133 (44)	-	0.576	0.148	0.195:0.490
HbA_{1C}, %	6.7 (1.0)	-	6.6 (1.0)	-	6.8 (1.3)	-	0.466	0.191	-0.151:0.534
Physical Functioning	78 (22)	0.0- 20.0	78 (21)	0.0-14.3	75 (24)	0.0-5.4	0.337	0.140	-0.202: 0.482
Role-Physical	74 (24)	0.0- 20.9	75 (22)	0.0-20.6	65 (27)	0.0-18.4	0.047*	0.440	0.096: 0.784
Bodily Pain	67 (24)	0.0-20.0	67 (23)	0.0-19.0	60 (29)	0.0-13.2	0.180	0.293	-0.050: 0.636
General Health	57 (17)	0.0-1.7	57 (17)	0.0-2.4	53 (17)	0.0-0.0	0.126	0.235	-0.107: 0.578
Vitality	66 (20)	0.0-10.0	67 (20)	0.0-4.0	61 (20)	0.0-2.6	0.094	0.300	-0.043: 0.643
Social Functioning	82 (21)	0.0-43.8	82 (20)	0.0-44.0	77 (28)	0.0-23.7	0.302	0.235	-0.107: 0.578
Role-Emotional	75 (24)	0.0-32.4	76 (23)	0.0-32.1	71 (26)	0.0-20.1	0.179	0.213	-0.129: 0.556
Mental Health	72 (20)	0.0-11.7	73 (19)	0.0-6.0	68 (22)	0.0-2.6	0.135	0.257	-0.085: 0.600
Physical Component Score	70 (18)	0.0-0.0	69 (16)	0.0-0.0	62 (21)	0.0-0.0	0.056	0.418	0.074: 0.762
Mental Component Score	74 (18)	0.0-0.0	74 (17)	0.0-0.0	69 (19)	0.0-0.0	0.080	0.263	-0.080: 0.605
SF-36 Total	72 (17)	0.0-0.0	72 (15)	0.0-0.0	66 (19)	0.0-0.00	0.063	0.385	0.041: 0.728

Data are expressed as mean (SD). * Differences between groups ($P \leq 0.05$). ** Differences between groups ($P \leq 0.01$).

4.1.4.3. Differences between evaluations

Comparisons between the baseline and the 24-months evaluations are presented in Table 4.1.2. LTMEX group decreased BW, WC, BMI, SBP, DBP ($P < 0.001$), increased CRF ($P < 0.001$) and improved HDL-C ($P < 0.05$). Inversely, the CO group increased WC, BMI, WHR ($P < 0.05$) and SBP ($P < 0.001$). Glycaemia, TC, LDL-C, and TG maintained unchanged in both LTMEX and CO groups during the 24-months period.

After the 24-months intervention, LTMEX improved PF, RP, GH, SF, RE, PCS, MCS, and Total SF-36 ($P < 0.05$), and maintained V and MH ($P > 0.05$), while CO group decreased V and MH ($P < 0.05$), showing also scores beneath mean standardize scale in GH domain. These changes led to the emergence of differences between LTMEX and CO group at 24-months evaluation, after adjusting to baseline score values, age and sex, specifically in BMI, CRF, SBP, DBP, PF, BP, GH, V, SF, RE, MH, PCS, MCS, and Total SF-36 ($P < 0.05$). The differences between groups observed at baseline in BW, WC, WHR and RP maintained at 24-months evaluation ($P < 0.05$).

Table 4.1.3 shows the comparisons of the mean change in HRQoL in the two groups and the respective effect size and MID between baseline and the final 24-months evaluation. After exercise intervention, PF, GH, V, MH, PCS, MCS and Total SF-36 domains presented improved moderate effect sizes, contrary to the CO group that showed an aggravated pattern in these domains, despite, only V and MH scales showed statistical difference ($P < 0.05$).

Table 4.1.2 – Differences between evaluations using a two-way ANOVA and ANCOVA adjusted to baseline values, age and sex (*N*=216)

Variables	CO Group (*n* = 36)			LTMEX Group (*n* = 178)			Effect Size	Confidence Interval (95%)	Differences between groups At Baseline	Differences between Groups After 2 years [a]
	Baseline	After 2 years	*P* Values	Baseline	After 2 years	*P* Values			*P* Values	*P* Values
Body Weight, Kg	84.6 (12.5)	85.0 (12.8)	0.147	76.5 (13.0)	75.5 (12.8)	<0.001**	0.742	0.377: 1.107	0.002*	0.005*
Waist circumference, cm	98.6 (10.4)	100.1 (10.0)	0.012*	94.8 (9.5)	92.0 (9.5)	<0.001**	0.845	0.478: 1.212	0.046*	<0.001**
BMI, kg/m^2	30.7 (4.5)	30.9 (4.7)	0.024*	29.9 (4.4)	29.6 (4.4)	<0.001**	0.292	-0.067: 0.651	0.411	0.005*
Waist-to-hip ratio	0.95 (0.09)	0.98 (0.08)	0.003**	0.91 (0.07)	0.90 (0.07)	0.088	1.115	0.742: 1.488	0.011*	<0.001**
6-min walk distance, m	431 (72)	422 (58)	0.248	423 (108)	536 (101)	<0.001**	1.197	0.821:1.573	0.433	<0.001**
Systolic BP, mmHg	137 (15)	143 (15)	<0.001**	143 (18)	128 (14)	<0.001**	1.059	0.687: 1.431	0.100	<0.001**
Diastolic BP, mmHg	77 (9)	78 (10)	0.262	79 (11)	73 (9)	<0.001**	0.545	0.183-0.907	0.185	0.003*
Total cholesterol, mg/dL	169 (24)	153 (59)	0.279	182 (36)	179 (40)	0.325	0.595	0.232: 0.957	0.071	0.107
HDL-cholesterol, mg/dL	45 (10)	45 (8)	0.554	48 (10)	50 (11)	0.042*	0.473	0.112: 0.834	0.236	0.760
LDL-cholesterol, mg/dL	100 (21)	102 (24)	0.489	109 (33)	106 (34)	0.272	0.123	-0.481: 0.236	0.106	0.204
Triglycerides, mg/dL	130 (67)	133 (96)	0.753	129 (57)	126 (70)	0.535	0.093	-0.265: 0.452	0.680	0.519
Glycaemia, mg/dL	137 (49)	143 (57)	0.569	129 (34)	132 (39)	0.230	0.259	-0.100: 0.618	0.589	0.221
Physical Functioning	76 (24)	74 (19)	0.488	79 (20)	86 (13)	<0.001**	0.847	0.480: 1.214	0.286	<0.001**
Role-Physical	65 (27)	66 (25)	0.923	75 (22)	79 (22)	0.015*	0.557	0.215: 0.940	0.038*	0.001*
Bodily Pain	61 (29)	64 (21)	0.497	67 (24)	72 (22)	0.001**	0.366	0.006: 0.726	0.142	0.049*
General Health	54 (16)	49 (15)	0.083	58 (18)	61 (17)	0.006*	0.719	0.355: 1.084	0.086	0.001*
Vitality	61 (20)	54 (17)	0.009*	67 (20)	67 (17)	0.839	0.765	0.399: 1.130	0.066	<0.001**
Social Functioning	77 (28)	75 (20)	0.562	83 (20)	89 (17)	<0.001**	0.799	0.433: 1.165	0.271	<0.001**
Role-Emotional	72 (26)	73 (20)	0.736	76 (23)	81 (21)	0.008*	0.384	0.024: 0.744	0.146	0.017*
Mental Health	69 (22)	61 (24)	0.038*	73 (19)	74 (17)	0.494	0.709	0.344: 1.073	0.103	0.001*
Physical Component Score	63 (21)	63 (16)	0.949	69 (16)	75 (15)	<0.001**	0.791	0.425: 1.157	0.040*	<0.001**
Mental Component Score	70 (19)	66 (17)	0.059	75 (16)	78 (14)	0.014*	0.825	0.459: 1.192	0.057	<0.001**
SF-36 Total	67 (18)	64 (15)	0.140	72 (15)	76 (14)	<0.001**	0.847	0.480: 1.214	0.044*	<0.001**

Data are expressed as mean (SD). * Differences between evaluations ($P \leq 0.05$). ** Differences between evaluations ($P \leq 0.01$). [a] Differences between groups after 2 years, adjusted to baseline values, age and sex.

Table 4.1.3 – Mean changes between groups in HRQoL, effect size and minimum important difference (*N*=216)

Variables				Mean Change		Effect Size	SEM		MID	
	Total Mean Change	SEM	MID	CO	LTMEX		CO	LTMEX	CO	LTMEX
Physical Functioning	8.3 (2.9)	0.71	2.0	-2.4 (3.4)	6.9 (1.2)	0.707	0.87	0.28	2.4	0.8
Role-Physical	12.4 (3.5)	0.86	2.4	0.4 (4.0)	4.2 (1.8)	0.117	1.01	0.43	2.8	1.2
Bodily Pain	8.2 (3.8)	0.93	2.8	2.4 (3.5)	5.4 (1.7)	0.073	0.89	0.40	2.5	1.1
General Health	9.0 (2.8)	0.69	1.9	-4.7 (2.7)	3.2 (1.4)	0.484	0.69	0.33	1.9	0.9
Vitality	10.8 (2.9)	0.71	2.0	-7.8 (2.8)	-0.3 (1.5)	0.540	0.71	0.35	2.0	1.0
Social Functioning	10.2 (2.9)	0.71	2.0	-2.6 (4.5)	5.6 (1.5)	0.564	1.15	0.36	3.2	1.0
Role-Emotional	6.4 (3.3)	0.80	2.2	1.2 (3.6)	4.7 (1.8)	0.171	0.92	0.43	2.6	1.2
Mental Health	9.8 (2.9)	0.71	2.0	-7.6 (3.5)	0.5 (1.5)	0.452	0.89	0.36	2.5	1.0
Physical Component Score	10.0 (2.7)	0.66	1.8	-0.1 (2.1)	4.9 (1.1)	0.373	0.54	0.26	1.5	0.7
Mental Component Score	9.3 (2.6)	0.64	1.8	-4.2 (2.2)	2.7 (1.3)	0.562	0.56	0.31	1.6	0.9
SF-36 Total	9.7 (2.4)	0.59	1.6	-2.4 (1.6)	3.9 (1.1)	0.462	0.41	0.26	1.1	0.7

CO- Control Group. LTMEX- Exercising Group.SEM- Standard Error of measurement. MID- Minimum Important Difference.

4.1.5. Discussion

The main finding of this longitudinal, large sample study involving T2D older adults is that LTMEX intervention improves HRQoL. LTMEX also enhanced anthropometric, hemodynamic profile, and CRF. The current research provides the strongest evidence to date that LTMEX has beneficial effects on both physical and mental HRQoL in older adults with T2D through time, who generally report reduced HRQoL comparing with individuals without diabetes (V. Myers & McVay, 2013).

While some authors have related reductions in BW with improvements in cardiovascular health and HRQoL (Snowling & Hopkins, 2006), others have observed that a mechanism other than weight-loss may positively affect metabolic function (Li et al., 2011). In fact, Gaterer and colleagues (Gatterer, Ulmer, Dzien, Somavilla, & Burtscher, 2011) observed that increasing CRF is the key goal for men, while the reduction of BW is more beneficial in women to augment glucose tolerance. These inconsistent results address for the need to better understand the underlying mechanisms, if total caloric expenditure, exercise duration or mode (Chae et al., 2012; S. R. Colberg et al., 2010). Both men and women included in the LTMEX decreased BW and BMI, but also increased CRF, which could contribute to explain the gains on HRQoL. On the other side, in the CO group, the obesity association with impaired HRQoL may contributed to the negative impact on V and MH domains, particularly the increases in anthropometrics (WC, BMI and WHR) and SBP (Dale et al., 2013; Snowling & Hopkins, 2006).

Overall, the present findings confirm previous results from shorter intervention studies addressing to the positive impact of different modes of exercise on well-being, and cardiometabolic risk (Marwick et al., 2009)(S. Colberg & Grieco, 2009). In fact, some have found improvements on HRQoL after 9-months of aerobic, resistance, and combined exercising, even though the combined training has revealed greater improvements (V. Myers & McVay, 2013). Similarly, 12-months of combined exercise promoted positive changes on the HRQoL (Nicolucci et al., 2012). However, after 5.5-months of exercising, from a randomized controlled trial, improvements in physical QoL were found only in the resistance group, but not in aerobic or combined exercise groups (Reid et al., 2010). Our 24-months multicomponent exercise intervention impact moderately physical HRQoL (Cohen, 1988), particularly PCS but also PF, GH and Total-SF-36 but had no intention to

explore dose-response effects. Some authors, however, have pointed higher volumes or intensities as causing more benefits on QoL (Nicolucci et al., 2012; Wadden, 2014). In fact, Taylor and colleagues (Taylor et al., 2010) found that people with pre-diabetes who achieved exercise guidelines had higher levels of physical and mental HRQoL than people who were inactive.

Nevertheless, the published guidelines should be interpreted as a minimum recommendation and so, less than an optimum situation (Praet & van Loon, 2008). Therefore, our results demonstrated that future studies on the effects of exercise should focus on long-term maintenance interventions, rather than just short-term programs (Madden, Loeb, & Smith, 2008). Additionally, the current study reinforces the positive exercise effect in older adults with T2D on PF and GH domains, that are related to participant´s functioning in physical activities required for daily living and self-perception on their general health, that may be reduced by the effects of ageing and the disease itself (American Diabetes Association, 2016; R.E. Rikli & Jones, 1999).

The lack of improvements in mental HRQoL in previous researches (V. Myers & McVay, 2013; Wadden, 2014) or even deterioration (Reid et al., 2010), contrast with our gains in MCS observed in the LTMEX group. However, similarly to our findings, Nicolucci and colleagues (Nicolucci et al., 2012) also obtained widespread mental QoL improvements with MEX intervention in diabetes. These contrasting results appear to emphasize the importance of the length of the program intervention in the relationship between exercise-HRQoL in individuals with T2D. In fact, some authors have stated that improvements in mental HRQoL in T2D participants require exercising programs with more than 12 months (V. Myers & McVay, 2013; Nicolucci et al., 2012; Reid et al., 2010; Wadden, 2014).

After the 24-month intervention, the differences in BP and RE had small effect size (Cohen, 1988), and the SF scale presented statistical difference between groups and a high effect size. Nevertheless, due to the high ceiling effect in baseline our explanatory capacity was reduced by the sensitivity ability of this instrument to evaluate exercise effect in these domains. In fact, floor and ceiling effects negatively impact the sensitivity and responsiveness of the questionnaire, reducing the value for measuring the change effects or discriminating between participants with small differences in health status (Ware. Jr, 2000).

This longitudinal intervention research has several strengths including strong methodological design, large community sample exclusively of older adults with T2D, long-term supervised exercise training intervention and well-validated questionnaires. Nevertheless, further studies should be conducted with a control group proportional to the study group. A randomized controlled trial could emphasize our results. Additionally, although the SF-36 scale is a reliable and well-validated scale for assessing HRQoL, it has been recommended that a diabetes specific measure should be used in conjunction with the SF-36 scale, as scores are strongly affected by non-diabetic comorbidity (Speight et al., 2009). Despite limitations, these results have important clinical implications, demonstrating that long term exercise regimens should be adopted into standard care and communities for older individuals with T2D, particularly elderly with comorbidity because people with higher QoL have greater motivation to increase their knowledge about diabetes, and consequently enhancing their behaviors to diabetes, leading to positive attitudes, and promoting self-management activities to maintain their health status or limit the negative physical impact of diabetes (Kueh, Morris, Borkoles, & Shee, 2015).

Current evidence reinforces the importance of long-term multicomponent exercise to mental and physical health-enhancing, to manage and delay the deleterious effects of diabetes and age-related declines, assuring a multidimensional model, promoting a successful and active ageing among those with T2D.

4.2. Study II- Back to basic with active lifestyles: exercise is more effective than metformin to reduce cardiovascular risk in older adults with type 2 diabetes.

Back to basic with active lifestyles: exercise is more effective than metformin to reduce cardiovascular risk in older adults with type 2 diabetes

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4.2.1. Abstract

Objective – To establish the effect of three types of treatment – multicomponent exercise (MEX); oral hypoglycemic drug - metformin (MET); combined therapy- exercise plus metformin (MEXMET) – on cardiovascular risk in older adults with type 2 diabetes (T2D), and with comorbidity in an early stage of the disease (HbA1c < 7.5 %).

Methods – A sample of 284 participants was evaluated on multifactorial cardiovascular risk at baseline and at 24-months intervention on anthropometric, hemodynamic components, lipid profile, glycaemia and cardiorespiratory fitness (CRF). Participants underwent one of 3 conditions: MEX (n = 59), trained three sessions per week; MET (n = 30), used metformin 850 mg twice daily; MEXMET (n = 195), combined exercise plus metformin.

Results – Differences between MEX and MET groups after 24-month intervention presented large effect sizes in body mass (BM), waist circumference (WC), waist-to hip ratio (WHR), systolic (SBP) and diastolic blood pressure (DBP) and cardiorespiratory fitness (CRF) and moderate effect size in body mass index (BMI) and glycaemia. Additionally, differences between MEXMET and MET revealed moderate effect size in BMI, SBP and DBP and large effect size in BM, WC, WHR and CRF. MEX decreased BM (4%), WC (4%), BMI (3%), SBP and DBP (11%), triglycerides (21%), glycaemia (12%), and increased CRF (18%). MET group increased WC (2%), WHR (3%), SBP (5%).

Conclusions – MEX was the most effective therapy decreasing cardiovascular risk in early stage of T2D in older adults with multimorbidity and attenuated the adverse effects of the pharmacological therapy in the MEXMET treatment.

Keywords: diabetes, exercise, metformin, multifactorial cardiovascular risk factors, older adults

4.2.2. Introduction

The management of diabetes in elderly is a complex process due to the increased prevalence of comorbidities, heterogeneous functional status, and geriatric syndromes (Bell & Saraf, 2016; Richman & Schub, 2015). Therefore, an holistic approach to the multiple aetiopathogenic mechanisms of the disease has been recommended to minimize long-term complications (American Diabetes Association, 2016; Gadsby, 2014; Strain et al., 2014)

International organizations (Aschner et al., 2014; Inzucchi et al., 2012) recommend a stepwise management approach based on lifestyle modification which includes a behavioral change on nutritional and exercise habits as the first step, but they differ in the introduction of a first-line oral hypoglycemic drug at the initial diagnose, usually metformin. Nevertheless, in the elderly population these previous recommendations are based in expert consensus and clinical experience, due to the absence of evidence from clinical trials with older adults, particularly to identify the efficacy of such treatments. Additionally, there is growing evidence demonstrating the adverse side effects of pharmacologic treatment and drug-diseases interactions in this specific population (Abdelhafiz & Sinclair, 2015; Bell & Saraf, 2016; Richman & Schub, 2015); in fact, metformin was associated with initial gastrointestinal side effects and it was not recommended for frail older people with weight loss (American Diabetes Association, 2016).

On the other hand, randomized controlled trials have shown that intensive lifestyle may decrease the rate of diabetes onset in adults at high risk for developing T2D (Diabetes Prevention Program Research Group, 2009; Griffin et al., 2011; Pan et al., 1997; The Look AHEAD Research Group, 2010); and reducing cardiovascular risk (American Diabetes Association, 2016), but it has also been suggested that pharmacological therapies alone, or in combination with diet and exercise could even be more (Schellenberg et al., 2013; Stevens et al., 2015; Thompson et al., 2014). However, once more, these results should be interpreted with caution, because these previous studies have used wide range age samples, mixing adults of all ages, with different physical cardiovascular profiles, highlighting the need to understand how it acts in exclusively older adult's population. Additionally, it has been reported that greater reductions in morbidity and mortality could come from the result

of the control of other cardiovascular risk factors, especially hypertension and lipid profile, rather than from the independent tight glycemic control (American Diabetes Association, 2016). It seems crucial understand the relative value of exercise training and/or drug treatment in the elderly, face to the lack of evidence previously demonstrated in this specific population (Thompson et al., 2014).

Therefore, in context of the preceding trends, the aim of the present study is to analyze the effect of three types of treatment: *i*) lifestyle modification with multicomponent exercise; *ii*) pharmacologic treatment with oral hypoglycemic drug – metformin; *iii*) and a combined therapy including exercise and metformin; on multifactorial cardiovascular risk factors in T2D older adults in early stage of the disease.

4.2.3. Methods

4.2.3.1. Participants

This cohort study is part of a larger research involving 1473 community-dwelling adults aged 60 and over to study the effects of long-term multicomponent exercise (MEX) on several variables. Participants were referred to the study by their physician or self-referred from flyers distributed at community centers, media advertisements or word of mouth. Study design has been previously reported (Baptista, Machado-Rodrigues, & Martins, 2017).

After the initial evaluation, a sub-group of physically independent participants fulfilled the criteria for T2D defined by the IDF (Aschner et al., 2014).

Exclusion criteria included (a) uncontrolled hypertension; (b) severe autonomic neuropathy; (c) severe peripheral neuropathy or history of foot lesions; (d) unstable proliferative retinopathy; (e) participants who were not under regular supervision of the treating physician for the period of the study; (f) known cancer or limited life expectancy, acute emergencies; (g) Parkinson's disease; (h) Alzheimer's disease; (i) dementia; (j) severe visual impairment; and (k) further reasons that made it impossible or highly problematic for the patient to participate and come to the follow-up visits completing baseline and follow-up testing (program log $\geq$ 80 %). Thus, a sub-group of 284 were retained as eligible participants.

This group was then divided according to 3 therapy conditions as follows: i) lifestyle modification – exercise (MEX; n = 59: 29% male); ii) oral hypoglycemic therapy – metformin (MET; n = 30: 60% male); and iii) combined therapy – exercise and oral hypoglycemic therapy with metformin (MEXMET; n = 195: 32% male). After the 24-months intervention, the trial was completed by 217 participants: MEX group (n = 47); MET (n = 29) and MEXMET group (n = 141) (Figure 1).

The criteria for inclusion in the MEX group was exercise engagement according the guidelines (World Health Organization, 2014), while MET group used pharmacological therapy with oral hypoglycemic metformin (i.e., 850 mg twice daily) to manage their disease, and the MEXMET combined both multicomponent exercise training with oral hypoglycemic metformin treatment.

4.2.3.2. Interventions and procedures

After the afore-mentioned recruitment period, in a preliminary meeting, participants were informed about the nature, the benefits and the risks of their participation in this study. Furthermore, in a second meeting, participants completed the health history questionnaire and were measured the anthropometric, hemodynamic components and aerobic fitness. BP, body mass (BM), waist and hip circumferences, and stature were assessed by trained nurses according to standard procedures (American College of Sports Medicine, 2010). Self-reported questionnaires were used to collect data on demographic factors, medical outcomes and lifestyle factors, which were completed by trained interviewers only to carry on data collection with illiterate participants.

Evaluation procedures were performed in the same order at the baseline and at the end of the follow-up, after 24 months. Baseline interviews and clinical examination were performed in September 2013 with follow up until September 2015.

Participants of the MEX and MEXMET groups met three times a week for one hour over the 24-months intervention period to perform the multicomponent exercise program in the local centers of Santa Maria da Feira. The MET and MEXMET group held trimester consultations with their physician to control their medication treatment. In addition, all participants were informed to maintain the same nutritional pattern throughout the intervention period and maintain regular supervision of their physician during the follow-up intervention.

All participants agreed to participate in this study and they gave their written informed consent, consistent with Helsinki Declaration. Methods and procedures were approved by Institutional Scientific Board of the University of Coimbra, local institution (Santa Maria da Feira County) and national ethics committees Data Protection Authority-CNPD; Health Administration from North Ethics Committee-ARS/Norte).

4.2.3.3. Multicomponent exercise program

The supervised exercise program consisted in three 60-minutes sessions/week, on Monday, Wednesday and Friday. Aerobic, resistance, balance and flexibility were trained according with these items: 5-10 minutes of warm-up, 20-30 minutes of aerobic, 15-20 minutes of resistance training, 10 minutes of balance, 10 minutes of stretching, and 5-10

minutes of cool down exercises. Aerobic exercise started with participants in a standing position and involved continuous movement of major muscles of the upper limb, performed alternately with movement of the lower limb. Time and intensity of aerobic exercise was increased from 20 minutes per session at 50%HRmax (maximum heart rate) to 30 minutes at 70%HRmax per session (American College of Sports Medicine, 2010).

Resistance training was conducted every Monday and Friday; on these 2 days, the aerobic session was shortened to approximately 20 minutes.

Resistance training involved five to eight exercises from large muscle groups, with one to three sets of 8 to 15 repetitions for each upper and lower body muscle group and came from participants' own body weight or with light free weights. Intensity was set at 50-70% of 1-repetition maximum (1-RM), with 90 to 120 seconds of rest between sets, consistent with recommended guidelines (American College of Sports Medicine, 2010).

Balance training was also based on functional tasks required by older adults. Prior to cool down, participants performed stretching exercises designed to improve flexibility of the major muscle groups; each stretch was sustained between 15 and 30 seconds to the point of tightness, and repeated three times.

Over the 24-months intervention, progression was guaranteed every 6 weeks through adjustments on duration, repetitions, resistance, and/or difficulty (e.g., transition from sitting to standing to complete exercises). Exercise modifications such as reduced duration, number of repetitions, or use of an exercise auxiliary were recommended by the group instructor when needed.

4.2.3.4. Anthropometrics

Stature was measured using a standard stadiometer to 0.1 cm in the upright position, with the participants´ back square against the wall and eyes looking straight ahead, without shoes. BM was measured by a calibrated digital balance-beam scale (SECA 770, Germany) with a precision nearest to 100 grams, with barefoot participants and in light clothing.

Waist circumference (WC) was measured at the midpoint between the lowest rib and the top of the iliac crest at minimal respiration, and hip circumference was taken in a horizontal plan along pubic symphysis. Body mass index (BMI) and waist-to-hip ratio (WHR) were calculated by standard methods.

4.2.3.5. Hemodynamics

Resting BP was measured using a sphygmomanometer (Aneroid Sphygmomanometer-HICO HM 1001, Germany) and stethoscope (Nurse Type Professional Stethoscope-HICO HM-3005, Germany) in the seated position, after 5 minutes rest; the measurements were taken three times with 2-minutes intervals [18] and the mean value of the 2 nearest measures was used for calculate the systolic (SBP) and diastolic (DBP) BP.

Trained nurses collected venous blood in the morning after 12 hours of fasting. Glycaemia, HbA1c, triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), HDL-C and total cholesterol (TC) were determined by standard methods in an accredited laboratory.

4.2.3.6. Health history

The participants´ health history was obtained by questionnaire, and data included age, gender, education level, living situation, exercise practice, smoking status and the presence of several conditions like heart disease, hypertension, stroke, diabetes, dyslipidemia, osteoarthritis, pulmonary diseases, liver diseases, thyroid diseases, visual and audio problems, cancer, or other comorbidities.

Medication type and dosage were assessed by detailed questionnaire with visual confirmation of prescription drugs which was recorded by the staff of the present study.

4.2.3.7. Cardiorespiratory Fitness

Cardiorespiratory fitness (CRF) was evaluated using the six-minute walk test (6MWT) performed on a flat 50-meters rectangular course, marked off in 5-meters segments (R.E. Rikli & Jones, 1999).

The 6MWT were performed in the morning, between the 8 and the 10 hours, to minimize intraday variability, temperature effects, and biological rhythms. Participants were instructed to avoid vigorous exercise in the 2 hours prior to testing, to wear comfortable clothes and appropriate walking shoes, and to continue their usual medication. Recommended reasons for immediately stopping the 6MWT include the following: chest

pain, intolerable dyspnea, leg cramps, staggering, diaphoresis, and pale or ashen appearance.

4.2.3.8. Statistical analysis

Descriptive analysis was carried out with measures of central tendency and dispersion; baseline participants' characteristics were compared using means and standard deviations (M ± SD) for the variables: age, BM, WC, BMI, WHR, SBP, DBP, TC, HDL-C, LDL-C, TG, glycaemia, HbA1c and 6MWT. Kolmogorov-Smirnov and Levene´s tests were performed to verify, for all continuous variables, normality of the distribution and the homoscedasticity.

One-way ANOVA and analysis of covariance (ANCOVA) were used for comparisons between groups, controlling for the effect of age, sex and number of comorbidities at baseline. A two-way ANOVA for repeated measures was performed in factors groups (MEX, MET and MEXMET) for analysis within groups and differences between groups after 24-month intervention were performed with analysis of covariance (ANCOVA), adjusting to baseline score values, age and sex and with pairwise comparisons.

Responsiveness was used to detect the magnitude of differences between groups at baseline and after 24-months intervention. It was measured with Hedges´s g effect size and the respective 95% confidence intervals, providing a measure of the effect size weighted according to the relative different sample size within our study population (Hedges & Olkin, 1985). Standardized effects sizes were classified as small (<0.20), moderate (0.20-0.79) and large (>0.80) (Cohen, 1988).

The equation $\underline{\Delta}$% [(Post-pre follow-up/Total Test) x 100] was used to determine the percentage difference across all variables analyzed from baseline to final 24-months evaluation within each group.

All analysis were performed using Statistical Package for the Social Sciences for Windows (IBM-SPSS, Inc. Chicago, IL, USA), software version 22 at the 95% level of significance.

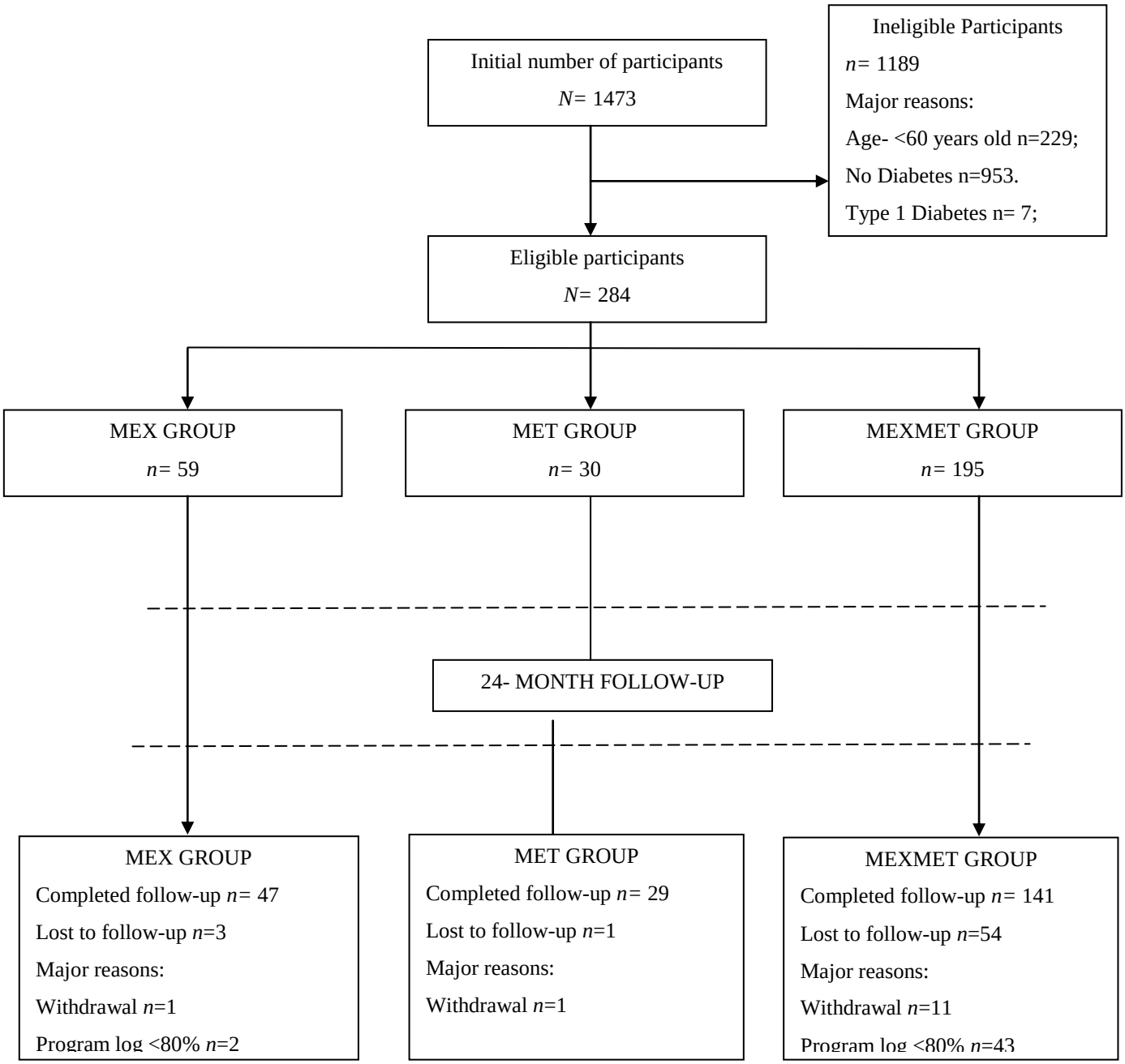


Figure 4.2.1. Cohort flux diagram

4.2.4. Results

4.2.4.1. Baseline characteristics

The most prevalent comorbidities were hypertension (93%), central obesity (74%), and hypertriglyceridemia (64%). At baseline (Table 4.2.1), the 3 therapy groups did not revealed statistical differences ($P > 0.05$), except for sex ($P = 0.006$), age ($P = 0.044$), BM ($P = 0.005$), WHR ($P = 0.027$), TC ($P = 0.001$), and LDL-C ($P < 0.001$). MET group had more males, was younger, heavier and had lower TC than the other groups ($P < 0.05$); MET group had higher WHR than MEXMET group (0.04 cm; $P = 0.010$). After controlling to the effect of sex, age and number of comorbidities all these differences disappeared. Differences between groups presented small to moderate effect sizes in all variables, except for the large effect size in LDL-C in the MEX group comparatively to MET group.

4.2.4.2. Differences between group evaluation

At 24-months evaluation (Table 4.2.2 and 4.2.3) several significant differences occurred ($P < 0.05$). Differences between MEX and MET groups presented large effect sizes in BM, WC, WHR, SBP, DBP and CRF and moderate effect size in BMI and glycaemia. Additionally, differences between MEXMET and MET revealed moderate effect size in BMI, SBP and DBP and large effect size in BM, WC, WHR and CRF.

The MEX group decreased BM (3.6 %), WC (4.2%), BMI (2.7%), SBP (11.1%), DBP (11.3%), TG (21.2%), glycaemia (12.3%), and increased CRF (17.7%) (Figure 4.2.2). Reversely, MET group increased WC (2.2%), WHR (3.1%), BMI (1.6%), and SBP (5.4%). The MEXMET group exhibited reductions in BM (1.1%), WC (2.4%), BMI (1.4%), and DBP (8.2%), while increased SBP (0.7%), glycaemia (6.7%), and CRF (18.0%). All differences between groups at 24-months were kept after controlling for the effect of the sex, age and baseline score values, except for TC and LDL-C.

Table 4.2.1 –Descriptive baseline characteristics of participants (*N*=284)

Variables	Total (*N*=284)	MEX (*n*= 59)	MET (*n*= 30)	MEXMET (*n*=195)	Group Effect *P* Values	Between-group differences (95% CI) *P* Value	Group Effect Adjusted *P* Values [a]	Effect Size	Confidence Interval 95%
Male, *n*	97	17	18	62	0.006*				
MEX vs. MET						0.3 (0.1 to 0.6); 0.008 *			
MEXMET vs. MET						0.3 (0.1 to 0.5); 0.003*			
MEX vs. MEXMET						0.0 (-0.1 to 0.2); 0.959			
Age, years	70.6 (6.1)	71.4 (6.4)	68.1 (4.3)	70.7 (6.1)	0.044*				
MEX vs. MET						3.3 (0.1 to 6.5); 0.042*		-0.570	-1.018- -0.123
MEXMET vs. MET						2.4 (0.1 to 5.3); 0.042*		-0.441	-0.827- -0.054
MEX vs. MEXMET						0.6 (-1.5 to 2.7); 0.854		-0.113	-0.405-0.178
Comorbid disease	1.79 (1.3)	1.9 (1.3)	2.2 (1.5)	1.7 (1.3)	0.070				
MEX vs. MET						-0.3 (-1.0 to 0.4); 0.669		0.219	-0.222-0.660
MEXMET vs. MET						-0.6 (-1.1 to 0.0); 0.062		0.377	-0.009-0.763
MEX vs. MEXMET						0.3 (-0.2 to 0.7); 0.451		-0.154	-0.445-0.138
Body mass, kg	77.5(13.5)	77.4(13.0)	84.9(12.8)	76.4(13.5)	0.005*		0.743		
MEX vs. MET						-7.5 (-14.6 to -0.4); 0.033*		0.580	0.132-1.028
MEXMET vs. MET						-8.6 (-14.3 to -2.8); 0.001*		0.634	0.245-1.023
MEX vs. MEXMET						1.1 (-3.5 to 5.6); 0.925		-0.075	-0.366-0.217
Waist circumference, cm	94.9(10.1)	94.5 (8.7)	98.7(10.2)	94.4(10.4)	0.091		0.392		
MEX vs. MET						-4.2 (-9.5 to 1.1); 0.166		0.455	0.011-0.900
MEXMET vs. MET						-4.3 (-8.6 to 0.1); 0.054		0.414	0.028-0.801
MEX vs. MEXMET						0.1 (-3.4 to 3.5); 1.000		-0.010	-0.301-0.281
BMI, kg/m^2	30.0 (4.6)	30.1 (4.3)	30.4 (4.2)	30.0 (4.7)	0.805		0.309		
MEX vs. MET						-0.4 (-2.8 to 2.0); 0.976		0.070	-0.369-0.510
MEXMET vs. MET						-0.6 (-2.6 to 1.4); 0.866		0.086	-0.298-0.471
MEX vs. MEXMET						0.2 (-1.4 to 1.8); 0.987		-0.022	-0.313-0.270
Waist-to-hip ratio	0.91(0.07)	0.91(0.07)	0.95(0.08)	0.91(0.07)	0.027*		0.684		
MEX vs. MET						-0.03 (-0.07 to 0.04); 0.099		0.544	0.098-0.991
MEXMET vs. MET						-0.04 (0.01 to 0.06); 0.010*		0.560	0.173-0.948
MEX vs. MEXMET						0.04 (-0.02 to 0.03); 0.966		0.000	-0.291-0.291
Systolic BP, mmHg	140 (18)	140 (20)	139 (15)	141 (19)	0.911		0.339		
MEX vs. MET						1.3 (-8.3 to 10.9); 0.982		-0.054	-0.494-0.385
MEXMET vs. MET						1.5 (-6.3 to 9.3); 0.952		-0.108	-0.492-0.277
MEX vs. MEXMET						-0.2 (-6.4 to 6.0); 1.000		0.052	-0.239-0.343
Diastolic BP, mmHg	79 (11)	79 (13)	77 (10)	79 (11)	0.673		0.505		

MEX vs. MET						1.9 (-3.9 to 7.8); 0.811		-0.166	-0.606-0.275
MEXMET vs. MET						1.9 (-2.9 to 6.6); 0.718		-0.184	-0.569-0.201
MEX vs. MEXMET						0.1 (-3.7 to 3.9); 1.000		0.000	-0.291-0.291
Total cholesterol, mg/dL	182 (35)	199 (37)	169 (26)	180 (34)	0.001**		0.084		
MEX vs. MET						30.6 (9.6 to 51.6); 0.002*		0.889	0.431-1.348
MEXMET vs. MET						11.4 (-4.5 to 27.3); 0.237		-0.333	-0.718-0.053
MEX vs. MEXMET						19.2 (5.2 to 33.2); 0.003*		-0.547	-0.842- -0.252
HDL-cholesterol, mg/dL	49 (17)	48 (9)	45 (10)	50 (19)	0.334		0.663		
MEX vs. MET						2.9 (-7.8 to 13.7); 0.883		0.321	0.121-0.763
MEXMET vs. MET						5.1 (-2.9 to 13.1); 0.330		-0.276	-0.662-0.109
MEX vs. MEXMET						-2.2 (-9.5 to 5.1); 0.856		0.116	-0.175-0.408
LDL-cholesterol, mg/dL	108 (32)	127 (33)	97 (26)	106 (31)	<0.001**		0.055		
MEX vs. MET						29.9 (9.9 to 49.9); 0.001*		0.973	0.510- 1.435
MEXMET vs. MET						8.9 (-6.1 to 23.9); 0.395		-0.296	-0.681-0.089
MEX vs. MEXMET						21.1 (7.7 to 34.4); 0.001*		-0.667	-0.964-0.370
Triglycerides, mg/dL	129 (59)	126 (56)	131 (70)	130 (58)	0.941		0.443		
MEX vs. MET						-4.9 (-42.7 to 32.9); 0.985		0.082	-0.358-0.522
MEXMET vs. MET						-1.5 (-29.9 to 27.0); 0.999		0.017	-0.368-0.401
MEX vs. MEXMET						-3.4 (-28.6 to 21.8); 0.983		0.070	-0.222-0.361
Glycaemia, mg/dL	129 (34)	128 (27)	136 (47)	128 (33)	0.547		0.079		
MEX vs. MET						-8.3 (-29.1 to 12.5); 0.711		0.229	-0.212-0.670
MEXMET vs. MET						-7.6 (-23.6 to 8.3); 0.578		0.228	-0.157-0.613
MEX vs. MEXMET						-0.7 (-14.8 to 13.5); 0.999		0.000	-0.291-0.291
HbA1c, %	6.69 (1.0)	6.54(0.7)	6.81 (1.4)	6.67 (1.0)	0.800		0.913		
HbA1c, mmol/mol	50 (10.9)	48 (7.7)	51 (15.3)	49 (10.9)					
MEX vs. MET						-0.3 (-1.3 to 0.7); 0.878		0.273	-0.169-0.714
MEXMET vs. MET						-0.1 (-0.7 to 0.5); 0.943		0.132	-0.253-0.517
MEX vs. MEXMET						-0.2 (-0.9 to 0.6); 0.941		0.138	-0.153-0.430
6-min walk distance, m	441 (113)	429 (127)	427 (76)	447 (113)	0.430		0.248		
MEX vs. MET						2.4 (-57.7 to 62.4); 1.000		-0.018	-9.457-0.422
MEXMET vs. MET						20.4 (-28.6 to 69.5); 0.682		-0.184	-0.568-0.201
MEX vs. MEXMET						-18.1 (-57.1 to 20.9); 0.604		0.155	-0.137-0.446

Data are expressed as mean (SD). * Differences between evaluations ($P \leq 0.05$). ** Differences between evaluations ($P \leq 0.001$). a Differences between groups adjusting for age, sex and comorbidity number.

Table 4.2.2- Comparisons between group therapy after 24-month intervention using one- way ANOVA and ANCOVA adjusted to baseline values, age and sex (*N*=217)

Variables	MEX (n= 47)	MET (n= 29)	MEXMET (n=141)	Group Effect *P* Value	Group Effect Adjusted [a] *P* Value	Between group differences (95% CI) *P* Value	Effect Size	Confidence Intervals 95%
Body mass, kg	75.1 (13.6)	86.0 (12.7)	75.6 (12.3)	0.001**	0.020*			
MEX vs. MET						-1.9 (-3.2 to -0.6); 0.006*	0.819	0.363-1.275
MEXMET vs. MET						-1.3 (-2.4 to -0.2); 0.027*	0.842	0.450-1.234
MEX vs. MEXMET						-0.7 (-1.6 to 0.3); 0.189	0.040	-0.252-0.331
Waist circumference, cm	90.7 (9.7)	100.9 (9.4)	92.2 (9.7)	0.002**	<0.001**			
MEX vs. MET						-4.8 (-7.0 to -2.5); <0.001**	1.062	0.596-1.529
MEXMET vs. MET						-4.2 (-6.1 to -2.4); <0.001**	0.900	0.507-1.294
MEX vs. MEXMET						-0.5 (-2.1 to 1.1); 0.527	0.155	-0.137-0.446
BMI, kg/m2	29.3 (4.7)	30.9 (4.3)	29.6 (4.3)	0.503	0.014*			
MEX vs. MET						-0.8 (-1.3 to 0.3); 0.004*	0.350	-0.092-0.793
MEXMET vs. MET						-0.5 (-0.9 to -0.1); 0.026*	0.302	-0.083-0.688
MEX vs. MEXMET						-0. 3(-0.7 to 0.1); 0.134	0.068	-0.223-0.360
Waist-to-hip ratio	0.90 (0.07)	0.98 (0.08)	0.91 (0.07)	0.002**	0.001*			
MEX vs. MET						-0.04 (-0.06 to -0.01); 0.001*	1.098	0.621-1.556
MEXMET vs. MET						-0.03 (-0.05 to -0.01); <0.001**	0.981	0.586-1.376
MEX vs. MEXMET						-0.00 (-0.02 to 0.01); 0.651	0.143	-0.149-0.434
Systolic BP, mmHg	126 (15)	147 (14)	129 (14)	0.011*	<0.001**			
MEX vs. MET						-22.2 (-28.6 to -15.9); <0.001**	1.431	0.944-1.918
MEXMET vs. MET						-18.4 (-24.0 to – 13.6); <0.001**	0.300	-0.085-0.686
MEX vs. MEXMET						-3.4 (-8.0 to 1.2); 0.147	0.211	-0.081-0.503
Diastolic BP, mmHg	71 (7)	79 (11)	73 (10)	0.439	0.007*			
MEX vs. MET						-7.0 (-11.4 to -2.7); 0.002*	0.936	0.476-1.397
MEXMET vs. MET						-4.7 (-8.3 to -1.1); 0.011*	0.592	0.204-0.980
MEX vs. MEXMET						-2.4 (-5.5 to 0.8); 0.144	0.213	-0.079-0.505
Total cholesterol, mg/dL	189 (41)	156 (50)	177 (39)	0.001***	0.602			
MEX vs. MET						10.7 (-12.3 to 33.7); 0.360	0.747	0.294-1.200
MEXMET vs. MET						9.5 (-9.8 to 28.8); 0.333	0.517	0.130-0.905
MEX vs. MEXMET						1.2 (-13.7 to 16.1); 0.874	0.304	0.012-0.596
HDL-cholesterol, mg/dL	49 (10)	43 (7)	50 (11)	0.110	0.882			

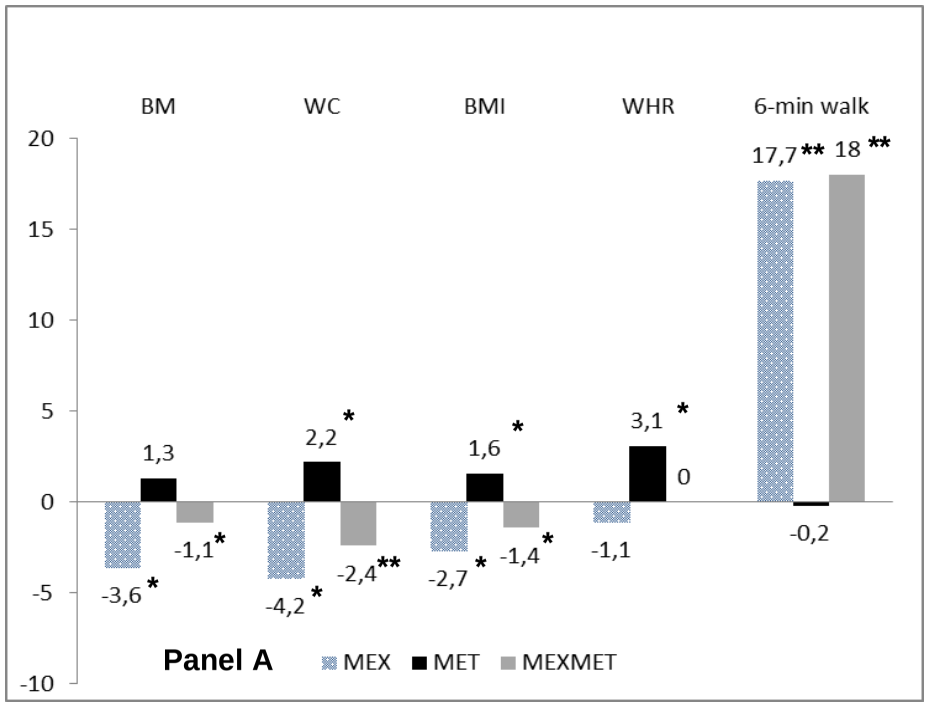
MEX vs. MET						1.3 (-3.8 to 6.4); 0.621	0.659	0.209-1.109
MEXMET vs. MET						0.8 (-3.7 to 5.2); 0.735	0.663	0.273-1.052
MEX vs. MEXMET						0.5 (-2.8 to 3.8); 0.754	0.093	-0.199-0.384
LDL-cholesterol, mg/dL	121 (36)	102 (23)	102 (32)	0.005*	0.418			
MEX vs. MET						-4.8 (-22.4 to 12.8); 0.592	0.589	0.141-1.037
MEXMET vs. MET						-8.9 (-23.6 to 5.8); 0.231	0.000	-0.384-0.384
MEX vs. MEXMET						4.1 (-7.5to 15.8); 0.485	-0.576	-0.872—0.281
Triglycerides, mg/dL	104 (44)	130 (99)	133 (74)	0.441	0.100			
MEX vs. MET						-26.6 (-60.1 to 6.9); 0.118	0.385	-0.058-0.828
MEXMET vs. MET						-3.6 (-32.5 to 25.3); 0.805	0.039	-0.423-0.346
MEX vs. MEXMET						-23.0 (-44.7 to -1.3); 0.038*	0.425	0.131-0.718
Glycaemia, mg/dL	114 (27)	142 (54)	137 (39)	0.090	0.008*			
MEX vs. MET						-19.6 (-37.6 to -1.6); 0.033*	0.733	0.281-1.186
MEXMET vs. MET						0.0 (-15.0 to 15.0); 0.995	0.121	-0.263-0.506
MEX vs. MEXMET						-19.7 (-32.2 to -7.2); 0.002*	0.629	0.332-0.925
HbA1c, %	6.21 (0.4)	6.76 (1.1)	6.75 (0.9)	0.521	0.179			
HbA1c, mmol/mol	44 (4.4)	50 (12.0)	50 (9.8)					
MEX vs. MET						-0.5 (-1.0 to 0.1); 0.114	0.770	0.316-1.224
MEXMET vs. MET						-0.0 (-0.4 to 0.4); 0.877	0.011	-0.374-0.395
MEX vs. MEXMET						-0.4 (-0.9 to 0.0); 0.068	0.664	0.368-0.961
6-min walk distance, m	521 (83)	426 (62)	545 (110)	0.004**	<0.001**			
MEX vs. MET						131.9 (87.8 to 175.9); <0.001**	1.240	0.764-1.715
MEXMET vs. MET						144.4 (107.9to 180.6); <0.001**	1.133	0.735-1.532
MEX vs. MEXMET						-12.5 (-44.5to 19.5); 0.440	0.230	-0.062-0.522

Data are expressed as mean (SD). * Differences between evaluations ($P \leq 0.05$). ** Differences between evaluations ($P \leq 0.001$). [a] Differences between groups adjusting for age, sex and baseline score values.

Table 4.2.3 – Percentage difference within groups from baseline to final 24 month intervention

Variables	Δ MEX %	Within Group Effect *P* Value	Δ MET %	Within Group Effect *P* Value	Δ MEXMET %	Within Group Effect *P* Value
Body mass, kg	-3.6	0.008*	1.3	0.247	-1.1	0.005*
Waist circumference, cm	-4.2	0.004*	2.2	0.021*	-2.4	<0.001**
BMI, kg/m2	-2.7	0.007*	1.6	0.048*	-1.4	0.016*
Waist-to-hip ratio	-1.1	0.343	3.1	0.005*	0	0.246
Systolic BP, mmHg	-11.1	<0.001**	5.4	0.001*	-0.7	<0.001**
Diastolic BP, mmHg	-11.3	<0.001**	2.5	0.416	-8.2	<0.001**
Total cholesterol, mg/dL	3.7	0.196	-8.3	0.489	-1.7	0.537
HDL-cholesterol, mg/dL	0	0.212	-11.6	0.492	0	0.214
LDL-cholesterol, mg/dL	-5.0	0.338	4.9	0.579	-3.9	0.328
Triglycerides, mg/dL	-21.2	0.019*	-0.8	0.763	2.3	0.547
Glycaemia, mg/dL	-12.3	0.003*	4.2	0.769	6.7	0.017*
HbA1c, %	-5.3	0.194	-0.7	0.908	0.01	0.579
6-min walk distance, m	17.7	<0.001**	-0.2	0.716	18.0	<0.001**

Data are expressed as mean (SD). * Differences between evaluations ($P \leq 0.05$). ** Differences between evaluations ($P \leq 0.001$).



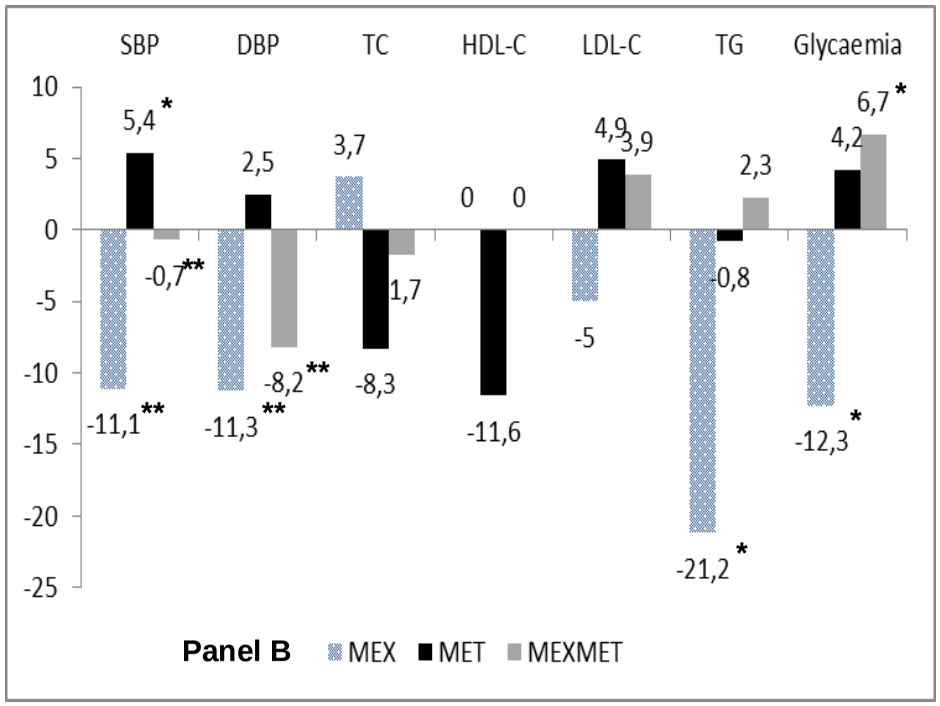


Figure 4.2.2- Differences within groups after 24-month intervention in anthropometric and cardiorespiratory fitness (Panel A) and in hemodynamic components (Panel B). * Differences between evaluations ($p \leq 0.05$). ** Differences between evaluations ($p \leq 0.001$). BM- Body mass; WC- Waist circumference; BMI; Body mass index; WHR- Waist-to-hip ratio; SBP- Systolic blood pressure; DBP- Dyastolic blod pressure; TC- Total cholesterol; HDL-C- High density lipoprotein cholesterol; LDL-C- Low density lipoprotein cholesterol; TG- Tryglicerides.

4.2.5. Discussion

The main finding of this longitudinal study of T2D older adults with comorbidity in early stage of the disease (mean HbA1c percentage < 7.5 %) is that MEX was the most successful and effective therapy to reduce cardiovascular risk, demonstrating the relative/single value of exercise as a multifactorial intervention. These results are consistent with previous lifestyle interventions (Griffin et al., 2011)(The Look AHEAD Research Group, 2010)(Diabetes Prevention Program Research Group, 2009), that produced long-term benefits on BM, CRF, CVD risk factors, diabetes management, and ultimately, morbidity and mortality. However, the independent effect of exercise has been difficult to determine because the lifestyle interventions usually combine exercise with caloric restrictions (Thompson et al., 2014), with pharmacological treatment (Stevens et al., 2015), or with another form of intervention (Thomas et al., 2006). Nevertheless, our results reinforce the importance of the independent effect of exercise training in the enhancement of the glucose control, presenting similar effects as with intensive metformin treatment (The Diabetes Prevention Program Research Group, 1999).

The majority of patients with T2D are overweight or obese (Inzucchi et al., 2012) but weight-loss have been shown to improve glycemic control, diminishing the risk of progression of T2D in overweight and obese older adults (Beavers et al., 2014; Grandy, Fox, & Hardy, 2013). In fact, even small decreases as little as 1 kg or 1% of the BM can benefit glycemic control, morbidity, and mortality (Ross et al., 2011), which means that the reductions in BM, WC, and BMI observed particularly in our MEX group, and with less extension in MEXMET group, are surely important to decrease the risk of aggravated morbidity and mortality. On the other hand, pharmacological treatments, including some oral antidiabetic agents, are usually associated with BM gains, which is considered a negative side effect (American Diabetes Association, 2016). In this context, metformin therapy is generally considered the first oral medication choice because the favorable effects on BM, low risk of hypoglycaemia, and low cost (Aschner et al., 2014). However, findings from the present study showed that MET therapy augmented BM, WC and BMI after 24-months intervention, indicating that long-term effects of metformin may have a pro-inflammatory anthropometric evolution that is still necessary to understand. Moreover, the effects of metformin on all-cause mortality, cardiovascular mortality or incidences of

myocardial infarction, stroke and heart failure have been studied in patients aged less than 30 years, which limits the generalization of the conclusions to older adults with multimorbidity (Lamanna, Monami, Marchionni, & Mannucci, 2011).

Hypertensive adults with T2D have benefits by reducing BP (Emdin et al., 2015)(Eckel et al., 2014). In fact, there is a strong linear association between BP and incidence of adverse outcomes for stroke, and J-shaped curve for mortality and cardiac events (Aschner et al., 2014). Consequently, pharmacological therapy has been recommended in individuals with diabetes for BP above 140/90 mmHg, along with non-pharmacological therapy. Nevertheless, exercise seems to have an effective effect for lowering BP in adults, including those with hypertension, on average by 2–5 mmHg in SBP and 1–4 mmHg in DBP (American Diabetes Association, 2016).

In the present study, after 24-months of intervention, the MEX group decreased surprisingly 14 mmHg in SBP and 8 mmHg in DBP, while the MET group increased 8 mmHg in SBP, and the MEXMET group increased 1 mmHg in SBP and decreased 6 mmHg in DBP. These results show the importance of exercising and also seem to point that in MEXMET group the pharmacological treatment mitigated the positive effects of the exercise on BP. This finding may be explained by the molecular effect of metformin on the T2D cardiovascular mechanism (Rena, Pearson, & Sakamoto, 2013), once an alteration on copper handling on T2D has been shown (Garth J S Cooper et al., 2005). Furthermore, copper sequestration has been shown to improve diabetes-related cardiovascular disease (G. J S Cooper et al., 2009), which might not occur with the metal-binding properties of metformin on the copper-ion transport or exchange (Rena et al., 2013). Contrarily, exercise has shown an anti-inflammatory status, by acting through several mechanisms involving inhibition of pro-inflammatory, and stimulation of anti-inflammatory pathway (Balducci et al., 2010).

MEXMET group increased surprisingly glycaemia in 6.7%, which may be explained by lifestyle choices, that is, since the participants are taking metformin to control the diabetes they expect full benefits from medicine, without taking care about other risk behaviors. Contrarily, MEX therapy diminished glycaemia in 12.3% highlighting the clinical benefits of exercise as the best strategy to glycemic control, minimizing the effects on an aggregate composite of macro-microvascular, and nonvascular end points, similar to what is produced with an intensive pharmaceutical intervention (Grandy et al., 2013).

The lipid profile is within recommended values not only at baseline but also at 24-months evaluation in all groups. Nevertheless, differences between groups disappeared after controlling to covariates of age, sex and baseline score values revealing that baseline scores differences influenced the 24-month evaluation in all groups, except in TG for MEX and MEXMET groups. These differences occurred because MEX group suffered an interesting reduction of 21% in TG, from 126 mg/dL to 104 mg/dL reversely to the 2 % augment in MEXMET group. TG has been emerged as significant risk factor (International Diabetes Federation, 2006) which could be of high importance. In fact, assuming that 1-mmol/L (18.02 mg/dL) augments in TG imply an increase of 13% in CVDs and 12% in all-cause mortality (J. Liu et al., 2013), our decrease of 1.22 mmol/L (22 mg/dL) in MEX group would represent a decrease of respectively 16% and 15% which highlight the clinical significance of exercise therapy (Srikanth & Deedwania, 2011).

Finally, results of the present study revealed very promising gains of 18% in CRF in both MEX and MEXMET groups. An interesting study (Cadeddu et al., 2014), showed that MET decreased the peak VO2 and the ability to work, unlike the exercise, that not only improved the CRF when used alone, but also canceled the negative effects of MET in MEXMET group. In fact, these conclusions are in line with our results and the physiologic mechanisms underlying aerobic exercise, including cardiac output and arteriovenous oxygen difference may explain the unchanged CRF in the MET and the improvements achieved by the MEXMET group in our intervention. Importantly, several studies have reported an inverse relationship between CRF and mortality risk in the context of T2D with and without additional risk factors (P. F. Kokkinos, Faselis, Myers, Panagiotakos, & Doumas, 2013; J. Myers et al., 2015; Pedersen & Saltin, 2015; Warburton & Bredin, 2016).

This longitudinal intervention research has several strengths including: a strong methodological design; a large community sample exclusively of older adults with T2D; a long-term supervised exercise training; pharmacologic treatment; an inclusion of several confounders relevant to older age and diabetes, such as sex and number of comorbidities. The major limitations of this study are: the different sample size within each group; and the lack of control of nutritional intake as potential confounder.

Future studies should be address to different types, intensity and volumes of exercise that may lead to different results (Eijsvogels et al., 2016; Warburton & Bredin,

2016). Additionally, a randomized controlled trial could explore whether these 3 treatment therapies may lead to greater and sustained multifactorial cardiovascular risk benefits particularly in the lipid profile in high-risk group, such as those with unstable diabetes.

Despite the limitations, regular exercise emerged as important therapy to manage T2D in older adults reducing overall CVD risk comparatively to a major reduction in one risk factor as occurs with the pharmacological treatment, because CVD risk factors tend to cluster leading to an deleterious additive/synergistic cumulative effect (Aschner et al., 2014). These clusters of risk factors have relevant clinical significance as explaining 59% of the CVD (Eijsvogels et al., 2016).

These results have important clinical implications, demonstrating that long-term MEX should be highly adopted into standard care and communities for older adults with T2D, particularly elderly with multimorbidity, as highly effective therapy to improve multifactorial cardiovascular profile and attenuate the negative effects of pharmacological therapy.

In summary, MEX it seems to be the most effective therapy decreasing multi-cardiovascular risk factors in early stage of T2D in older adults with multimorbidity and attenuated the adverse effects of the pharmacological therapy in the MEXMET treatment.

4.3. Study III- Exercise but not metformin improves health-related quality of life and mood states in older adults with type 2 diabetes

Exercise but not metformin improves health-related quality of life and mood states in older adults with type 2 diabetes

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4.3.1. Abstract

Objective- The aim of this cohort study is to analyze the effect of three types of treatment: i) exercise training with multicomponent exercise (E); ii) pharmacologic treatment with oral hypoglycemic drug – metformin (M); and iii) a combined therapy – exercise and metformin (E+M) on health related quality of life (HRQoL) and mood states in older adults with type 2 diabetes (T2D) with comorbidity in an early stage of the disease.

Methods- Participants (n = 284) underwent one of the following 3 conditions: i) E (n = 59) trained three times/week; ii) M (n = 30) used 850 mg of metformin twice daily; and iii) E+M (n = 195) combined exercise and metformin. Furthermore, participants completed baseline, and 2-year follow-up evaluations including a Short Form Health Survey 36, Profile of Mood States – Short Form, the health history questionnaires, anthropometric and blood biochemistry.

Results- E and E+M revealed improved mood states, with large effect size on the vigor domain, and moderate effect size in the anger, and total mood disturbance ($P< 0.05$) domains, in comparison with the M group. After the 24-months intervention, the E and E+M groups perceived better physical and mental HRQoL than the M group. Contrarily, the M group unchanged HRQoL domains ($P> 0.05$).

Conclusions- Metformin had no significant effect on self-referred HRQoL in T2D participants aged above 60 years, in an early stage of the disease. The E and E+M were the most effective long-term therapies to improve mood states, and HRQoL in older adults with T2D.

Keywords: diabetes, exercise, metformin, mood states, quality of life, older adults.

4.3.2. Introduction

Type 2 diabetes (T2D) is a high-impact complex multi-factorial disease that imposes a life-long physical and psychological burden (Aschner et al., 2014), particularly in older adults (Gadsby, 2014) due to the added effect of co-morbidities, utilization of diabeticogenic drugs, heterogeneous functional status, low exercise training and frequently disruptive negative effects such as restlessness, distress, anxiety, depression (Abdelhafiz & Sinclair, 2015; Chew, Sherina, & Hassan, 2015; Gadsby, 2014) and dementia (Cardoso et al., 2013; Chin et al., 2016; Gudala, Bansal, Schifano, & Bhansali, 2013; Rawlings et al., 2014; Sinclair et al., 2014) reducing the efficacy of T2D management and quality of life (QoL) (American Diabetes Association, 2016).

Metformin is the first-oral anti-diabetic agent recommended in T2D (American Diabetes Association, 2016) but its long-term use in interventional studies is quite inconsistent in health related quality of life (HRQoL) (Florez et al., 2012; Huang-Tzou, Chen, Wu, & Lin, 2016; Marrero et al., 2014).

On the other hand, exercise has been consistently considered the cornerstone of the non-pharmacologic treatment of T2D (American Diabetes Association, 2016) (Aschner et al., 2014), being also associated with improvements in HRQoL (V. Myers & McVay, 2013).

However, there are not studies measuring the isolated effects of exercise and metformin, or the combination of both, and HRQoL in older adults with T2D (Imayama, Alfano, et al., 2011; V. Myers & McVay, 2013; Nicolucci et al., 2012; Wadden, 2014) because the existing evidence included weight-loss adding to exercise training (Florez et al., 2012; Green et al., 2011; Marrero et al., 2014; Wadden, 2014), or measured different modes (V. Myers & McVay, 2013) and volumes of exercise (Nicolucci et al., 2012), or different time-lengths between 6 months (Marrero et al., 2014), 9 months (V. Myers & McVay, 2013), 12 months (Imayama, Alfano, et al., 2011; Nicolucci et al., 2012) up to 9.6 years (Wadden, 2014), or used different stages of the disease (Cadeddu et al., 2014; Florez et al., 2012; Marrero et al., 2014).

Furthermore, while the prevalence of mental health problems, including depression, cognitive impairment and dementia in older adults with T2D exceeds values found in the general population (American Diabetes Association, 2016; Aschner et al., 2014; Rhyner &

Watts, 2016; Sinclair et al., 2014), previously inconsistent results (Cadeddu et al., 2014; Florez et al., 2012; Marrero et al., 2014; V. Myers & McVay, 2013; Wadden, 2014), highlight the need to promote the appropriate strategies (E or M) to improve the mental component of QoL. Therefore, given the abovementioned discrepancies, the main purpose of this study is to analyze the independent effects of exercise training and metformin, or the combination of both treatments, on mood states and HRQoL in older adults with T2D in an early stage of the disease (HbA1c < 7.5%), after 24-months intervention.

4.3.3. Methods

4.3.3.1. Study participants

This non-randomized longitudinal cohort study, addressed to the effect of long-term multicomponent exercise training on several variables, involved an initial sample of 1473 community-dwelling older adults that were either referred to the study by their physician or self-referred from flyers distributed at community centers, media advertisements or word of mouth. Inclusion criteria included aged 60 years or above and T2D defined by the International Diabetes Federation (IDF) (Aschner et al., 2014) for at least 1 year. Participants were excluded if presented: (a) uncontrolled hypertension; (b) severe autonomic neuropathy; (c) severe peripheral neuropathy or history of foot lesions; (d) unstable proliferative retinopathy; (e) participants who were not under regular supervision of the treating physician for the period of the study evaluation; (f) known cancer or limited life expectancy, acute emergencies; (g) Parkinson's disease; (h) Alzheimer's disease; (i) dementia; (j) severe visual impairment; and (k) further reasons that made it impossible or highly problematic to participate and come to the follow-up visits, completing baseline and follow-up testing (program log $\geq$ 80 %).

After these procedures, 1189 ineligible participants were excluded; the major reasons included age under 60 years (n=229), no T2D diagnose (n=953) and type 1 diabetes (n=7); a sub-group of 284 physically independent (completed Senior Fitness Test battery (R.E. Rikli & Jones, 1999)) older adults with T2D for at least one year, and at an early stage of the disease (HbA1c < 7.5%) that fulfill all the requirements, were retained as eligible participants.

This group was then divided according with 3 therapy conditions: i) multicomponent exercise training (E; n = 59; 71% female); ii) oral hypoglycemic therapy-metformin (M; n = 30; 40% female); iii) combined therapy with exercise training and oral metformin (E+M; n = 195; 68% female).

The inclusion criteria in the E group was exercise training engagement, according the guidelines (American College of Sports Medicine, 2010); the M group used pharmacological therapy with oral hypoglycemic metformin (850 mg twice daily) to manage their disease; the E+M group combined both forms of treatment – multicomponent

exercise training, and oral hypoglycemic metformin therapy. After the 24-months intervention, 57 participants were lost to follow-up due to: the drop-out (2 from E, and 10 from E+M group); and the exercise program adherence under 80% (7 from E, and 38 from E+M group). The trial was completed by 80% of the participants (n = 227): E (n = 50); M (n = 30) and E+M group (n = 147). Participants lost to follow-up did not differ significantly in baseline characteristics from those completing the study.

4.3.3.2. Study procedures

At the preliminary meeting, participants were informed about the nature, benefits and risks of the study and completed a self-reported health history, the Medical Outcomes Study 36-item Short-form Health Study questionnaire (SF-36) and the Profile of Mood States Short-form questionnaire (POMS-SF). When needed, in the case of an illiterate participant, trained interviewers helped to complete the questionnaires. Furthermore, the assessments of the anthropometric profile, blood chemistry and cardiorespiratory fitness (CRF) components were carried out at the second meeting.

Baseline interviews, clinical examination and follow up testing occurred between September 2013 and September 2015 and were performed at the same order at the baseline and at the end of the follow-up.

Participants of the E and E+M group met 3 times/ week for one hour over the 24-months intervention period to perform the multicomponent exercise program in local centers of Santa Maria da Feira. The M and E+M group held trimester consultations with their physician, to control medication treatment. All participants were requested to maintain the same nutritional pattern and regular supervision with their physician during the follow-up intervention.

Methods and procedures were approved by Institutional Scientific Board of the University of Coimbra, local institution (Santa Maria da Feira County) and national ethics committees Data Protection Authority-CNPD; Health Administration from North Ethics Committee-ARS/Norte). All participants gave their written informed consent, consistent with Helsinki Declaration.

4.3.3.3. Multicomponent exercise program

The supervised multi-component exercise program consisted in three 60-min sessions/week, on three non-consecutive days. Aerobic, resistance, balance and flexibility were trained accordingly with these items: 5-10 minutes of warm-up, 20-30 minutes of aerobic, 15-20 minutes of resistance training, 10 minutes of balance, 10 minutes of stretching, and 5-10 minutes of cool down exercises. Aerobic exercise started with participants in a standing position (e.g., walking in place with arm movements), and progressively involved continuous movement of major muscles of the upper-extremity, performed alternately with movement of the lower-extremity. Time and intensity of aerobic exercise was increased from 20 minutes per session at 50% HRmax (maximum heart rate) to 30 minutes at 70% HRmax per session (American College of Sports Medicine, 2010).

Resistance training involved 5-8 exercises from large muscle groups, with 1-3 sets of 8-15 repetitions for each upper and lower body muscle group and came from participants' own BM or with light free weights. Intensity was set at 50% to 70% 1-repetition maximum (1-RM), with 90 to 120 seconds of rest between sets.

Balance training was also based on functional tasks required by older adults. Prior to cool down, participants performed stretching exercises designed to improve flexibility of the major muscle groups; each stretch was sustained between 15 and 30 seconds to the point of tightness, and repeated three times.

Over the 24-months intervention, progression increased every 6 weeks through augments on duration, repetitions, resistance, and/or difficulty (e.g., transition from sitting to standing to complete exercises). Exercise modifications such as reduced duration, number of repetitions, or use of an exercise auxiliary were recommended by the group instructor when needed. Exercise intensity is in line with the safety limits established to this disease group, reducing the risk of exercise induce myocardial infarction and sudden death(American College of Sports Medicine, 2010).

4.3.3.4. Subjective health-related quality of life

Self-perception of HRQoL was assessed using the SF-36 questionnaire, adapted and validated for the Portuguese population (Ferreira, 1998). This instrument with high

internal consistency and reliability (Ferreira, 1998) was developed to measure generic health status and HRQoL (Anderson et al., 1996), through the evaluation of eight health-related categories: Physical Functioning (PF), Role-Physical limitations (RP), Bodily Pain (BP), General Health (GH), Vitality (V), Social Functioning (SF), Role-Emotional limitations (RE) and Mental Health (MH). Two summary norm-based were derived from SF-36 and grouped as Physical Component Score (PCS) and Mental Component Score (MCS). A Total SF-36 Score was also calculated. The standardized summary scores for physical and mental components were calculated using the methods set out by Ware (Ware. Jr, 2000) and separately used as outcome measures. The scores range from 0 to 100, with higher values indicating better functional health and well-being.

4.3.3.5. Mood States

Mood profile was measured by the POMS-SF questionnaire, validated and adapted to the Portuguese population (Cruz & Mota, 1997). This self-report has a substantial internal consistency and reliability (Cruz & Mota, 1997) and describes feelings/mood states that participants have been feeling in the past week. The POMS-SF is a 22-item version of the standard 65-item form (McNair et al., 1971) being expressed into a Likert scale (0-4). Scores fit into 6 categories: tension-anxiety, depression, anger-hostility, vigor, fatigue and confusion. The global score (Total Mood Disturbance – TMD) is computed by subtracting the positive category (vigor) from the sum of the five negative dimensions (tension, depression, fatigue, anger and confusion) adding a constant (+100) in order to eliminate negative scores (Cruz & Mota, 1997), with higher values indicating worst mood profile.

4.3.3.6. Anthropometrics Profile

Stature was measured using a standard stadiometer to 0.1 cm in the upright position, with the participant´s back square against the wall and eyes looking straight ahead, without shoes. Body mass (BM) was measured by a calibrated digital balance-beam scale (SECA 770, Germany) with a precision nearest to 100 grams, with barefoot participants and in light clothing. Body mass index (BMI) was calculated dividing BM in kilograms by stature in meters squared.

4.3.3.7. Blood biochemistry

Trained nurses collected venous blood in the morning after 12 hours fasting. Glycaemia and glycated hemoglobin (HbA1c) were performed by standard methods by an accredited laboratory.

4.3.3.8. Cardiorespiratory Fitness

CRF was evaluated using the six-minute walk test (6MWT) performed on a flat 50-meters rectangular course, marked off in 5-meters segments (R.E. Rikli & Jones, 1999). The 6MWT were performed in the morning (8-10 hours), to minimize intraday variability, temperature effects, and biological rhythms. Participants were instructed to avoid vigorous exercise in the 2 hours prior to testing, to wear comfortable clothes and appropriate walking shoes, and to continue their usual medication. Recommended reasons for immediately stopping the 6MWT include chest pain, intolerable dyspnea, leg cramps, staggering, diaphoresis, and pale or ashen appearance.

4.3.3.9. Health history

Participants´ health history data were obtained by questionnaire, including age, gender, education level, living situation, exercise practice, smoking status and the presence and duration of several conditions like heart disease, hypertension, stroke, diabetes, dyslipidemia, osteoarthritis, pulmonary diseases, liver diseases, thyroid diseases, visual and audio problems, cancer, Parkinson's disease, Alzheimer disease, dementia or other comorbidities. Medication type and dosage were assessed by detailed questionnaire with visual confirmation of prescription drugs recorded by the study staff.

4.3.3.10. Statistical analysis

Baseline participant's characteristics was carried out with measures of mean and standard deviation (SD) for the following variables: age, comorbidities, BMI, glycaemia, HbA1c, CRF, depression, tension, fatigue, vigor, confusion, anger, TMD, PF, RP, BP, GH, V, SF, RE, MH, PCS, MCS, SF-36, anti-depressant and anti-anxiolytic medication.

Exploratory analysis of the data quality included the measure of the reliability, floor and ceiling effects and responsiveness of the participants at baseline.

The reliability in the study population was measured by the internal consistency using alpha Cronbach´s in the POMS-SF (Cronbach´s alpha = 0.716), the SF-36 (Cronbach´s alpha = 0.947), and in the medication variables (Cronbach´s alpha = 0.667) (Cohen, 1988).

Floor and ceiling effects were measured on the POMS-SF and the SF-36 domains at baseline, by the percentage of the participants who achieved the highest or the lowest scores, in total sample group and in the three sub-group.

To test responsiveness at baseline and after 24-months intervention, we calculated Hedges´s g effect size, providing a measure of the effect size weighted according to the relative different sample size within our study population (Hedges & Olkin, 1985). Standardized effects sizes were classified as small (<0.20), moderate (0.20-0.79) and large (>0.80) (Cohen, 1988). Responsiveness to change was also used to measure differences between groups after the intervention in the mood and HRQoL outcomes, by the estimation of the minimum important difference (MID) using the formula: MID = 1.96 x √2 x standard error of measurement (SEM) (Crosby et al., 2003). SEM was estimated for each group by the equation: SEM = SD x √(1-r), where r represents the reliability of the current study and was estimated by alpha Cronbach´s (Crosby et al., 2003). Additionally, correlational analyses examined associations between the global mood, HRQoL, anthropometric, CRF and blood biochemistry measures at baseline and after follow-up.

For all continuous variables, normality of distribution and homoscedastic variance were verified with Kolmogorov-Smirnov and Levene´s tests. One-way analysis of variance (ANOVA) test was used at the baseline analysis for comparisons between groups. Longitudinal changes within groups were tested with a two-way ANOVA for repeated measures. Differences between groups after 24-month intervention were performed with analysis of covariance (ANCOVA), adjusting to baseline score values, age and sex and with pairwise comparisons. Data analysis were performed using Statistical Package for the Social Sciences for Windows (IBM-SPSS, Inc. Chicago, IL, USA), software version 24. Statistical tests were 2-tailed and $P < 0.05$ was considered significant.

4.3.4. Results

4.3.4.1. Participants' characteristics

Overall 66% were female, mean (±SD) age was 70.6 (6.1) years, HbA1c percentage was 6.69 (1.0), BMI was 30.0 (4.6) Kg/m2 and mean comorbidity number was 1.79 (1.3), being the hypertension (93%), central obesity (74%), and hypertriglyceridemia (64%) the most prevalent comorbidities.

4.3.4.2. Baseline characteristics

At baseline (Table 4.3.1 and Table 4.3.2), the 3 therapy groups had similar mood states and HRQoL, except for RP ($P = 0.043$), PCS ($P = 0.031$), and anti-depressant and anti-anxiolytic medication ($P < 0.001$). The E group comprised more females (71%), which were older (71.4 ± 6.4 years-old) and had the highest anti-depressant and anti-anxiolytic medication consumption ($P < 0.001$) than the other 2 therapy groups. The E+M group perceived better RP (10.7; $P = 0.029$) and PCS (9.0; $P = 0.014$) than the M group.

Completeness of data was 100%, there were no missing responses but there were high floor effects (>20%) for tension, fatigue and confusion scales in the POMS-SF, and high ceiling effects on the RP and SF domains in the SF-36 for all groups.

4.3.4.3. Differences within group from baseline to 24-months follow-up

After the 24-months of intervention (Table 4.3.3), the E and the E+M groups had benefits on depressive mood, vigor, anger, and TMD ($P < 0.05$), whereas the M group decreased the anger but increased the tension ($P \leq 0.01$). All the 3 therapy groups augmented the fatigue mood state ($P < 0.01$).

The E and E+M therapies improved the HRQoL, specifically the PF and PCS ($P < 0.01$). The E group also increased GH, whereas the E+M group also augmented RP, SF, RE, and Total SF-36 ($P < 0.05$). Furthermore, both therapies increased the BP ($P < 0.05$). The M group did not change any component of the HRQoL ($P > 0.05$).

Table 4.3.1- Descriptive baseline characteristics (*N*=284)

Variables	Total (*N*=284)	Floor-Ceiling Effect (%)	E (n=59)	Floor-Ceiling Effect (%)	M (n=30)	Floor-Ceiling Effect (%)	E+M (n=195)	Floor-Ceiling Effect (%)	Group Effect *P* values
Female, n	187	-	42	-	12	-	133	-	0.006*
Age, years	70.2 (6.1)	-	71.4 (6.4)	-	68.1 (4.3)	-	70.7 (6.1)	-	0.044*
Comorbid diseases, *n*	1.8 (1.4)	-	1.9 (1.3)	-	2.2 (1.5)	-	1.7 (1.3)	-	0.070
BMI, Kg/m^2	30.0 (4.6)	-	30.1 (4.3)	-	30.4 (4.2)	-	30.0 (4.7)	-	0.805
Glycaemia, mg/dL	128.6 (31.2)	-	128 (27)	-	136 (47)	-	128 (33)	-	0.547
HbA1c, %	6.7 (1.0)	-	6.54 (0.7)	-	6.81 (1.4)	-	6.67 (1.0	-	0.800
6-min walk test, m	441 (113)	-	429 (127)	-	427 (76)	-	447 (113)	-	0.430
MOOD STATES									
Depression	3.9 (3.3)	17.2-0.3	3.9 (3.1)	11.9-0.0	3.9 (3.2)	16.7-0.0	3.9 (3.3)	19.0-0.5	0.980
Tension	3.0 (3.5)	33.8-0.0	2.9 (3.5)	37.3-0.0	2.5 (2.7)	36.7-0.0	3.1 (3.6)	32.0-0.0	0.632
Fatigue	1.4 (1.9)	49.3-0.0	1.4 (1.9)	52.5-0.0	1.7 (1.8)	30.0-0.0	1.3 (2.0)	52.0-0.0	0.498
Vigor	9.1 (3.4)	0.0-0.0	8.9 (2.8)	8.5-0.0	8.2 (2.9)	0.0-0.0	9.3 (3.6)	0.0-0.0	0.242
Anger	3.7 (3.5)	19.7-0.4	3.7 (3.3)	18.6-0.0	5.0 (5.0)	16.7-0.0	3.6 (3.3)	19.5-0.5	0.128
Confusion	1.3 (1.6)	45.9-0.0	1.3 (1.7)	49.2-0.0	1.5 (1.7)	43.3-0.0	1.3 (1.6)	45.1-0.0	0.829
Total Mood Disturbance	104.2 (11.9)	0.0-0.0	104.2 (12.2)	0.0-0.0	106.6 (12.5)	0.0-0.0	104.6 (12.1)	0.0-0.0	0.528
HRQoL									
Physical Functioning	79 (21)	0.0-20.0	78 (21)	0.0-23.7	73 (25)	0.0-20.0	79 (20)	0.0-19.0	0.284
Role Physical	74 (23)	0.3-26.3	76 (24)	1.7-35.6	64 (27)	0.0-13.3	75 (22)	0.0-26.7	0.043*
Bodily Pain	67 (25)	0.3-20.0	68 (26)	0.0-20.3	60 (29)	3.3-13.3	68 (23)	0.0-20.5	0.195
General Health	58 (18)	0.0-1.7	59 (18)	0.0-3.4	53 (16)	0.0-10.0	59 (19)	0.0-1.5	0.270
Vitality	67 (20)	0.0-10.0	68 (21)	0.0-10.2	61 (20)	0.0-6.7	68 (20)	0.0-10.8	0.193
Social Functioning	82 (21)	0.0-43.8	81 (22)	0.0-45.8	78 (29)	0.0-13.3	83 (19)	0.0-43.1	0.509
Role Emotional	76 (23)	0.3-12.4	79 (23)	0.0-13.7	73 (24)	0.0-10.0	76 (23)	0.5-12.3	0.412
Mental Health	73 (20)	0.0-11.7	73 (21)	0.0-13.6	70 (22)	0.0-13.3	74 (19)	0.0-11.3	0.501
Physical Component Score	69 (18)	0.0-0.0	70 (18)	0.0-0.0	61 (21)	0.0-0.0	70 (17)	0.0-0.0	0.031*
Mental Component Score	75 (17)	0.0-0.0	75 (19)	0.0-0.0	70 (19)	0.0-0.0	75 (17)	0.0-0.0	0.342
Total SF-36	72 (16)	0.0-0.0	73 (17)	0.0-0.0	66 (19)	0.0-0.0	73 (16)	0.00.0	0.096
Anti-depressant medication, *n*	0.2 (0.4)	-	0.8 (0.9)	-	0.1 (0.4)	-	0.2 (0.4)	-	<0.001**
Anti-anxiolytic medication, *n*	0.4 (0.6)	-	0.9 (0.1)	-	0.2 (0.1)	-	0.3 (0.0)	-	<0.001**

Data are expressed as mean (SD). * Differences between evaluations ($P \leq 0.05$). ** Differences between evaluations ($P \leq 0.001$).

Table 4.3.2- Differences between groups at baseline in mood states and HRQoL using one-way ANOVA (*N*=284)

Variables	E vs M	*P* Values	Effect Size	E+M vs M	*P* Values	Effect Size	E vs E+M	*P* Values	Effect Size
MOOD STATES									
Depression	-0.1 (-1.8 to 1.6)	0.999	0.000	0.0 (-1.4 to 1.4)	1.000	0.000	-0.1 (-1.2 to 1.0)	0.996	0.000
Tension	0.4 (-1.5 to 2.3)	0.933	-0.123	0.6 (-0.9 to 2.2)	0.679	-0.172	-0.2 (-1.4 to 1.0)	0.960	0.056
Fatigue	-0.4 (-1.4 to 0.7)	0.780	0.161	-0.5 (-0.4 to 1.3)	0.486	0.203	0.1 (-0.6 to 0.8)	0.986	-0.050
Vigour	0.7 (-2.5 to 1.1)	0.717	-0.247	1.1 (-2.6 to 0.4)	0.214	-0.313	-0.4 (-1.5 to 0.8)	0.828	0.116
Anger	-1.3 (-3.1 to 0.6)	0.279	0.329	-1.4 (-2.9 to 0.1)	0.080	0.392	0.1 (-1.1 to 1.3)	0.991	-0.030
Confusion	-0.2 (-1.1 to 0.7)	0.915	0.118	-0.2 (-0.9 to 0.5)	0.897	0.124	-0.0 (-0.6 to 0.5)	0.999	0.000
Total Mood Disturbance	-2.4 (-8.8 to 4.0)	0.742	0.195	-2.7 (-7.9 to 2.5)	0.523	0.165	0.3 (-3.9 to 4.4)	0.999	0.033
HEALTH RELATED QUALITY LIFE									
Physical Functioning	5.6 (-5.6 to 16.8)	0.550	-0.233	6.6 (-2.5 to 15.7)	0.231	-0.290	-1.0 (-8.3 to 6.2)	0.981	0.049
Role Physical	12.0 (-0.1 to 24.2)	0.054	-0.479	10.7 (0.8 to 20.6)	0.029*	-0.484	1.3 (-6.6 to 9.1)	0.971	0.000
Bodily Pain	8.3 (-4.6 to 21.2)	0.326	-0.296	8.6 (-1.9 to 19.1)	0.145	-0.335	-0.3 (-8.6 to 8.1)	1.000	0.000
General Health	5.7 (-4.1 to 15.4)	0.416	-0.346	5.8 (-2.2 to 13.7)	0.224	-0.322	-0.1 (-6.4 to 6.2)	1.000	0.000
Vitality	7.5 (-3.4 to 18.4)	0.267	-0.339	7.1 (-1.8 to 15.9)	0.158	-0.350	0.4 (-6.6 to 7.5	0.998	0.102
Social Functioning	3.3 (-7.9 to 14.6)	0.855	-0.122	4.7 (-4.4 to 13.9)	0.516	-0.243	1.4 (-8.6 to 5.9)	0.956	-0.130
Role Emotional	6.8 (-5.4 to 19.0)	0.456	-0.257	3.8 (-6.1 to 13.7)	0.735	-0.130	3.0 (-4.9 to 10.8)	0.747	0.051
Mental Health	2.8 (-7.7 to 13.4)	0.888	-0.145	4.4 (-4.2 to 13.0)	0.523	-0.206	-1.6 (-8.4 to 5.3)	0.927	0.000
Physical Component Score	8.9 (-0.4 to 18.2)	0.063	-0.472	9.0 (-16.6 to -1.4)	0.014*	-0.512	-0.0 (-6.0 to 5.9)	1.000	0.000
Mental Component Score	5.1 (-4.1 to 14.3)	0.461	-0.263	4.9 (-2.6 to 12.4)	0.320	-0.289	0.2 (-5.7 to 6.2)	1.000	0.000
Total SF-36	7.0 (-1.8 to 15.7)	0.158	-0.396	6.9 (-0.2 to 13.9)	0.061	-0.426	0.1 (-5.5 to 5.7)	1.000	0.000
Anti-depressant medication	0.7 (0.4 to 0.9)	<0.001**	-0.909	0.0 (-0.2 to 0.2)	0.994	-0.250	0.6 (0.5 to 0.8)	<0.001**	-1.112
Anti-anxiolytic medication	0.6 (0.3 to 0.9)	<0.001**	1.000	0.0 (-0.2 to 0.3)	0.994	-0.773	0.6 (0.4 to 0.8)	<0.001**	-3.362

Data are expressed as mean (SD). * Differences between evaluations ($P \leq 0.05$). ** Differences between evaluations ($P \leq 0.001$).

Table 4.3.3- Differences within groups from baseline to 24 month evaluation using two-way ANOVA (*N*=227)

	E (n=50)			M (n=30)			E+M (n=147)		
Variables	Baseline	24-months	*P* Values	Baseline	24-months	*P* Values	Baseline	24-months	*P* Values
MOOD STATES									
Depression	3.8 (2.7)	2.2 (3.1)	0.001*	4.0 (3.2)	2.9 (2.2)	0.143	4.1 (3.2)	2.4 (2.9)	<0.001**
Tension	2.8 (3.5)	3.3 (2.8)	0.372	2.6 (2.8)	4.3 (2.5)	0.011*	3.2 (3.4)	3.4 (2.9)	0.537
Fatigue	1.3 (1.8)	2.5 (2.5)	0.003*	1.8 (1.8)	3.8 (3.1)	0.006*	1.3 (2.1)	3.1 (2.8)	<0.001**
Vigor	9.0 (2.8)	10.5 (2.8)	0.004*	8.3 (3.0)	8.0 (2.2)	0.513	9.6 (3.9)	10.3 (2.7)	0.046*
Anger	3.6 (3.0)	0.7 (1.3)	<0.001**	5.0 (5.0)	1.9 (2.7)	0.005*	3.6 (3.2)	0.6 (1.2)	<0.001**
Confusion	1.2 (1.7)	1.0 (1.3)	0.482	1.5 (1.7)	1.3 (1.1)	0.779	1.3 (1.6)	1.3 (1.4)	0.871
Total Mood Disturbamce	104 (11)	99 (10)	0.008*	107 (13)	106 (9)	0.788	104 (11)	101 (10)	<0.001**
HEALTH RELATED QUALITY LIFE									
Physical Functioning	79.6 (10.1)	86.4(13.3)	0.004*	73.5 (25.5)	71.6 (19.5)	0.644	79.5 (20.6)	86.4 (13.3)	<0.001**
Role Physical	77.7 (24.3)	80.7 (20.7)	0.441	63.0 (26.9)	63.7 (24.1)	0.880	74.5 (21.7)	79.9 (22.1)	0.025*
Bodily Pain	66.9 (26.0)	75.8 (21.1)	0.017*	59.6 (29.9)	64.8 (21.1)	0.162	67.9 (23.8)	72.1 (23.0)	0.032*
General Health	59.1 (18.1)	64.6 (18.1)	0.033*	53.5 (16.2)	48.1(13.8)	0.078	59.0 (19.5)	61.2 (16.7)	0.182
Vitality	68.8 (20.5)	71.0 (18.5)	0.509	60.5 (20.8)	54.4 (18.7)	0.076	68.2 (20.2)	66.8 (17.2)	0.383
Social Functioning	83.5 (22.0)	88.8 (16.0)	0.131	77.3 (29.6)	77.0 (18.6)	0.955	83.3 (19.5)	88.6 (16.7)	0.002*
Role Emotional	81.8 (22.0)	84.8 (17.5)	0.380	73.6 (24.3)	72.7 (21.1)	0.978	74.8 (23.4)	80.1 (21.2)	0.017*
Mental Health	73.3 (20.7)	75.9 (17.7)	0.430	70.0 (22.7)	62.5 (23.7)	0.065	74.4 (18.8)	73.9 (17.2)	0.773
Physical Component Score	70.8 (17.1)	76.9 (15.0)	0.010*	61.3 (21.1)	62.1 (16.0)	0.739	70.3 (17.0)	74.8 (15.1)	0.001*
Mental Component Score	76.8 (17.8)	80.1 (14.8)	0.257	70.1 (19.5)	66.6 (17.1)	0.129	75.1 (16.2)	77.3 (14.3)	0.113
Total SF-36	74.8 (16.6)	78.5 (14.3)	0.065	65.7 (19.1)	64.2 (15.9)	0.371	72.7 (15.6)	76.1 (13.9)	0.006*
Anti-depressant medication	0.80 (0.87)	0.80 (0.87)	1.000	0.13 (0.35)	0.07 (0.25)	0.161	0.15 (0.36)	0.15 (0.36)	1.000
Anti-anxiolytic medication	0.86 (0.84)	0.80 (0.87)	0.209	0.23 (0.43)	0.27 (0.45)	0.573	0.26 (0.44)	0.24 (0.43)	0.372

Data are expressed as mean (SD). * Differences between evaluations ($P \leq 0.05$). ** Differences between evaluations ($P \leq 0.001$).

4.3.4.4. Differences between groups after 24 month intervention

At 24-months evaluation (Table 4.4.4), the E and E+M groups revealed improved mood states, with large effect size on the vigor domain, and moderate effect size in the anger, and TMD ($P < 0.05$) domains, in comparison with the M group. Additionally, after the 24-months intervention, the E and E+M groups perceived better HRQoL than the M group, with moderate and large effect sizes, specifically on the PF, RP, GH, V, SF, MH, PCS, MCS, and Total SF-36 ($P < 0.05$). The E group also had higher RE than the M group. The E group maintained higher anti-depressant medication than the M and E+M groups ($P < 0.01$), as it was observed at baseline.

4.3.4.5. Correlations among global variables

CRF was associated with TMD ($r = -0.130$; $P = 0.029$), PCS ($r = 0.298$; $P \leq 0.001$), MCS ($r = 0.256$; $P \leq 0.001$) and Total SF-36 ($r = 0.293$; $P \leq 0.001$). BMI was associated with TMD ($r = 0.146$; $P = 0.013$), PCS ($r = -0.195$; $P = 0.001$), MCS ($r = -0.152$; $P= 0.010$), and Total SF-36 ($r = -0.185$; $P = 0.002$). These correlations, observed at baseline, were kept at the 24-months evaluation. Glycaemia and HbA1c were not associated with mood states or HRQoL **(**Table 4.3.5).

Table 4.3.4- Differences between groups, effect size and minimum importance difference after 24-month intervention using ANCOVA adjusted to baseline values, age and sex (*N*=227)

Variables	E vs M	*P* Values	Effect Size	MID	E+M vs M	*P* Values	Effect Size	MID	E vs E+M	*P* Values	Effect Size	MID	Differences Between Groups [a] *P* Values
MOOD STATES													
Depression	-1.1 (-2.4 to 0.2)	0.670	0.251	0.99	-1.2 (-2.3 to -0.1)	0.038*	0.179	0.85	-0.3 (-1.2 to 0.6)	0.551	0.068	0.68	0.241
Tension	-1.2 (-2.5 to 0.1)	0.072	0.372	0.97	-1.0 (2.2 to 0.3)	0.204	0.317	0.84	-0.0 (-0.9 to 0.9)	0.451	0.035	0.67	0.107
Fatigue	-1.7 (-3.0 to -0.5)	0.009*	0.474	0.97	-1.1 (-2.2 to 0.1)	0.062	0.245	0.84	-0.7 (-1.6 to 0.2)	0.133	0.220	0.66	0.031*
Vigor	2.5 (1.3 to 3.8)	<0.001**	0.965	0.91	2.1 (1.1 to 3.2)	<0.001**	0.877	0.79	0.4 (-0.4 to 1.2)	0.335	0.073	0.63	<0.001**
Anger	-1.1 (-1.8 to -0.4)	0.003*	0.615	0.54	-1.3 (-1.9 to -0.6)	<0.001**	0.837	0.47	0.2 (-0.3 to 0.7)	0.516	0.082	0.37	0.001*
Confusion	-0.4 (-1.0 to 0.2)	0.193	0.244	0.44	-0.1 (-0.7 to 0.4)	0.574	0.000	0.38	-0.3 (-0.7 to 0.2)	0.232	0.218	0.30	0.358
Total Mood Disturbance	-7.0 (11.2 to -2.8)	0.001*	0.717	3.16	-5.5 (-9.1 to -1.8)	0.003*	0.568	2.73	-1.5 (-4.4 to 1.4)	0.297	0.138	2.16	0.004*
HRQoL													
Physical Functioning	14.0 (8.3 to 19.7)	<0.001**	0.929	1.84	13.7 (8.8 to 18.6)	<0.001**	1.019	1.59	0.3 (-3.7 to 4.1)	0.897	0.000	1.24	<0.001**
Role Physical	15.0 (5.0 to 25.0)	0.003*	0.771	3.23	14.2 (5.6 to 22.8)	0.001*	0.722	2.77	0.8 (-5.8 to 7.5)	0.809	0.037	2.15	0.004*
Bodily Pain	8.8 (-0.5 to 18.1)	0.064	0.521	3.02	4.4 (-3.6 to 12.5)	0.279	0.322	2.61	4.4 (-2.0 to 10.7)	0.174	0.164	2.04	0.162
General Health	13.4 (6.2 to 20.7)	<0.001**	0.994	2.32	10.2 (3.9 to 16.4)	0.002*	0.806	2.03	3.3 (-1.7 to 8.2)	0.194	0.199	1.60	0.001*
Vitality	15.2 (7.5 to 22.9)	<0.001**	0.894	2.49	11.0 (4.4 to 17.6)	0.001*	0.710	2.15	4.2 (-1.0 to 9.4)	0.110	0.240	1.68	0.001*
Social Functioning	10.8 (3.2 to 18.5)	0.006*	0.693	2.48	10.6 (4.0 to 17.2)	0.002*	0.681	2.15	0.2 (-5.0 to 5.5)	0.929	0.012	1.69	0.006*
Role Emotional	11.7 (2.9 to 21.0)	0.015*	0.639	3.03	8.7 (0.7 to 16.6)	0.034	0.349	2.59	3.0 (-3.4 to 9.4)	0.356	0.231	2.07	0.046*
Mental Health	11.2 (3.0 to 19.3)	0.008*	0.664	2.64	8.9 (1.9 to 16.0)	0.013*	0.618	2.28	2.2 (-3.3 to 7.8)	0.429	0.115	1.80	0.021*
Physical Component Score	10.9 (4.5 to 17.0)	0.001*	0.962	1.97	8.9 (3.6 to 14.2)	0.001*	0.833	1.72	1.9 (-2.2 to 6.0)	0.354	0.139	1.33	0.002*
Mental Component Score	11.7 (5.1 to 18.2)	0.001*	0.859	2.12	9.4 (3.8 to 15.1)	0.001*	0.723	1.82	2.2 (-2.2 to 6.6)	0.322	0.194	1.43	0.001*
Total SF-36	11.1 (5.2 to 17.1)	<0.001**	0.958	1.93	9.2 (4.1 to 14.3)	<0.001**	0.835	1.66	1.9 (-2.1 to 5.9)	0.345	0.171	1.29	0.001*
Anti-depressant medication	0.2 (0.1 to 0.5)	0.002*	1.038	0.11	0.1(-0.0 to 0.2)	0.088	0.232	0.09	0.1 (0.0 to 0.2)	0.013*	1.218	0.07	0.006*
Anti- anxiolytic medication	0.0 (-0.1 to 0.2)	0.562	0.717	0.12	-0.0 (-0.2 to 0.1)	0.697	0.069	0.11	0.1 (-0.0 to 0.2)	0.181	0.980	0.08	0.400

Data are expressed as mean (SD). * Differences between evaluations ($P \leq 0.05$). ** Differences between evaluations ($P \leq 0.001$). [a] Differences between groups after 2 years, adjusted to baseline values, age and sex.

Table 4.3.5- Correlations between variables at baseline and at 24-months evaluation

Variables	Comorbidities	BMI	Glycaemia	HbA1c	CRF	TMD	PCS	MCS	TSF-36
Baseline									
Comorbidities	1.000								
BMI	0.133*	1.000							
Glycaemia	0.010	0.045	1.000						
HbA1c	-0.031	0.256*	0.540**	1.000					
CRF	-0.210**	-0.300**	-0.014	0.085	1.000				
TMD	0.185*	0.146*	-0.019	0.035	-0.130*	1.000			
PCS	-0.319**	-0.195*	-0.024	0.111	0.298**	-0.460**	1.000		
MCS	-0.332**	-0.152*	-0.012	0.089	0.256**	-0.543**	0.733**	1.000	
TSF-36	-0.345**	-0.185*	-0.017	0.106	0.293**	-0.532**	0.942**	0.941**	1.000
Follow- up									
Comorbidities	1.000								
BMI	0.187*	1.000							
Glycaemia	-0.071	0.268*	1.000						
HbA1c	-0.064	0.133	0.466**	1.000					
CRF	-0.270**	-0.262**	-0.066	0.093	1.000				
TMD	0.134*	0.065	0.144	0.007	-0.208*	1.000			
PCS	-0.090	-0.248*	-0.125	0.053	0.370**	-0.467**	1.000		
MCS	-0.105	-0.190*	-0.143	-0.017	0.362**	-0.585**	0.784**	1.000	
TSF-36	-0.103	-0.234*	-0.143	0.016	0.386**	-0.558**	0.946**	0.942**	1.000

BMI- Body mass index; HbA1c- Glycated hemoglobin; CRF- Cardiorespiratory fitness; TMD- Total mood disturbance; PCS- Physical component score; MCS- Mental component score; TSF-36 - Total SF-36; ** Significant $P \leq 0.001$; * Significant $P \leq 0.05$.

4.3.5. Discussion

The main finding of the current study was that the exercise training alone or combined with metformin are more effective therapies than isolated metformin therapy to improve the mood states and HRQoL in older adults with T2D. To our knowledge, this is the first study to analyze the independent effect of E and M on mood states and HRQoL in older adults with T2D, who generally report reduced QoL than individuals without diabetes (Green et al., 2011).

After 24-months of intervention, the E and E+M groups revealed extensive gains on mood, reducing the negative states like tension, anger and TMD and largely augmenting positive state of vigor. These results have significant clinical implications because diabetes-related distress may lead to poor self-care activity, diminished disease control, increased risk of both hypoglycemia and hyperglycemia, worst HRQoL, that can progress to depression and increased risk of cognitive impairment and dementia (Cardoso et al., 2013; Chin et al., 2016; Gudala et al., 2013; Rawlings et al., 2014; Sheen & Sheu, 2016; Sinclair et al., 2014; Van Der Heijden, Van Dooren, Pop, & Pouwer, 2013).

Previous reports in individuals with T2D have observed deterioration on the physical domain of HRQoL after M therapy, but also after lifestyle modification with weight-loss and exercise training (Florez et al., 2012; Marrero et al., 2014). Our results, however, revealed large gains in physical HRQoL domains in the E and E+M groups, particularly on PF, GH and PCS, and unchanged HRQoL in M group.

Moreover, the associations found in our study between CRF, BMI and PCS, and the time of diagnose could also explain these contradictory results because previous studies (Marrero et al., 2014) reported greater declines immediately post-diagnosis and at 6-months post-diagnosis in PCS scores; others have suggested that the physical component is affected by obesity (Florez et al., 2012), but also by the type (Reid et al., 2010), volume (Nicolucci et al., 2012), and time-length of exercise training intervention (Imayama, Alfano, et al., 2011; Marrero et al., 2014; V. Myers & McVay, 2013; Nicolucci et al., 2012; Wadden, 2014).

In our study, the E and E+M groups, combining both aerobic and resistance training during 24-months, successfully improve all physical HRQoL scores, demonstrating the benefic effect of improved CRF to reduce diabetes burden and improving participants

perceived functioning in physical activities required for daily living following one year of diagnose.

To our knowledge, this is the first study to successfully prove that exercise alone is effective to promote gains in mental HRQoL in older adults with T2D, improving the emotional and social engagement in a long-term perspective (Baernholdt, Hinton, Yan, Rose, & Mattos, 2012). Actually, after the 24-months of interventions we obtained large gains in V and MCS and moderate gains in the SF, RE and MH scales in the E reversely to the M group. Differences between groups at the 24-months evaluation doubled in the V, SF, RE, MH and MCS scores comparatively to baseline. Nevertheless, due to the high ceiling effect at baseline of the SF domain, our explanatory capacity is reduced by the sensitivity ability of this instrument to evaluate exercise effect. In fact, floor and ceiling effects negatively impact the sensitivity and responsiveness of the questionnaire, reducing the value for measuring the change effects or discriminating between participants with small differences in health status (Crosby et al., 2003).

Despite our improvements in mental HRQoL that are consistent with those observed by Nicolucci and colleagues (Nicolucci et al., 2012), several other works have not observed any changes (Florez et al., 2012; Marrero et al., 2014; V. Myers & McVay, 2013) or even observed lower benefits in the exercise training group than in the control group (Reid et al., 2010). These discrepancies may be due, as previously mentioned, to different exercise training modalities, characteristics and stage of the disease, time-length of intervention, anthropometric and CRF levels. Additionally, ageing is associated with changes in the dynamic functions of the hypothalamic-pituitary axis that may be modified by exercise training (Janssen, 2016) and may impact the mental HRQoL outcomes.

Finally, the results of the present study seem to support the idea that exercise training may mitigate the negative effects of T2D pharmacologic treatment in older adults with comorbidities, because throughout the intervention period, the M treatment showed a decrease in the physical and mental HRQoL domains and in mood states, reversely to the E+M that enhance all HRQoL sub-scales and mood states, decreasing the risk for therapeutic competition, poor adherence to treatment and adverse drug events due not only to the number of medications, but also to the treatment and regimen complexity (Bell & Saraf, 2016).

The longitudinal design of the present study has several strengths including the large community sample exclusively composed by older adults with T2D, long-term supervised exercise training intervention, and utilization of well-validated instruments. Nevertheless, some limitations can also be pointed including the different group sample sizes, the non-randomized methodological design, and the reliance on generic measures of HRQoL like SF-36, that may impact on the results, because it might not be specifically addressed to dimensions of HRQoL that are linked to the diagnosis of diabetes (Speight et al., 2009). Future studies on this topic should use a randomized controlled trial design, testing for other comorbidities, long-standing diabetes and other treatment types use (different medication), to strengthen the generalization to other older adults T2D populations.

Findings of the present study may have important clinical implications because it is the first long-term investigation to access how an older adult with T2D perceived their mood states and HRQoL after different treatment modalities following diagnosis.

Such information is critical to build a successful, cost-effective T2D management plan where exercise training should appear as the primary effective therapy, through the implementation and promotion of exercise programs into the communities and health care systems, to improve diabetes burden, increasing effective ways to regulate their physical, mental and emotional responses (Helvik et al., 2016).

Additionally, this study proved the important role of exercise training mediation in HRQoL and mood states when pharmacologic treatment like M therapy is employed, counteracting the absence or even the negative effects of drug therapy, contributing to an increasing patient-treatment compliance, which is known to be a crucial component in the clinical management (Aschner et al., 2014; Cadeddu et al., 2014).

In summary, the current study provides evidence that metformin has no effect on HRQoL; furthermore, older adults with T2D in an early stage of the disease are likely to benefit from adopting a regular exercise training regimen to promote positive mood states and HRQoL

4.4. Study IV- Exercise training improves functional status in hypertensive older adults under angiotensin converting enzymes inhibitors medication

Exercise training improves functional status in hypertensive older adults under angiotensin converting enzymes inhibitors medication

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4.4.1. Abstract

Objective- The study aims to analyze the effect of three types of treatment on functional status, and cardiovascular risk outcomes in hypertensive older adults with comorbidities.

Methods- Participants (n = 418) underwent one of the following 3 conditions: i) multicomponent exercise training 3 times/week (MEX; n = 116); ii) angiotensin converting enzyme inhibitors used mono-dose daily (ACEi; n = 70); iii) combined exercise and ACEi drugs (ACEiMEX; n = 232). The trial was completed by 82% of the participants (*n* = 342): MEX (*n* = 90); ACEi (*n* = 66); ACEiMEX (*n* = 186). Baseline and 2-year follow-up evaluations included the Senior Fitness Test battery, Short Form Health Survey 36 (SF-36), the health history questionnaires, anthropometric and hemodynamic profile.

Results- MEX and ACEiMEX improved all physical functional status outcomes, decreased systolic (SBP) and diastolic blood pressure ($p<0.001$) and augmented the physical functioning, role physical and physical component score (PCS) ($p<0.05$), but also bodily pain ($p<0.05$). The ACEi group reduced the upper body strength, upper and lower body flexibility and aerobic endurance ($p<0.05$); worsened the anthropometric profile, and SBP ($p<0.001$); and decreased general health and PCS ($p<0.05$).

Conclusions- The improvement of the physical functioning and HRQoL in older hypertensive adults using ACEi medications only occur if they adopt an exercise training regimen, increasing also the management of the blood pressure and other cardiovascular risk factors

Keywords: Functional status, exercise, angiotensin converting enzyme inhibitors, cardiovascular risk factors, physical health related quality of life.

4.4.2. Introduction

Aging and hypertension tend to act as an interactive mechanism in the prevalence of several collateral health effects including increased risk of dementia, falls/fractures and physical disability (Buford, 2016). Therefore, older adults with hypertension represent a specific high risk group, experiencing accelerated rates of functional decline and associated cardiovascular events (Buford et al., 2015), comparatively with normotensive individuals of the same ages (Dumurgier et al., 2010).

The identification of interventions capable of reducing physical decline is an important goal with dramatic public health implications given the increased number of hypertensive older adults (P. James et al., 2014). To date, only exercise interventions have shown promising results in functional decline (C. K. Liu et al., 2014; Pahor et al., 2006). Nevertheless, in the last decade, pharmacological interventions with angiotensin converting enzyme inhibitors (ACEi) have been associated with clinical benefits on cardiovascular outcomes (Simon et al., 2015) and on physical function (Buford et al., 2012).

The afore-mentioned issue, however, still remains controversial. In fact, while some studies have found improvements in physical function (George & Verghese, 2016; Hutcheon et al., 2002; Kurklinsky & Levy, 2013; Sumukadas et al., 2007), others failed to obtain any gains (Matteo Cesari et al., 2010; Spira et al., 2016; Zi et al., 2003), and others even found a negative association between ACEi use and physical performance and muscle strength (Gray et al., 2012). These different conclusions may be the result of different types and dosages of ACEis drugs (including perindopril, ramipril and quinalapril) and participant´s different cardiovascular risk profiles characteristics (Kurklinsky & Levy, 2013)(Sumukadas et al., 2007). Moreover, the complexity of the blood pressure control mechanisms remains elusive to treatment decisions due to the variety of hypertensive phenotypes among older adults (Sever & Messerli, 2011), particularly on their functional status, since mono and combined therapy have also some pros and cons (Mancia et al., 2013). Actually, while monotherapy can only reduce the blood pressure in a limited number of hypertensive individuals (Gu Q Dillon CF, et al., 2012; Mancia et al., 2013), the combined medication has been associated with the increased risk of drug duplication, drug–drug interactions and adverse drug reactions side effects such as reduced alertness,

vision, and muscle strength, which relates with decreased physical functioning (Charlesworth et al., 2015a). More recently, it has been suggested that the benefits may only occur when ACEis are combined with exercise training (Buford et al., 2012; Christy S. Carter et al., 2012), even though, contradictory evidence from a randomized control trial exist (Sumukadas et al., 2014). Unfortunately, the biggest limitation, concurring in feeding the existent controversy, is the scarce number of clinical trials specifically exploring this topic (Buford et al., 2012; Christy S. Carter et al., 2012; Sumukadas et al., 2014). In context of the preceding trends, the aims of the present study are twofold: firstly, to analyze the effect of three types of treatment on functional status in independently hypertensive older adults with comorbidities: *i)* multicomponent exercise training (MEX); *ii)* pharmacologic treatment with oral antihypertensive drug (ACEi); *iii)* combined therapy including exercise and ACEi medications (ACEiMEX); secondly, to examine others cardiovascular risk outcomes including blood variables, the anthropometric profile, and physical self-perception of health-related quality of life (HRQoL).

4.4.3. Methods

4.4.3.1. Study design

This three-arm non- randomized cohort study is part of a larger research involving community dwelling older adults aged 60 and over, who were referred to the study by their physician or self-referred from flyers distributed at community centers, media advertisements or word of mouth. The baseline interviews, clinical examination and the follow up testing occurred between September 2013 and September 2015, which were performed by the same order at the baseline and at the end of the follow-up.

After the recruitment period, participants were invited to a preliminary meeting in which they were informed about the nature, benefits and risks of the study. At this meeting, they completed the health history questionnaire and the Medical Outcomes Study 36-item Short-form Health Study questionnaire (SF-36).

A second meeting was then scheduled for the assessment the following measures: anthropometric, hemodynamic profile and Senior Fitness Test battery. Stature, body mass (BM), waist and hip circumferences, and blood pressure were assessed by trained nurses who were periodically supervised to minimize any systematic error associated with variation in measurement techniques, and to ensure the precision and accuracy of the measurements (American College of Sports Medicine, 2010). When needed, in the case of an illiterate participant, trained interviewers helped to complete the questionnaires.

Participants of the MEX and ACEiMEX group met three times a week for one hour over the 24-months intervention period to perform the multicomponent exercise program in local centers of Santa Maria da Feira. The ACEi and ACEiMEX group held trimester consultations with their physician, to control medication treatment. During the intervention period it was requested that all participants maintained the same nutritional pattern and the regular supervision of their primary care physician.

The afore-mentioned methods and procedures were approved by the Institutional Scientific Board of the University of Coimbra, the local institution (Santa Maria da Feira County) and national ethics committees Data Protection Authority-CNPD; Health Administration from North Ethics Committee-ARS/Norte). All participants gave their written informed consent, consistent with Helsinki Declaration.

4.4.3.2. Study participants

Participants were eligible if they were aged 60 or more years, presented the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC) (Mancia et al., 2013) criteria for hypertension and presented physically independent functional status, determined by responses to the 12-item of Composite Physical Functioning Scale (Roberta E. Rikli & Jones, 2013).

They were considered independent if they were able to perform all basic and all instrumental activities of daily living without assistance (Roberta E. Rikli & Jones, 2013).

Exclusion criteria included: (a) unstable angina; (b) uncontrolled symptomatic heart failure; (c) uncontrolled cardiac dysrhythmias; (d) symptomatic aortic stenosis; (e) participants who were not under regular supervision of the treating physician for the period of the study evaluation; (f) known cancer or limited life expectancy, acute emergencies; (g) Parkinson's disease; (h) Alzheimer's disease; (i) dementia or mild/severe cognitive impairment; (j) severe visual impairment; (k) further reasons that made it impossible or highly problematic to participate and come to the follow-up visits, completing baseline and follow-up testing (program log ≥ 80 %) and (l) using thiazide diuretic medication, calcium channel blockers, angiotensin receptor blockers medication or combined therapy.

A sub-group of 418 inactive [according to the guidelines (American College of Sports Medicine, 2014)] hypertensive older adults that fulfilled all the conditions exposed was retained as participants and was then divided according with 3 therapy criteria: i) multicomponent exercise training (MEX; n=116; 79% females); ii) oral antihypertensive medication- angiotensin converting enzyme inhibitors (ACEi; n = 70; 68% female); iii) combined therapy with exercise training and oral angiotensin converting enzyme inhibitors (ACEiMEX; n = 232; 77% female). Furthermore, the inclusion criteria for the MEX group was exercise training engagement according the guidelines (American College of Sports Medicine, 2010); the ACEi group used daily mono-pharmacological therapy with oral antihypertensive angiotensin converting enzyme inhibitors; and the ACEiMEX group combined both forms of treatment –multicomponent exercise training, and oral antihypertensive ACEi therapy. Thus, after the 24-months intervention, the trial was completed by 82% of the participants (n = 342); MEX group (n = 90; 81% female); ACEi (n = 66; 68% Female) and ACEiMEX group (n = 186; 76% Female). Participants lost to

follow-up did not significantly differ at the baseline characteristics from those who completed the study.

Completeness of data was 100%, having no missing responses (Figure 4.4.1).

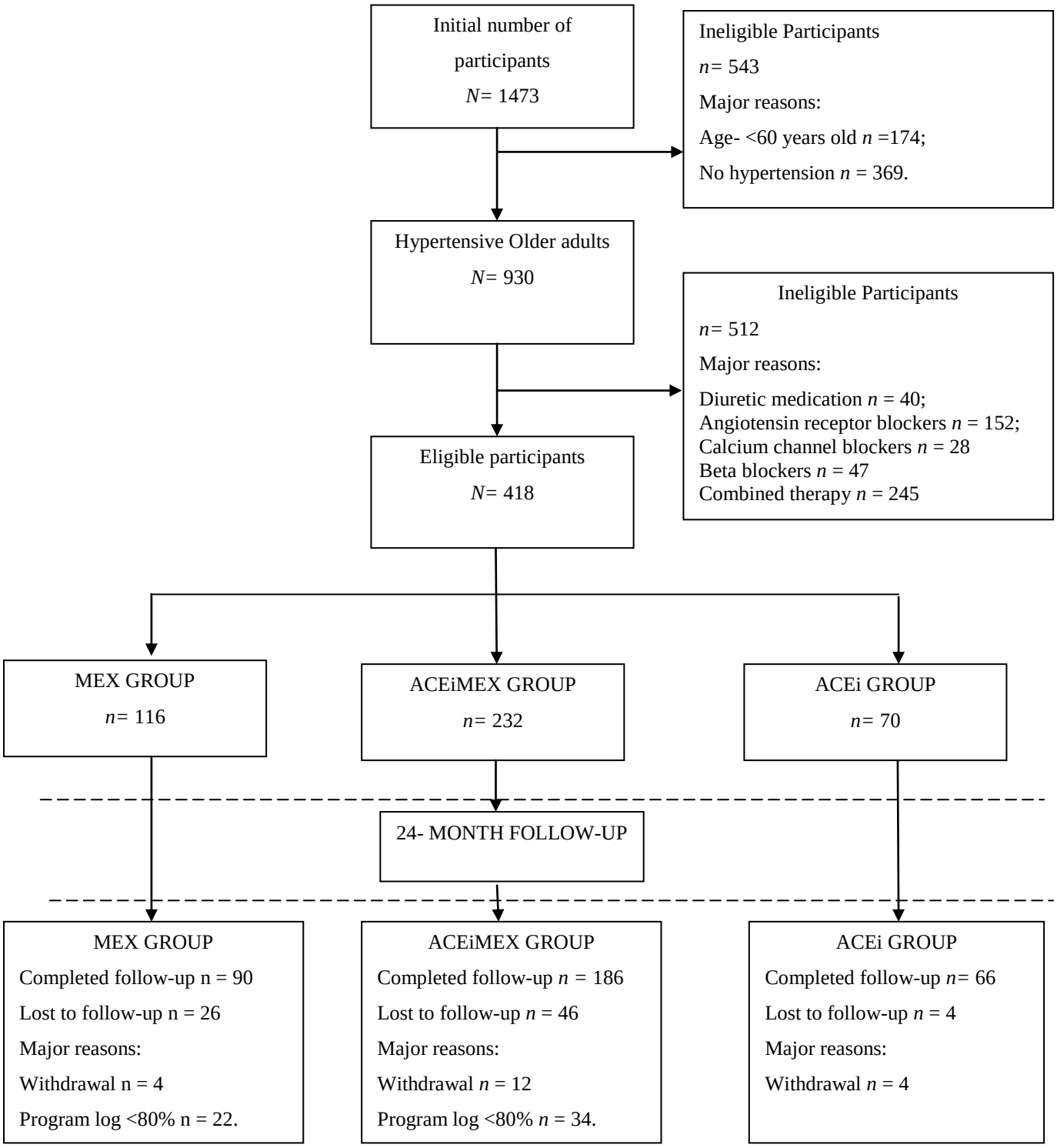


Figure 4.4.1. Cohort flux diagram

4.4.3.3. Interventions

Multicomponent exercise program

This exercise training program was designed to meet the exercise and physical activity guidelines for older adults with hypertension established by American College of Sport Medicine (American College of Sports Medicine, 2010). The supervised multi-component exercise program consisted in three 60-min sessions/week, on three non-consecutive days. Exercise modifications such as duration, number of repetitions, or use of an exercise auxiliary were recommended by the group instructor when needed. Exercise intensity was in line with the safety limits established to this disease group (American College of Sports Medicine, 2010) and was monitored using a subjective 0-10 scale for physical exertion (Borg, 1988) and a heart rate monitor (Polar, SWE).

Multicomponent exercise training included aerobic, resistance, balance and flexibility according with these items: 5-10 minutes of warm-up, 20-30 minutes of aerobic, 15-20 minutes of resistance training, 10 minutes of balance, 10 minutes of stretching, and 5-10 minutes of cool down exercises. Aerobic exercise started with participants in a standing position (e.g., walking in place with arm movements), and progressively involved continuous movement of major muscles of the upper-extremity, performed alternately with movement of the lower-extremity. Time and intensity of aerobic exercise was increased from 20 minutes per session at 50% HRmax (maximum heart rate) to 30 minutes at 60% HRmax per session (American College of Sports Medicine, 2010).

Resistance training involved a set of 5-8 exercises from the large muscle groups, with 1-3 sets of 8-12 repetitions for each upper and lower body muscle group and came from participants' own BM or with free weights. Intensity was set at 50% to 70% 1-repetition maximum (1-RM), with 90 to 120 seconds of rest between sets. Resistance included the use of concentric and eccentric muscle action, with bilateral and unilateral single and multiple joint exercises including: squats (half squats), seated/ upright row, sitting and standing biceps curl, triceps extension, shoulder press, leg extension (hip extension), side leg raise and leg curl.

The 1-RM assessment occurred after one week of familiarization/practice sessions for each of the previous exercises within four trials, with progressive resistance augments, until the participant cannot complete the repetitions with the same speed of movement or

range of motion. Each person's 1-RM was determined every 6 weeks to adjust for improvements in resistance.

Balance training was also based on functional tasks required by older adults. Prior to cool down, participants performed stretching exercises designed to improve flexibility of the major muscle groups; each stretch was sustained between 15 and 30 seconds to the point of tightness, and repeated three times.

Over the 24-months intervention, exercise progression increased every 6 weeks through augments on duration, repetitions, resistance, and/or difficulty (e.g., transition from sitting to standing to complete exercises). All training sessions were carefully supervised by 34 experienced exercise specialists (degree in physical education and sport sciences) (ratio of supervision 1:9- 1 professor for 9 participants). The exercise specialists were regularly supervised by the general study coordinator. Monthly meetings were conducted by the general study coordinator to minimize any systematic error associated with variation in training sessions (American College of Sports Medicine, 2014).

Pharmacological procedure

Participants of the ACEi and ACEiMEX group had used mono-dose daily of ACEi medication during at least one year prior to this study start, prescribed by their primary care physician, according with the presence or not of others comorbidities and blood pressure levels. All the necessary dose prescription adjustments were made throughout the intervention period by the primary care physician to maintain a medically supervised symptom-limited, reducing the risk of hypotension, cough and hyperkalemia (American College of Sports Medicine, 2010). The ACEi drugs prescribed to this sample group included: Enalapril- 10-20 mg; Perindopril-2, 4, 10 mg; Lisinopril- 5-20 mg; Ramipril- 2,5-5 mg; and Captopril- 25 mg. Participants held trimester medical consultations with their physician to control blood pressure levels and antihypertensive medications doses. To ensure participants safety, all abnormal symptoms detected during intervention were discussed with their physician that decided the appropriate course of action.

4.4.3.4. Outcomes Measures

The primary end-point of this study was the change in functional status measured by the Senior Fitness Test battery (Jones, J., Rikli, 2002). Secondary outcomes included the anthropometric and hemodynamic profile changes and physical subjective HRQoL.

Functional Status

The SFT battery (Jones, J., Rikli, 2002), was employed to assess the individual functional status, and was develop to measure the underlying parameters associated with functional ability of older adults to perform the normal everyday activities (Roberta E. Rikli & Jones, 2013).

The SFT seemed especially well suited to measure our primary outcome due to the strong psychometric properties (validity and test-retest reliability between 0.80 and 0.98), (Roberta E. Rikli & Jones, 2013)) ease and safe use with a wide range of physical abilities.

This test battery includes measures of strength, aerobic endurance, flexibility, and agility/dynamic balance in a continuous scale that make it possible to assess gradual changes over time (improvements or decline) across a wide range of physical levels (Roberta E. Rikli & Jones, 2013). The individual´s upper/lower body strength was measured by the number of repetitions in 30-second arm curl and chair stand test; the back scratch and the chair sit-and-reach test was used to measure the upper/lower body flexibility; the agility/dynamic balance was measured by the 8-foot up-and-go; and the aerobic endurance was measured by the 6-minutes' walk test. To minimize intraday variability, temperature effects, and biological rhythms, this test battery was performed between 8 am and 10 am. Participants were told to avoid vigorous exercise in the 2 hours prior to testing, to wear comfortable clothes and appropriate walking shoes, and to continue their usual medication. Recommended reasons for immediately stopping the SFT evaluation and to ensure participants safety include chest pain, intolerable dyspnea, leg cramps, staggering, diaphoresis, and pale or ashen appearance.

Subjective physical health-related quality of life

Physical self-perception of HRQoL was assessed using the SF-36 questionnaire, adapted and validated for the Portuguese population (Ferreira, 1998). This instrument, with

high internal consistency and reliability (between 0.80 and 0.86) (Ferreira, 1998), was developed to measure generic health status and HRQoL (Anderson et al., 1996). In our study, only the 4 physical health-related subscales were utilized: Physical Functioning (PF); Role-Physical limitations (RP); Bodily Pain (BP); General Health (GH); and the summary dimension Physical Component Score (PCS), calculated using the methods set out by Ware and colleagues (Ware. Jr, 2000). Scores range from 0 to 100, with higher values indicating better functional health and well-being.

Anthropometric Profile

Stature was measured using a standard stadiometer to 0.1 cm in the upright position, with the participant´s back square against the wall and eyes looking straight ahead, without shoes. Body mass (BM) was measured by a calibrated digital balance-beam scale (SECA 770, Germany) with a precision nearest to 100 grams, with barefoot participants and in light clothing. Waist circumference (WC) was measured at the midpoint between the lowest rib and the top of the iliac crest at minimal respiration, and hip circumference was taken in a horizontal plan along pubic symphysis. Body mass index (BMI) was calculated dividing BM in kilograms by stature in meters squared. Waist-to-hip ratio (WHR) was calculated dividing waist by hip. Central obesity was defined has WC $\geq$ 94 cm for men and WC $\geq$ 80 cm for women (International Diabetes Federation, 2005).

Hemodynamic profile

Resting blood pressure was taken three times using a sphygmomanometer (Aneroid Sphygmomanometer-HICO HM 1001, Germany) and stethoscope (Nurse Type Professional Stethoscope-HICO HM-3005, Germany), in the seated position, after 5 minutes rest; the measurements were performed at 2 minutes intervals (American College of Sports Medicine, 2010).

The mean of the measurements was used for systolic (SBP) and diastolic blood pressure (DBP). Trained nurses collected venous blood in the morning after 12 hours fasting. Glycaemia, triglycerides (TG) and total cholesterol (TC) were carried out in plasma and were determined by standard methods (American College of Sports Medicine, 2014) by the same accredited laboratories at baseline and at 24-months evaluation.

Health history

Participants´ health history data were obtained by questionnaire and included the following information: age, gender, education level, living situation, smoking status and the presence of several conditions like heart disease, hypertension, stroke, diabetes, dyslipidemia, osteoarthritis, pulmonary diseases, liver diseases, thyroid diseases, visual and audio problems, cancer, Parkinson's disease, Alzheimer disease, dementia or other comorbidities. Medication type and dosage were also assessed by detailed questionnaire with visual confirmation of prescription drugs recorded by the study staff.

Statistical analysis

Baseline participant's characteristics were carried out with measures of central tendency – mean and standard deviation (SD), for the following variables: age, BM, BMI, WHR, SBP, DBP, TC, TG, glycaemia, upper/lower body strength, upper/ lower body flexibility, agility/dynamic balance, aerobic endurance and physical HRQoL domains PF, RP, BP, GH and PCS.

Furthermore, for all continuous variables, normality of distribution and homoscedastic variance were verified with Kolmogorov-Smirnov and Levene´s tests. One-way analysis of variance (ANOVA) test followed by Gabriel post-hoc was also used at the baseline analysis for comparisons between groups.

Longitudinal changes within groups were tested using a two-way ANOVA for repeated measures. Differences between groups after 24-month intervention were performed using the analysis of covariance (ANCOVA), adjusting for baseline score values, age, sex and comorbidity number.

To test responsiveness at baseline and after 24-months intervention, it was calculated the Hedges´s g effect size, providing a measure of the effect size weighted according to the relative different sample size within our study population (Hedges & Olkin, 1985). Standardized effects sizes were classified as small (<0.20), moderate (0.20-0.79) and large (>0.80) (Cohen, 1988).

Data analysis were performed using Statistical Package for the Social Sciences for Windows (IBM-SPSS, Inc. Chicago, IL, USA), software version 24. Statistical tests were 2-tailed and significance was set at 5%.

4.4.4. Results

4.4.4.1. Participants' characteristics

The final sub-group of 418 hypertensive older adults overall, were of the female sex (75.8%), had mean (±SD) age of 67.4 (6.1) years, BMI of 29.0 (4.1) Kg/m2, SBP of 140 (14) mmHg, DBP of 80 (11) mmHg and mean comorbidity number of 2.4 (1.6), being the central obesity (55%), dyslipidemia (51%), osteoarthritis (28%), diabetes (22%) and osteoporosis (22%) the most prevalent comorbidities. There were no significant differences in drug treatments and doses maintained throughout the intervention period. In the ACEiMEX group: 34% used Perindopril – 2mg (2%), 4mg (91%), 10mg (7%); 26% consumed Lisinopril – 10 mg (15%), 20 mg (85%); 12% used Enalapril – 5mg (10%), 20mg (90%); 19% used Ramipril – 2,5mg (92%), 5mg (8%)]; and 9% used Captopril 25mg. In the ACEi group: 37% used Perindopril – 2mg (5%), 4mg (90%), 10mg (5%); 23% used Lisinopril – 10mg (13%), 20mg (87%); 20% used Enalapril – 5mg (9%), 20 mg (91%); and 20% used Ramipril – 2,5mg (90%), 5mg (10%). No serious adverse events (life-threatening event, inpatient hospitalization or clinically significant abnormal laboratory or diagnostic test) were registered during the intervention period, except for soreness.

4.4.4.2. Baseline characteristics

At baseline, the MEX group had less comorbidities, and higher SBP and DBP than the other two groups ($p \leq 0.001$) (Table 4.4.1 and Table 4.4.2). The MEX group also had greater 30s arm-curl and chair-stand tests ($p<0.001$), and RP ($p=0.040$) than the ACEi group. The ACEiMEX participants were older ($p=0.006$), had higher SBP ($p=0.013$) and better 30s arm-curl and chair-stand tests ($p \leq 0.001$) than the ACEi group. Differences between groups had small to moderate effect size, except for SBP, DBP and 30s chair-stand test in the MEX group, comparatively to the ACEi group.

Table 4.4.1 – Descriptive baseline characteristics (N=418)

Variables	Total (n=418)	ACEiMEX (n=232)	ACEi (n=70)	MEX (n=116)	Group Effect (*P* Values)	Group Effect Adjusted [a] (*P* Values)
Female, %	75.8	77.4	67.6	78.6	0.120	
Age, years	67.4 (7.2)	67.9 (7.1)	65.1 (7.6)	67.2 (7.0)	0.013*	
Comorbidity, n	2.4 (1.6)	2.4 (1.6)	2.8 (1.6)	1.8 (1.5)	<0.001**	
Systolic BP, mmHg	140 (14)	139 (14)	133 (17)	147 (10)	<0.001**	<0.001**
Diastolic BP, mmHg	80 (11)	78 (11)	77 (9)	85 (10)	<0.001**	<0.001**
Body mass, kg	73.8 (11.5)	74.1 (11.6)	75.8 (9.1)	72.1 (12.5)	0.083	0.594
Body mass Index, kg/m^2	29.0 (4.1)	29.4 (4.1)	29.0 (3.5)	28.1 (4.4)	0.034*	0.091
Waist-to-hip ratio	0.89 (0.07)	0.90 (0.07)	0.91 (0.09)	0.88 (0.06)	0.028*	0.221
Glycaemia, mg/dL	104 (25)	104 (24)	106 (28)	100 (25)	0.347	0.519
Total cholesterol, mg/dL	200 (38)	198 (38)	203 (45)	205 (32)	0.299	0.325
Triglycerides, mg/dL	126 (64)	124 (57)	139 (82)	121 (65)	0.199	0.420
Lower body strength, n	14 (5)	14 (5)	12 (3)	15 (5)	<0.001**	<0.001**
Upper body strength, n	17 (4)	17 (5)	14 (3)	18 (4)	<0.001**	<0.001**
Lower body flexibility, cm	0.4 (8.1)	0.6 (8.5)	1.8 (8.6)	-0.8 (6.9)	0.094	0.217
Upper body, flexibility, cm	16.3 (10.9)	17.4 (10.3)	15.3 (11.8)	14.9 (11.2)	0.090	0.430
Agility/dynamic balance, s	5.6 (1.4)	5.6 (1.4)	5.8 (1.4)	5.5 (1.3)	0.517	0.051
Aerobic endurance, m	451 (113)	444 (116)	441 (77)	470 (122)	0.086	0.223
Physical Functioning	81 (20)	82 (19)	77 (22)	82 (18)	0.135	0.047*
Role Physical	74 (24)	75 (23)	67 (30)	77 (22)	0.018*	0.129
Bodily Pain	67 (25)	67 (25)	65 (31)	68 (24)	0.718	0.762
General Health	58 (18)	57 (18)	55 (20)	61 (18)	0.070	0.674
Physical Component Score	70 (18)	70 (17)	65 (22)	72 (16)	0.056	0.196

Data are expressed as mean (SD).). [a] Group effect adjusted to sex, age and comorbidities number. *Differences between evaluations ($p \leq 0.05$). ** Differences between evaluations ($p \leq 0.001$).

Table 4.4.2- Differences between groups at baseline in functional status and physical HRQoL outcomes using one- way ANOVA (N=418)

Variables	MEX vs ACEi	*P* Value	Effect Size	ACEiMEX vs ACEi	*P* Value	Effect Size	MEX vs ACEiMEX	*P* Value	Effect Size
Age, years	2.0 (-0.5 to 4.6)	0.168	0.290	2.8 (0.7 to 5.0)	0.006*	-0.094	-0.8 (-2.6 to 1.1)	0.679	0.099
Comorbidity, n	-1.1 (-1.6 to -0.5)	<0.001**	0.650	-0.4 (-0.9 to 0.1)	0.132	0.250	-0.6 (-1.0 to -0.2)	0.001*	0.383
Systolic BP, mmHg	14.2 (8.9 to 19.6)	<0.001**	1.071	6.6 (1.2 to 11.9)	0.013*	0.407	7.7 (4.7 to 10.7)	<0.001**	0.624
Diastolic BP, mmHg	8.1 (4.2 to 11.9)	<0.001**	0.830	1.2 (-2.1 to 4.6)	0.759	-0.095	6.8 (4.0 to 9.7)	<0.001**	0.655
Body mass, kg	-3.8 (-7.9 to 0.4)	0.089	0.326	-1.7 (-5.3 to 2.0)	0.610	0.153	-2.1 (-5.2 to 1.0)	0.280	0.168
Body mass Index, kg/m2	-0.8 (-2.3 to 0.7)	0.467	0.220	0.4 (-0.9 to 1.7)	0.844	0.101	-1.2 (-2.3 to -0.1)	0.025*	0.309
Waist-to-hip ratio	-0.03 (-0.06 to 0.00)	0.069	0.413	-0.01 (-0.04 to 0.02)	0.579	0.133	-0.02 (-0.03 to 0.00)	0.086	0.299
Glycaemia, mg/dL	-5.7 (-16.3 to 5.0)	0.490	0.229	-1.6 (-10.4 to 7.2)	0.963	0.080	-4.1 (-11.6 to 3.4)	0.470	0.164
Total cholesterol, mg/dL	1.7 (-14.9 to 18.2)	0.968	0.053	-5.2 (-20.6 to 10.2)	0.699	0.126	6.9 (-3.3 to 17.1)	0.250	0.194
Triglycerides, mg/dL	-18.1 (-44.7 to 8.5)	0.278	0.251	-15.6 (-36.8 to 5.7)	0.221	0.236	-2.6 (-22.0 to 16.9)	0.985	0.050
Lower body strength, n	2.9 (1.6 to 4.2)	<0.001**	0.688	1.8 (0.7 to 2.9)	0.001*	0.433	1.1 (-0.1 to 2.4)	0.081	0.200
Upper body strength, n	3.4 (2.1 to 4.6)	<0.001**	1.094	2.6 (1.5 to 3.7)	<0.001**	0.649	0.8 (-0.4 to 2.0)	0.275	0.213
Lower body flexibility, cm	-2.6 (-5.5 to 0.4)	0.104	0.325	-1.1 (-3.7 to 1.4)	0.643	0.172	-1.5 (-3.7 to 0.7)	0.295	0.141
Upper body, flexibility, cm	-0.4 (-4.4 to 3.5)	0.991	0.035	2.1 (-1.4 to 5.5)	0.389	0.197	-2.5 (-5.4 to 0.4)	0.116	0.236
Agility/dynamic balance, s	-0.2 (-0.7 to 0.3)	0.594	0.224	-0.2 (-0.6 to 0.3)	0.673	0.143	-0.1 (-0.4 to 0.3)	0.983	0.073
Aerobic endurance, m	29.2 (-5.4 to 63.8)	0.117	0.270	2.7 (-25.8 to 31.2)	0.973	0.028	26.5 (-5.5 to 58.6)	0.127	0.220
Physical Functioning	4.9 (-2.6 to 12.3)	0.271	-0.255	5.1 (-1.8 to 12.0)	0.188	0.253	-0.2 (-4.9 to 4.5)	0.993	0.000
Role Physical	10.1 (0.4 to 19.8)	0.040*	0.395	7.6 (-1.4 to 16.6)	0.115	0.323	2.5 (-3.3 to 8.2)	0.567	-0.088
Bodily Pain	3.1 (-7.1 to 13.2)	0.831	-0.112	2.3 (-7.1 to 11.6)	0.831	-0.075	0.8 (-5.4 to 6.9)	0.953	-0.041
General Health	5.9 (-0.7 to 12.5)	0.095	0.320	2.1 (-3.4 to 7.6)	0.734	-0.108	3.4 (-0.9 to 8.4)	0.148	0.222
Physical Component Score	6.3 (-1.0 to 13.6)	0.104	0.379	4.6 (-2.2 to 11.3)	0.250	0.274	1.7 (-2.4 to 5.9)	0.586	-0.120

Data are expressed as mean (SD). * Differences between evaluations ($p \leq 0.05$). ** Differences between evaluations ($p \leq 0.001$).

4.4.4.3. Differences within group from baseline to 24-months follow-up

After the 24-months intervention, the MEX and ACEiMEX improved all physical functional status dimensions (p<0.001) (Table 4.4.3, Figure 4.4.2). Moreover, both groups had lower levels of SBP and DBP (p<0.001), and perceived better physical HRQoL, particularly the PF, RP and PCS (p<0.05), however they have also augmented their Bodily Pain (p<0.05). The MEX group have also improved GH dimension (p=0.021) and the ACEiMEX participants have decreased anthropometric profile, specifically BM and BMI (p<0.001).

A decreased pattern was observed in the ACEi group throughout the 24-months intervention with diminished functional status, particularly, in the 30s arm-curl test, upper/lower body flexibility and aerobic endurance (p<0.05). Furthermore, this group, revealed worst anthropometric profile and SBP (p<0.001), and their perceived physical HRQoL decreased, particularly the GH and the PCS (p<0.05).

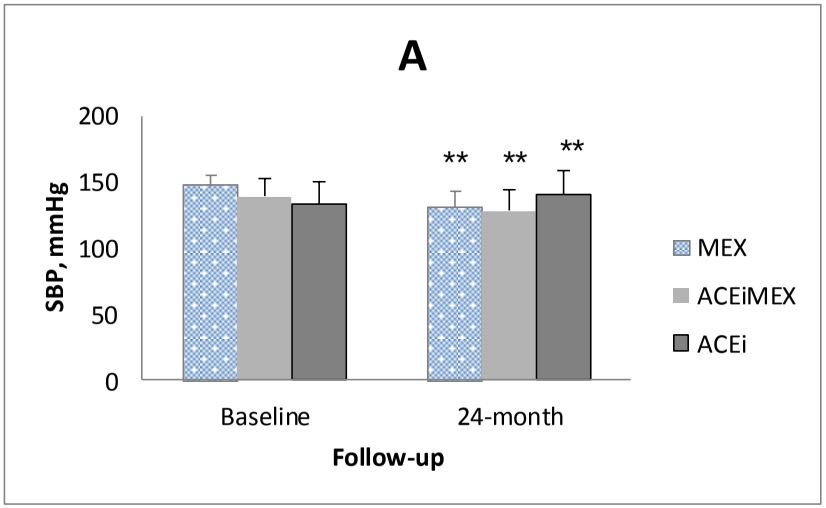
4.4.4.4. Differences between groups after 24 month intervention

After the intervention period, and adjustment for covariates, the differences between groups occurred in all variables (p<0.001), exception for the lipid profile outcomes and glycaemia (Table 4.4.4 and Table 4.4.5). The improvements observed in the MEX and ACEiMEX groups from the baseline to the 24-months evaluation were higher than in the ACEi group. In the functional status components, the MEX and ACEiMEX groups revealed improvements in all dimensions (p<0.001), with moderate to large effect sizes in the 30s arm-curl and chair-stand tests and aerobic endurance comparatively to the ACEi group. Additionally, these two groups decreased both the SBP and DBP with large effect size (p<0.001), having also revealed better perceived physical HRQoL (p<0.001) than the ACEi group, with moderate effect sizes in the MEX group and small effect size in the ACEiMEX participants. Nevertheless, both the groups have also revealed higher Bodily Pain, with higher mean values in the MEX group in GH and Bodily Pain than in the ACEiMEX group (p<0.05). For the anthropometric profile, the MEX and ACEiMEX groups showed small effect size improvements in central obesity, comparing with the ACEi group (p<0.05).

Table 4.4.3- Differences within groups from baseline to 24 month evaluation using a two-way ANOVA (N=342)

	MEX (n=90)			ACEiMEX (n=186)			ACEi (n=66)		
Variables	Baseline	24-months	*P* Value	Baseline	24-month	*P* Value	Baseline	24-months	*P* Value
Systolic BP, mmHg	147 (9)	131 (12)	<0.001**	139 (14)	128 (16)	<0.001**	133 (17)	141 (17)	<0.001**
Diastolic BP, mmHg	85 (11)	76 (9)	<0.001**	78 (10)	74 (10)	<0.001**	77 (9)	79 (10)	0.051
Body mass, kg	71.8 (10.8)	71.3 (11.0)	0.073	74.5 (11.0)	73.6 (11.1)	<0.001**	76.0 (9.1)	76.6 (9.1)	0.001*
Body mass Index, kg/m2	27.9 (3.8)	27.7 (3.8)	0.175	29.4 (3.8)	29.0 (3.8)	<0.001**	29.0 (3.5)	29.3 (3.6)	<0.001**
Waist-to-hip ratio	0.88 (0.07)	0.87 (0.07)	0.237	0.90 (0.07)	0.89 (0.07)	0.054	0.91 (0.09)	0.93 (0.09)	0.004*
Glycaemia, mg/dL	99 (19)	99 (19)	0.964	109 (27)	110 (29)	0.497	114 (35)	119 (51)	0.205
Total cholesterol, mg/dL	209 (32)	194 (49)	0.041*	197 (38)	192 (35)	0.069	203 (45)	184 (44)	0.024*
Triglycerides, mg/dL	132 (79)	121 (62)	0.211	131 (59)	132 (63)	0.845	151 (77)	135 (57)	0.194
Lower body strength, n	15 (5)	19 (5)	<0.001**	14 (5)	18 (5)	<0.001**	12 (3)	12 (2)	0.106
Upper body strength, n	18 (4)	23 (5)	<0.001**	17 (5)	22 (5)	<0.001**	14 (3)	13 (3)	<0.001**
Lower body flexibility, cm	-0.8 (6.8)	-4.5 (9.0)	<0.001**	0.9 (8.3)	-2.8 (8.5)	<0.001**	1.8 (8.7)	3.6 (9.3)	<0.001**
Upper body, flexibility, cm	13.1 (9.6)	10.5 (9.2)	<0.001**	17.7 (10.2)	14.0 (9.8)	<0.001**	15.2 (11.9)	16.8 (12.3)	0.005*
Agility/dynamic balance, s	5.5 (1.2)	4.8 (1.1)	<0.001**	5.5 (1.4)	5.1 (1.5)	<0.001**	5.7 (1.4)	5.8 (1.5)	0.184
Aerobic endurance, m	476 (119)	577 (92)	<0.001**	445 (111)	563 (106)	<0.001**	443 (77)	425 (60)	0.001*
Physical Functioning	82 (17)	87 (15)	0.011*	83 (18)	88 (12)	<0.001**	77 (22)	69 (23)	0.002*
Role Physical	78 (21)	84 (20)	0.010*	75 (23)	80 (21)	<0.001**	67 (30)	65 (26)	0.555
Bodily Pain	68 (23)	78 (22)	<0.001**	67 (24)	71 (23)	0.007*	65 (31)	62 (26)	0.269
General Health	61 (18)	65 (17)	0.021*	58 (19)	59 (16)	0.180	56 (20)	50 (15)	0.009*
Physical Component Score	72 (16)	79 (14)	<0.001**	71 (17)	75 (14)	<0.001**	66 (22)	61 (19)	0.029*

Data are expressed as mean (SD). * Differences between evaluations ($p \leq .05$). ** Differences between evaluations ($p \leq .001$).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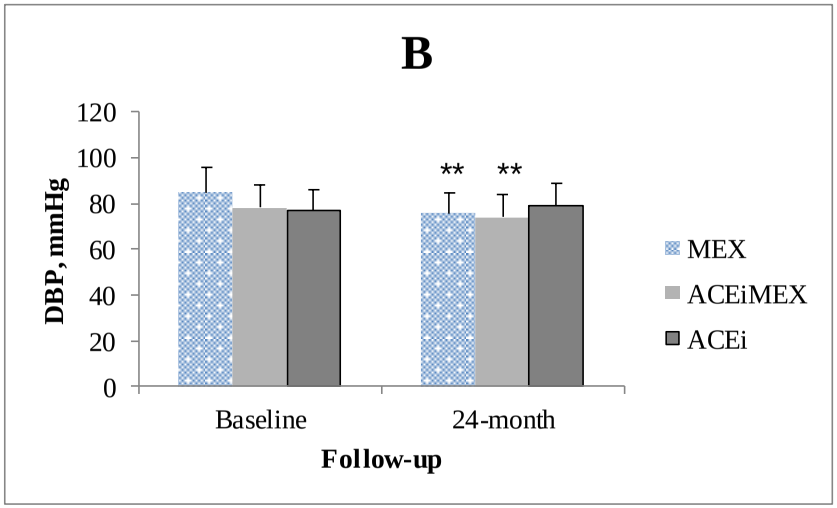
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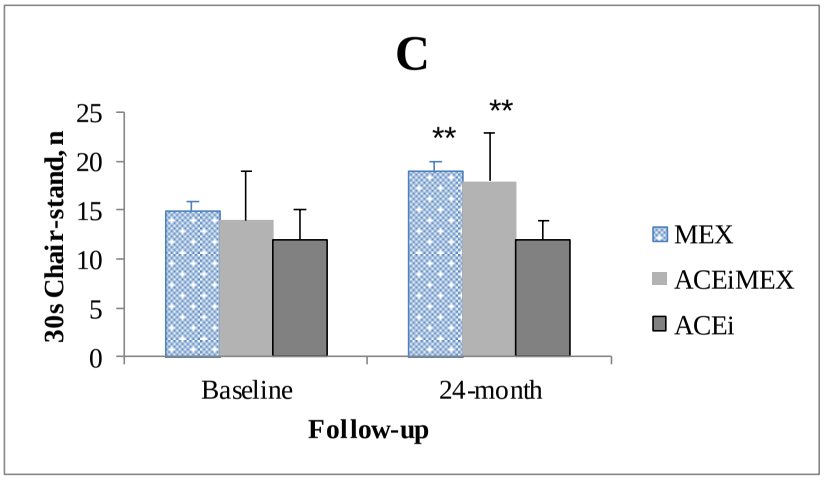
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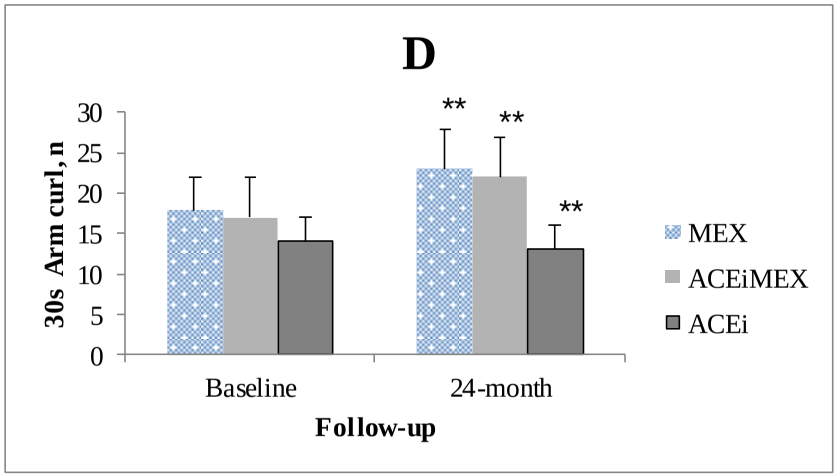
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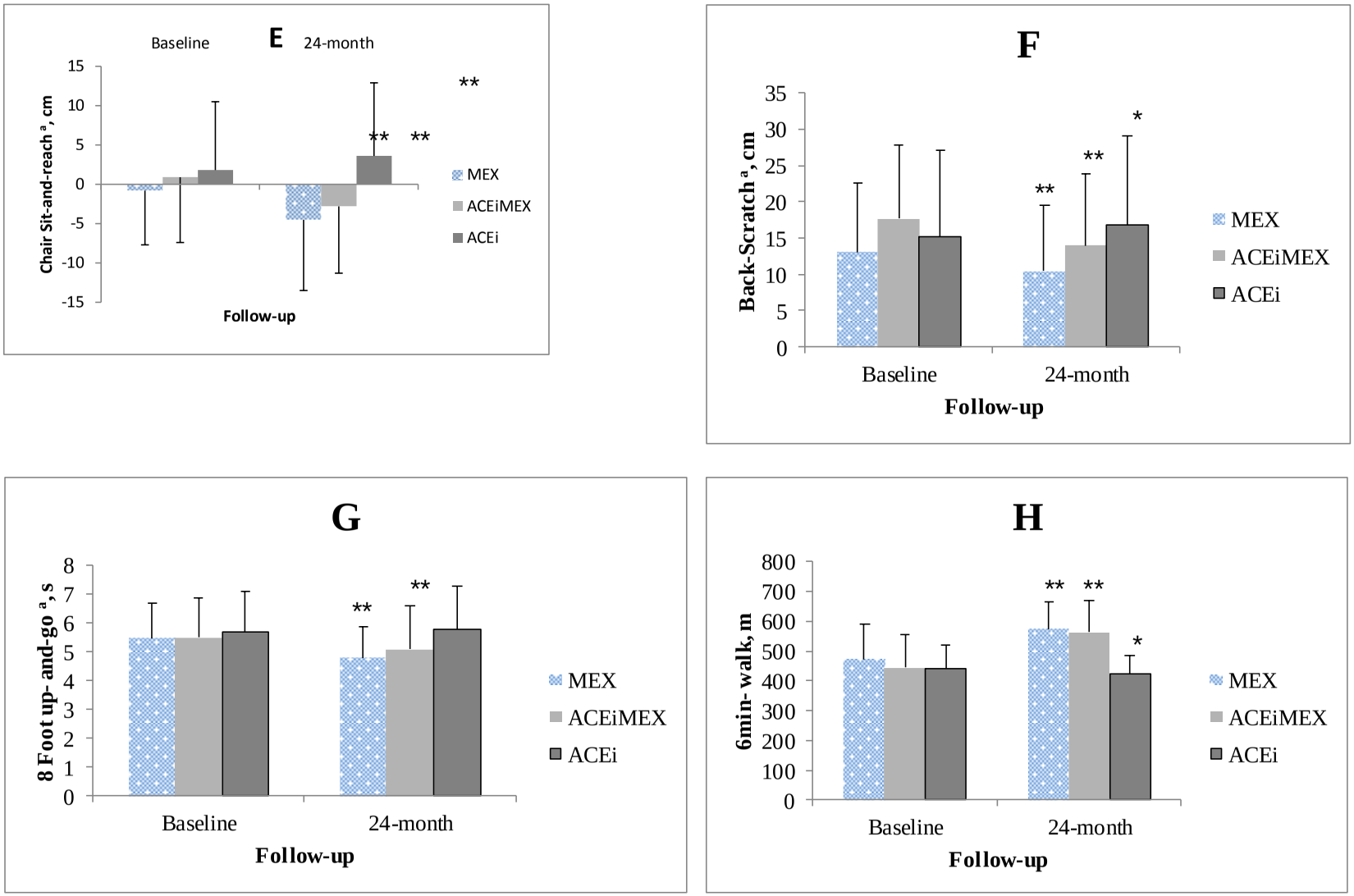

Figure 4.4.2- Values of Systolic blood pressure -SBP (Panel A), Diastolic blood-pressure-DBP (Panel B), lower body strength (Panel C), upper body strength (Panel D), lower body flexibility (Panel E), upper body flexibility (Panel F), agility/dynamic balance (Panel G) and aerobic endurance (Panel H) at baseline and after 24 month intervention. a Decrease means improvements. * Differences between evaluations ($p \leq 0.05$). ** Differences between evaluations ($p \leq 0.001$).

Table 4.4.4- Mean change between groups and effect size after 24-month intervention using a two-way ANOVA and ANCOVA adjusted to baseline values, age, sex and comorbidity number (N=342)

Variables	MEX vs ACEi	*P* Value	Effect Size	ACEiMEX vs ACEi	*P* Value	Effect Size	MEX vs ACEiMEX	*P* Value	Effect Size	Differences Between groups [a] *P* Value
Systolic BP, mmHg	-18.8 (-23.5 to -14.1)	<0.001**	1.833	-16.8 (-20.7 to -12.9)	<0.001**	1.206	-2.0 (-5.6 to 1.6)	0.272	0.390	<0.001**
Diastolic BP, mmHg	-6.3 (-9.1 to -3.5)	<0.001**	1.140	-4.6 (-6.9 to -2.3)	<0.001**	0.567	-1.7 (-3.9 to 0.5)	0.124	0.468	<0.001**
Body mass, kg	-1.3 (-2.2 to -0.4)	0.005*	0.141	-1.4 (-2.2 to -0.7)	<0.001**	0.117	0.1 (-0.6 to 0.8)	0.702	0.025	0.001*
Body mass Index, kg/m2	-0.5 (-0.9 to -0.2)	0.005*	0.171	-0.6 (-0.9 to -0.3)	<0.001**	0.176	0.1 (-0.2 to 0.4)	0.622	0.033	0.001*
Waist-to-hip ratio	-0.03 (-0.04 to -0.01)	<0.001**	0.412	-0.02 (-0.03 to -0.01)	<0.001**	0.399	-0.00 (-0.01 to 0.01)	0.708	0.013	<0.001**
Glycaemia, mg/dL	-4.7 (-14.1 to 4.7)	0.322	0.534	-2.5 (-10.3 to 5.3)	0.532	0.280	-2.2 (-8.8 to 4.3)	0.501	0.287	0.605
Total cholesterol, mg/dL	5.0 (-11.5 to 21.5)	0.550	0.214	9.0 (-4.7 to 22.7)	0.197	0.327	-4.0 (-15.8 to 7.8)	0.504	0.138	0.393
Triglycerides, mg/dL	-3.4 (-27.4 to 20.5)	0.778	0.056	8.1 (-11.7 to 28.0)	0.420	0.189	-11.6 (-28.5 to 5.4)	0.179	0.134	0.338
Lower body strength, n	5.5 (4.4 to 6.7)	<0.001**	0.916	5.7 (4.7 to 6.7)	<0.001**	0.865	-0.2 (-1.0 to 0.7)	0.692	0.000	<0.001**
Upper body strength, n	7.2 (6.0 to 8.4)	<0.001**	1.638	7.4 (6.4 to 8.5)	<0.001**	1.298	-0.2 (-1.1 to 0.7)	0.651	0.013	<0.001**
Lower body flexibility, cm	-6.3 (-8.4 to -4.3)	<0.001**	0.724	-6.0 (-7.8 to -4.2)	<0.001**	0.610	-0.3 (-1.9 to 1.3)	0.694	0.037	<0.001**
Upper body, flexibility, cm	-4.2 (-6.0 to -2.5)	<0.001**	0.556	-4.7 (-6.2 to -3.2)	<0.001**	0.459	0.5 (-0.9 to 1.9)	0.465	0.094	<0.001**
Agility/dynamic balance, s	-0.9 (-1.2 to -0.6)	<0.001**	0.555	-0.7 (-1.0 to -0.4)	<0.001**	0.357	-0.2 (-0.4 to 0.0)	0.100	0.146	<0.001**
Aerobic endurance, m	145.9 (119.4 to 172.4)	<0.001**	1.628	147.8 (124.8 to 170.7)	<0.001**	1.245	-1.9 (-22.5 to 18.6)	0.856	0.102	<0.001**
Physical Functioning	15.9 (11.7 to 20.0)	<0.001**	0.702	16.9 (13.3 to 20.5)	<0.001**	0.709	-1.0 (-4.2 to 2.1)	0.526	0.054	<0.001**
Role Physical	13.7 (7.5 to 20.0)	<0.001**	0.441	12.4 (7.0 to 17.7)	<0.001**	0.282	1.4 (-3.3 to 6.1)	0.566	0.088	<0.001**
Bodily Pain	14.1 (7.5 to 20.7)	<0.001**	0.484	9.1 (3.4 to 14.7)	0.002*	0.264	5.1 (0.1 to 10.0)	0.044*	0.243	<0.001**
General Health	13.4 (9.1 to 17.8)	<0.001**	0.607	9.5 (5.8 to 13.2)	<0.001**	0.379	3.9 (0.6 to 7.2)	0.019*	0.111	<0.001**
Physical Component Score	14.2 (10.3 to 18.2)	<0.001**	0.726	11.5 (8.1 to 14.8)	<0.001**	0.492	2.8 (-0.2 to 5.7)	0.068	0.120	<0.001**

Data are expressed as mean (SD). [a] Differences between groups after 2 years, adjusted to baseline values, age, sex and comorbidity number. * Differences between evaluations ($p \leq 0.05$). ** Differences between evaluations ($p \leq 0.001$).

Table 4.4.5- Differences between groups, time and time x group interception after 24-month intervention

Variables	Differences between groups [a]	Differences between Time	Time x Group
	P Value	*P* Value	*P* Value
Systolic BP, mmHg	<0.001**	<0.001**	<0.001**
Diastolic BP, mmHg	<0.001**	<0.001**	<0.001**
Body mass, kg	0.001*	0.102	0.001*
Body mass Index, kg/m2	0.001*	0.262	<0.001**
Waist-to-hip ratio	<0.001**	0.367	<0.001**
Glycaemia, mg/dL	0.605	0.179	0.471
Total cholesterol, mg/dL	0.393	<0.001**	0.105
Triglycerides, mg/dL	0.338	0.072	0.223
30s chair-stand, n	<0.001**	<0.001**	<0.001**
30s arm-curl, n	<0.001**	<0.001**	<0.001**
Chair sit-and-reach, cm	<0.001**	<0.001**	<0.001**
Back scratch, cm	<0.001**	<0.001**	<0.001**
8 Foot up-and-go, s	<0.001**	<0.001**	<0.001**
6 min walk, m	<0.001**	<0.001**	<0.001**
Physical Functioning	<0.001**	0.639	<0.001**
Role Physical	<0.001**	0.017*	0.055
Bodily Pain	<0.001**	0.014*	0.002*
General Health	<0.001**	0.651	0.001*
Physical Component Score	<0.001**	0.016*	<0.001**

Data are expressed as mean (SD). [a] Differences between groups after 2 years, adjusted to baseline values, age, sex and comorbidity number. * Differences between evaluations ($p \leq 0.05$). ** Differences between evaluations ($p \leq 0.001$).

4.4.5. Discussion

This cohort study, to our knowledge, is the first to support that exercise per se is an effective strategy to reach hypertensive and functional status goals, independently of the ACEi therapy. Nevertheless, our results also suggest that the combination of exercise and ACEi therapy (ACEiMEX) may have positive effects to maintain and to improve physical functioning in independently hypertensive older adults with comorbidities.

Previous studies, contrary to our findings, have suggested that exercise training alone would be insufficient to prevent physical disability in hypertensive older adults, and should be combined with ACEi medicines to produce benefits (Buford et al., 2012); others assessed the isolated impact of ACEi medication in functional status and found mixed conclusions (Matteo Cesari et al., 2010; George & Verghese, 2016; Gray et al., 2012; Hutcheon et al., 2002; Kurklinsky & Levy, 2013; Spira et al., 2016; Sumukadas et al., 2007; Zi et al., 2003); while others suggested that ACEi drugs combined with exercise do not enhanced exercise response (Sumukadas et al., 2014).

These previous contradictory results should be carefully interpreted because in the Buford and colleagues (2012) (Buford et al., 2012) research, participants could be using a combined therapy – ACEi and other antihypertensive drug, potentially masking the isolated effect of mono-dose ACEi therapy. On the other hand, the lack of response observed by Sumukadas and colleagues (2014) (Sumukadas et al., 2014) may be related with an exercise program design flaw to improve the aerobic capacity, but also to the low adherence in the unsupervised home-based exercise regimen. Our results, collected from well characterized mono-dose ACEi and ACEiMEX groups, confirm that regular exercise training produce significant improvements in the functional status, particularly in upper and lower body strength, and in aerobic endurance. Moreover, and contrarily to the previous researches, in the present study, all physical components were improved in the supervised MEX group, independently of the baseline level of functionality. Additionally, it seems that the additive effect of exercise training in the ACEiMEX group, targeting different components of skeletal muscle function, preserved functional status (Simon et al., 2015) and improved the physiologic reserve, increasing the lower and upper body strength, the agility and dynamic balance, the upper body flexibility, and the cardiorespiratory endurance. These gains increase the ability to perform functional movements such as

walking, stair climbing and standing up, which in turn augments the capacity to perform everyday activities (e.g. personal care, shopping, housework) (Jones, J., Rikli, 2002), and ultimately prevent physical disability (Buford, 2016).

Exercise combined with ACEi medication has been linked, in the previous studies, to physiologic changes including improved capillary density and increased percentage of type-1 muscle fibers (Guo et al., 2010). Nevertheless, other studies have argued that the underlying mechanisms of these positive effects have not yet been clarified (Buford, 2016).

In fact, the cardiovascular protection properties of ACEi jointly with exercise training mechanisms, involving inhibition of pro-inflammatory and stimulation of anti-inflammatory pathways (Pedersen & Saltin, 2015), might be simply a result of the activation of a virtuous cycle determined by an improved cardiovascular system (Buford, 2016; Matteo Cesari et al., 2010), through a reduction in angiotensin II, resulting in reduced oxidative stress and inflammation, and ultimately, improved endothelial function (Buford, 2016; Simon et al., 2015). Actually, our results seem to support this rationale, due to the improvements in the secondary outcomes in the ACEiMEX and MEX group, including decreases in anthropometric measurements, and SBP and DBP (e.g. despite the higher baseline level in both groups, comparatively with the ACEi users). Furthermore, longitudinal age-related effects of hypertension on functional status (Buford, 2016), and the augments in blood pressure and anthropometric profile in the ACEi users also seem to reinforce this evidence. It appears that the long-term ineffectiveness of the ACEi monotherapy, as argued previously (Gu Q Dillon CF, et al., 2012; Mancia et al., 2013), may have hampered the functional status improvement, despite the "high normal" upper limit of the SBP target goal (Mancia et al., 2013). Moreover, in a recent study, no relationship was found between ACEi consumption and lean mass, strength, muscle quality or function (Spira et al., 2016), suggesting different pathways to explain these contradictory findings.

Genotype profile, specifically in the insertion (I allele) or deletion (D allele) of a 287 bp fragment in intron 16 of the angiotensin-converting enzyme gene (known to influence a variety of physiological adaptions to exercise), has been pointed out as a possible explanation to the variability in older adult's responsiveness to training (Buford et al., 2014). Nevertheless, the genotype profile was not assessed in the present study, being a field for future researches.

Finally, in contrast with the Kurklinsky and colleagues (Kurklinsky & Levy, 2013) study, our results seem to support the idea that exercise training may mitigate the effects of ACEi pharmacologic treatment in subjective physical HRQoL perception. In fact, while the ACEi group decreased the physical HRQoL (PF, GH and PCS), probably related to the ageing effect (Buford, 2016), the ACEiMEX and MEX groups enhanced their physical HRQoL sub-scales. Moreover, one surprising result was the augmented small to moderate effect in the Bodily Pain sub-scale, seen in the ACEiMEX and MEX group. Possible explanations might include muscle soreness caused by the exercise training, or by the augmented baseline age level that had significant impact on participants' self-perception in this domain, probably by the own characteristics of the hypertension, severity, and related comorbidities (Buford, 2016). Furthermore, the introduction of the exercise training regimen resulted in a more "active" therapy that in turn, for some individuals, could be more difficult to accomplish, requiring additional behavior changes. However, as confirmed by our results, are the most empowering, yielding the largest improvements in symptoms and overall quality of life (Ambrose & Golightly, 2015).

The longitudinal design of the present study has several strengths, including the large community sample exclusively composed by hypertensive older adults using ACEi mono-dose therapy, long-term supervised exercise training intervention, the use of well-validated instruments, and the range of outcomes measuring different aspects of physical function. However, some limitations should be also recognized, including the different group sample sizes, the non- randomized methodological design and the use of different types of ACEi medicines, even though they present similar action mechanism (Simon et al., 2015), which may mitigate this limitation. Additionally, although we controlled for several potential confounders, residual or unmeasured confounding may still be present. Indeed, the influence of treatment adhesion, dose and duration of ACEi use on functional status was not examined; those taking higher ACEi doses for longer period of time might have more severe hypertension. Nevertheless, these criteria seems to disappear once the differences at baseline were more harmful to the MEX group, than for the other two groups, showing after the intervention the biggest improvement in blood pressure level. Despite that, we also controlled for comorbidities.

Future studies on this topic should use a randomized controlled trial design with a similar sample size, testing for other comorbidities, long-standing hypertension and other

antihypertensive treatment types and dosages, combined with different types of exercise training programs, to strengthen the generalization to other hypertensive older adults populations.

Despite the limitations, our results have important clinical implications, demonstrating that exercise training may aid in the prevention of physical disability through a process that ultimately promotes functional status management in ageing-related hypertension (Buford, 2016). Furthermore, our benefits observed in the blood pressure management, in the other cardiovascular risk factors, and in the HRQoL are clinically important for this very high risk population for therapeutic competition, poor adherence to treatment and adverse drug events, including the number of medications, the treatment and the regimen complexity (Bell & Saraf, 2016; Charlesworth et al., 2015a). Finally, our findings will help to build a more solid clinical recommendation, including exercise training as the key ingredient in the ACEi effectiveness therapy to improve functional status, and creating a more successful, cost-effective management hypertension plan.

In summary, the current study provides evidence on the improvement of the physical functioning and HRQoL in older hypertensive adults using ACEi medications, only if they adopt an exercise training regimen, increasing also the management of the blood pressure and other cardiovascular risk factors.

4.5. Study V- Antihypertensive monotherapy or combined therapy: which is more effective on functional status?

Antihypertensive monotherapy or combined therapy: which is more effective on functional status?

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4.5.1. Abstract

Purpose: This study aims to analyze the effects of anti-hypertensive monotherapy and combined therapy on functional status, and cardiovascular risk outcomes in older adults.

Methods: This longitudinal non-randomized cohort study, involved hypertensive older adults (n = 440) aged 60 or more years with comorbidities. Participants underwent a community exercise training program and one of the following 2 conditions: i) use of daily mono-dose angiotensin converting enzyme inhibitors (ACEi; n = 232); ii) combined therapy including ACEi plus other class agent (Combined; n = 208). Baseline and 2-year follow-up evaluations included the functional fitness, health-related quality of life (HRQoL), health history questionnaires, anthropometric and hemodynamic profile.

Results: Both experimental groups have significantly improved physical functional status, and have significantly decreased blood pressure and waist circumference. ACEi group has significantly reduced body mass and body mass index, the Combined group significantly reducing the waist-to-hip ratio. Additionally, both groups perceived better physical HRQoL.

Conclusions: Functional status has improved with ACEi medication and exercise training, regardless the ACEi medication therapy. Exercise training plus ACEi antihypertensive therapy should be recommended into the standard prescription practice to reduce the rate of physical disability among hypertensive older adults.

Keywords: Functional status; exercise; angiotensin converting enzyme inhibitors; Combined therapy; cardiovascular risk factors; physical health related quality of life.

4.5.2. Introduction

Hypertensive older adults represent a specific high risk group of falls and fractures, and consequently they are more likely to have a compulsive hospitalization, adverse surgical outcomes, and even mortality (Dumurgier et al., 2009; Studenski et al., 2011). Indeed, one of the most problematic consequences also is physical disability (Buford, 2016), which clearly impact health-related quality of life (HRQoL) (Buford, 2016), especially due to the synergetic mechanism of the disease and the aging *per se.* Additionally, it seems that multimorbidity (Marventano et al., 2014), lifestyle habits (low level of exercise, smoking and excessive alcohol consumption, among others), and polypharmacy use (Charlesworth et al., 2015a; Peron et al., 2011) are also important risk factors for the functional status decline. Thus, interventions to reduce this negative symbiotic process may have important public health implications, given the increased number of hypertensive older adults (P. James et al., 2014).

The recent literature has suggested that pharmacological interventions with angiotensin converting enzyme inhibitors (ACEi) may have clinical benefits on cardiovascular outcomes (Simon et al., 2015) and on physical function (Buford et al., 2012; Christy S. Carter et al., 2012), but inconsistent results still exist among the best way to reduce the rate of physical disability in hypertensive older adults (Matteo Cesari et al., 2010; Gray et al., 2012; Spira et al., 2016; Zi et al., 2003). Moreover, it has been suggested that the benefits may only occur when ACEis are combined with exercise training (Buford et al., 2012; Christy S. Carter et al., 2012). However, different ACEi therapies (mono and combined therapy – ACEi and other antihypertensive drug) were categorized together (Buford et al., 2012) which probably masked the effect of ACEi therapy inhibiting the result of the best therapy to keep the functional status integrity. Furthermore, it is suggested that monotherapy can only reduce the blood pressure in a limited number of hypertensive individuals, leading that the majority of patients uses the combination of at least two agents to reach target levels (Gu Q Dillon CF, et al., 2012; Mancia et al., 2013).

On the other hand, the combined medication has been associated with the increased risk of drug duplication, drug–drug interactions and adverse drug reactions side effects such as reduced alertness, vision, and muscle strength which are related with the decreased physical functioning (Charlesworth et al., 2015a). Thus, it seems that a deeper

understanding of this topic could have major implications to hypertensive older adults. To date, however, no specific research has been conducted to understand how these differentiated therapies act in the functional status of hypertensive older adults. Moreover, the complexity of blood pressure control mechanisms remains elusive to treatment decisions due to the variety of hypertensive phenotypes among older adults (Sever & Messerli, 2011), particularly on their functional status, since mono and combined therapy have also some pros and cons (Mancia et al., 2013).

Therefore, given the inexistence of clinical trials specifically exploring this topic, the aims of the present study are twofold: firstly, to analyze the effect of exercise training and two types of ACEi treatment on functional status in independently hypertensive older adults with comorbidities: *i)* pharmacologic treatment with mono-dose ACEi drug (ACEi); and, *ii)* combined dual therapy with ACEi medication (Combined) plus other class agent; and secondly, to examine others cardiovascular risk outcomes including blood chemistry, anthropometric profile, and self-perception of their physical HRQoL. It was hypothesized that the Combined therapy would produce more pronounced effects on hypertensive older adults due to the pharmacodynamics properties (Mancia et al., 2013) of the two agents involved.

4.5.3. Methods

4.5.3.1. *Study design*

This non-randomized cohort study is part of a larger research involving community dwelling older adults to investigate the effect of long-term multicomponent exercise training on several variables. Details are available elsewhere (Baptista, Dias, Souza, Veríssimo, & Martins, 2017)

Participants were referred to the study by their physician or self-referred from flyers distributed at community centers, media advertisements or word of mouth. The methods and procedures were approved by the Institutional Scientific Board of the University of Coimbra, the local institution (Santa Maria da Feira County), and by the national ethics committees Data Protection Authority-CNPD and Health Administration of the North Ethics Committee-ARS/Norte.

The baseline interviews, clinical examination and the follow-up testing occurred between September 2013 and September 2015 and were performed by the same order at the baseline and at the end of the follow-up.

In brief, during the preliminary meeting, participants were informed about the nature, benefits and risks of the study, and gave their written informed consent, consistent with Helsinki Declaration. Additionally, participants completed the health history questionnaire and the Medical Outcomes Study 36-item Short-form Health Study questionnaire (SF-36). In the second meeting, the anthropometric, hemodynamic profile and the Senior Fitness Test were assessed.

Stature, body mass (BM), waist and hip circumferences, blood pressure and hemodynamic profile were assessed by highly trained nurses and by the study staff. For all the measurements that were considered to be affected by tester technique, the same investigator took the measurements at baseline and at the end-point, being periodically supervised to minimize any systematic error associated with variation in measurement techniques, and to ensure the precision and accuracy of the measurements (American College of Sports Medicine, 2010).

During the 24-months period of intervention all participants were encouraged to maintain the same nutritional pattern and to engage in a three sessions/week

multicomponent exercise program in local centers of Santa Maria da Feira. Several safety procedures were taken to ensure participants safety. Communication with participants' primary care physician and the trimester consultations with their physician were the key factor to maintain safety. Furthermore, potential adverse effects were explained in the preliminary meeting, and participants were encouraged to notify the study staff immediately if they experienced any abnormal symptom with medication, hypertension or exercise training. Posteriorly, the study staff was instructed to notify physicians that ultimately decided the appropriate course of action.

Physicians had full discretion to manage therapy regimen, doing all the necessary dose or drug changes prescription in order to maintain a medically supervised symptom-limited, to prevent hypokalemia, cardiac dysrhythmias, hypoglycemia, heat intolerance or other common symptoms associated with exercise, including shakiness, weakness, abnormal sweating, nervousness, anxiety, tingling of the mouth and fingers, hunger, headache, visual disturbances, mental dullness, confusion, amnesia, seizures, or coma. Resting systolic blood pressure (SBP) above 200 mmHg and/or diastolic blood pressure (DBP) higher than 110 mmHg was contra-indication to perform exercise training and criterion to communicate with the primary care physician. Nevertheless, no aggravated adverse event (life-threatening event, inpatient hospitalization or clinically significant abnormal laboratory or diagnostic test) was registered during the intervention period, except for soreness.

4.5.3.2. Study participants

Participants were eligible if they were aged 60 or more years, presented the *European Society of Hypertension* and the *European Society of Cardiology* (Mancia et al., 2013) criteria for hypertension, used ACEi medication for at least one year to manage hypertension, and presented physically independent functional status, determined by responses to the 12-item of Composite Physical Functioning Scale (Roberta E. Rikli & Jones, 2013). Participants were defined independent if they were able to perform all basic and all instrumental activities of daily living without assistance (Roberta E. Rikli & Jones, 2013).

Exclusion criteria included: (a) unstable angina; (b) uncontrolled symptomatic heart failure; (c) uncontrolled cardiac dysrhythmias; (d) symptomatic aortic stenosis; (e) not being under regular supervision of the treating physician for the period of the study evaluation; (f) known cancer or limited life expectancy, acute emergencies; (g) Parkinson's disease; (h) Alzheimer's disease; (i) dementia; (j) severe visual impairment; (k) further reasons that made it impossible or highly problematic to participate and come to the follow-up visits, completing baseline and follow-up testing (program log ≥ 80 %) and (l) using mono-dose of thiazide diuretic medication, calcium channel blockers, angiotensin receptor blockers medication or combined therapy without ACEi or with more than three agents.

A sub-group of 440 hypertensive older adults that fulfilled all the conditions exposed was retained as participants and was then divided according with 2 therapy criteria: i) mono-dose of oral antihypertensive medication - angiotensin converting enzyme inhibitors (ACEi; *n* = 232; 78% female); ii) and combined therapy (ACEi plus other antihypertensive medication) (Combined; *n* = 208; 72% female). Furthermore, the inclusion criteria for the ACEi group was daily mono-pharmacological therapy with ACEi and in the combined therapy group the use of ACEi plus other class of antihypertensive medication.

4.5.3.3. Interventions

Multicomponent exercise program

This exercise training program was designed to meet the exercise and physical activity guidelines for older adults with hypertension established by *American College of Sport Medicine* (American College of Sports Medicine, 2010). Exercise sessions were planned and adjusted according to the safety limits (American College of Sports Medicine, 2010), and intensity was monitored using the heart rate and a perceived exertion scale (Borg, 1988). Exercise modifications such as duration, number of repetitions, or use of an exercise auxiliary were recommended by the group instructor when needed.

The supervised multi-component exercise program consisted in three 60-min sessions/week, on three non-consecutive days. Aerobic, resistance, balance and flexibility

were trained accordingly with these items: 5-10 minutes of warm-up, 20-30 minutes of aerobic, 15-20 minutes of resistance training, 10 minutes of balance, 10 minutes of stretching, and 5-10 minutes of cool down exercises. Aerobic exercise started with participants in a standing position (e.g., walking in place with arm movements), and progressively involved continuous movement of major muscles of the upper-extremity, performed alternately with movement of the lower-extremity. Time and intensity of aerobic exercise was increased from 20 minutes per session at 50% HR_{max} (maximum heart rate) to 30 minutes at 60% HR_{max} per session (American College of Sports Medicine, 2010).

Resistance training involved a set of 5-8 exercises from the large muscle groups, with 1-3 sets of 8-12 repetitions for each upper and lower body muscle group and came from participants' own BM or with light free weights. Intensity was set at 50% to 70% 1-repetition maximum (1-RM), with 90 to 120 seconds of rest between sets.

Balance training was also based on functional tasks required by older adults. Prior to cool down, participants performed stretching exercises designed to improve flexibility of the major muscle groups; each stretch was sustained between 15 and 30 seconds to the point of tightness, and repeated three times.

Over the 24-months intervention, exercise progression increased every 6 weeks through augments on duration, repetitions, resistance, and/or difficulty (e.g., transition from sitting to standing to complete exercises).

Pharmacological procedure

Participants from each group used individualized daily prescriptions of antihypertensive drugs prescribed by their primary care physician, according with the presence or not of others comorbidities and blood pressure levels. All the necessary dose prescription adjustments were made throughout the intervention period by the primary care physician to maintain a medically supervised symptom-limited, reducing the risk of hypotension, hypokalemia, cardiac dysrhythmias and hyperglycemia/hypoglycemia (American College of Sports Medicine, 2010). In the ACEi therapy group, 34% of the participants used Perindopril (5-10 mg); 26% used Lisinopril (5-20 mg); 19% used Ramipril (10 mg); 12% used Enalapril (5-20 mg) and 9% used Captopril (25 mg). The

participants of the Combined therapy group used a combination of ACEi plus a thiazide related diuretic or a calcium channel blocker as the following description: 44% used Perindopril + Indapamide (5-10 mg/1.25-2.5 mg); 26% used Enalapril + Lercanadipine (10/10 mg); 19% used Lisinopril + Hydrochlorothiazide (20/12.5 mg) and 11% consumed Ramipril + Hydrochlorothiazide (5/25 mg).

4.5.3.4. Outcomes Measures

The primary end-point of our study was the change in functional status assessed by the Senior Fitness Test (SFT) battery (R.E. Rikli & Jones, 1999). Secondary outcomes included changes in the anthropometric, hemodynamic profile and physical subjective HRQoL outcomes; their details are provided below.

Functional Status

It was used the SFT battery (R.E. Rikli & Jones, 1999), a performance-based measure, developed to assess the underlying parameters associated with functional ability of older adults to perform the normal everyday activities (Roberta E. Rikli & Jones, 2013).

The SFT battery possesses strong psychometric properties (validity and test-retest reliability between 0.80 and 0.98), (Roberta E. Rikli & Jones, 2013) ease and safe use with a wide range of physical abilities, and his continuous scale allows a gradual assessment of changes over time (improvements or decline) (Roberta E. Rikli & Jones, 2013). Functional status assessment included measures of strength, aerobic endurance, flexibility, and agility/dynamic balance. The individual´s upper/lower body strength was measured by the number of repetitions in 30-second arm curl and chair stand test; the back scratch and the chair sit-and-reach test was used to measure the upper/lower body flexibility; the agility/dynamic balance was measured by the 8-foot up-and-go; and the aerobic endurance was measured by the 6-minutes' walk test. To minimize intraday variability, temperature effects, and biological rhythms, this test battery was performed between 8am and 10am.

Participants were told to avoid vigorous exercise in the 2 hours prior to testing, to wear comfortable clothes and appropriate walking shoes, and to continue their usual medication.

Hemodynamic Profile

Resting blood pressure was measured three times using a sphygmomanometer (Aneroid Sphygmomanometer-HICO HM 1001, Germany) and stethoscope (Nurse Type Professional Stethoscope-HICO HM-3005, Germany), in the seated position, after 5 minutes rest; the measurements were performed with 2 minutes intervals (American College of Sports Medicine, 2010). The mean of the measurements was used for SBP and DBP. Trained nurses collected venous blood in the morning after 12 hours fasting. Glycaemia, triglycerides (TG) and total cholesterol (TC) were determined by standard methods (American College of Sports Medicine, 2010) by an accredited laboratory

Anthropometric Profile

Stature was measured using a standard stadiometer to 0.1 cm in the upright position, with the participant´s back square against the wall and eyes looking straight ahead, without shoes. BM was measured by a calibrated digital balance-beam scale (SECA 770, Germany) with a precision nearest to 100 grams, with barefoot participants and in light clothing. Waist circumference (WC) was measured at the midpoint between the lowest rib and the top of the iliac crest at minimal respiration, and hip circumference was taken in a horizontal plan along pubic symphysis. Body mass index (BMI) and Waist-to-hip ratio (WHR) were calculated according to standard methods (American College of Sports Medicine, 2010).

Subjective physical health-related quality of life

Self-reported physical functioning domains of HRQoL were assessed using the SF-36 questionnaire, adapted and validated for the Portuguese population (Ferreira, 1998). This instrument, with high internal consistency and reliability (between 0.80 and 0.86) (Ferreira, 1998), was developed to measure generic health status and HRQoL (Anderson et al., 1996). For the purpose of the present study, only the 4 physical health-related subscales were utilized: Physical Functioning (PF); Role-Physical limitations (RP); Bodily Pain (BP); General Health (GH); and the summary dimension Physical Component Score (PCS), calculated using the methods set out by Ware and colleagues (Ware. Jr, 2000). Scores range from 0 to 100, with higher values indicating better functional health and well-being.

Health history

Demographic, medical and lifestyle data were obtained by questionnaire and included the following information: age, gender, education level, living situation, smoking status and the presence of several conditions like heart disease, hypertension, stroke, diabetes, dyslipidemia, osteoarthritis, pulmonary diseases, liver diseases, thyroid diseases, visual and audio problems, cancer, Parkinson's disease, Alzheimer disease, dementia or other comorbidities. Medication type and dosage were also assessed by detailed questionnaire with visual confirmation of prescription drugs recorded by the study staff.

4.5.3.5. Statistical analysis

Baseline participant's characteristics were carried out with measures of frequency, central tendency and dispersion – mean and standard deviation (SD), for the following variables: sex, age, BM, BMI, WHR, SBP, DBP, TC, TG, glycaemia, upper/lower body strength, upper/ lower body flexibility, agility/dynamic balance, aerobic endurance and physical HRQoL domains PF, RP, BP, GH and PCS.

Normality of the distributions was verified using the Kolmogorov-Smirnov test and the baseline demographic, physical performance and subjective HRQoL comparisons were performed using an independent sample *t*-Test Student. Additionally, adjustment for significant covariates such as age and comorbidity number was performed with an analysis of covariance (ANCOVA) for a group effect.

Longitudinal changes within groups were tested using a two-way analysis of variance for repeated measures. After the 24-months intervention, differences between groups were tested using the ANCOVA, adjusting for baseline score values, age and number of comorbidities. To test responsiveness at baseline and after the 24-months intervention, it was calculated the Hedges´s *g* effect size, providing a measure of the effect size weighted according to the relative different sample size within our study population (Hedges & Olkin, 1985). Corresponding standardized effects sizes were classified as small (<0.20), moderate (0.20-0.79) and large (>0.80) (Cohen, 1988).

Data analysis was performed using Statistical Package for the Social Sciences for Windows (IBM-SPSS, Inc. Chicago, IL, USA), software version 24, and the significance was set at 5%.

4.5.4. Results

After the 24-months intervention, 56 participants were lost to follow-up due to: the drop-out (12 from ACEi); and the exercise program adherence under 80% (34 from ACEi, and 10 from Combined therapy) (figure 4.5.1). The trial was completed by 87% of the participants (n = 384): ACEi (n = 186) and Combined group (n = 198). Participants lost to follow-up did not differ significantly in baseline characteristics from those completing the study. Completeness of data was 100%, having no missing responses.

4.5.4.1. Baseline participants' characteristics

Baseline demographic, anthropometric and hemodynamic profile, functional status and self-reported physical HRQoL characteristics, and differences between groups are presented in Table 4.5.1. The most prevalent comorbidities in the ACEi and Combined groups were respectively osteoarthritis (30% and 33%), osteoporosis (24% and 21%), diabetes (22% and 30%) and hypercholesterolemia (23% and 22%).

At baseline, the Combined group was older, it had significantly more comorbidities, higher SBP and DBP and glycaemia than the ACEi group. However, after adjustments to covariates there were just differences for SBP and DBP, glycaemia and upper body strength, even though with small effect size.

4.5.4.2. Differences within group from baseline to 24-months follow-up

After the 24-months intervention (Table 4.5.2), both groups have presented pronounced improvements in physical functional status ($P < 0.001$). Moreover, both groups have reduced their central obesity (WC), SBP and DBP ($P < 0.001$), even though, through different pathways; actually the ACEi group reduced significantly the BM and BMI ($P < 0.001$), and the Combined group had a better redistribution of the fat mass with reduction of their WHR ($P < 0.05$). Furthermore, both groups perceived better physical HRQoL with improvements in PF, RP and PCS, but also in BP. Only the Combined therapy group has perceived better GH ($P < 0.05$) at 24-months evaluation. No significant change occurred in lipid profile in both groups.

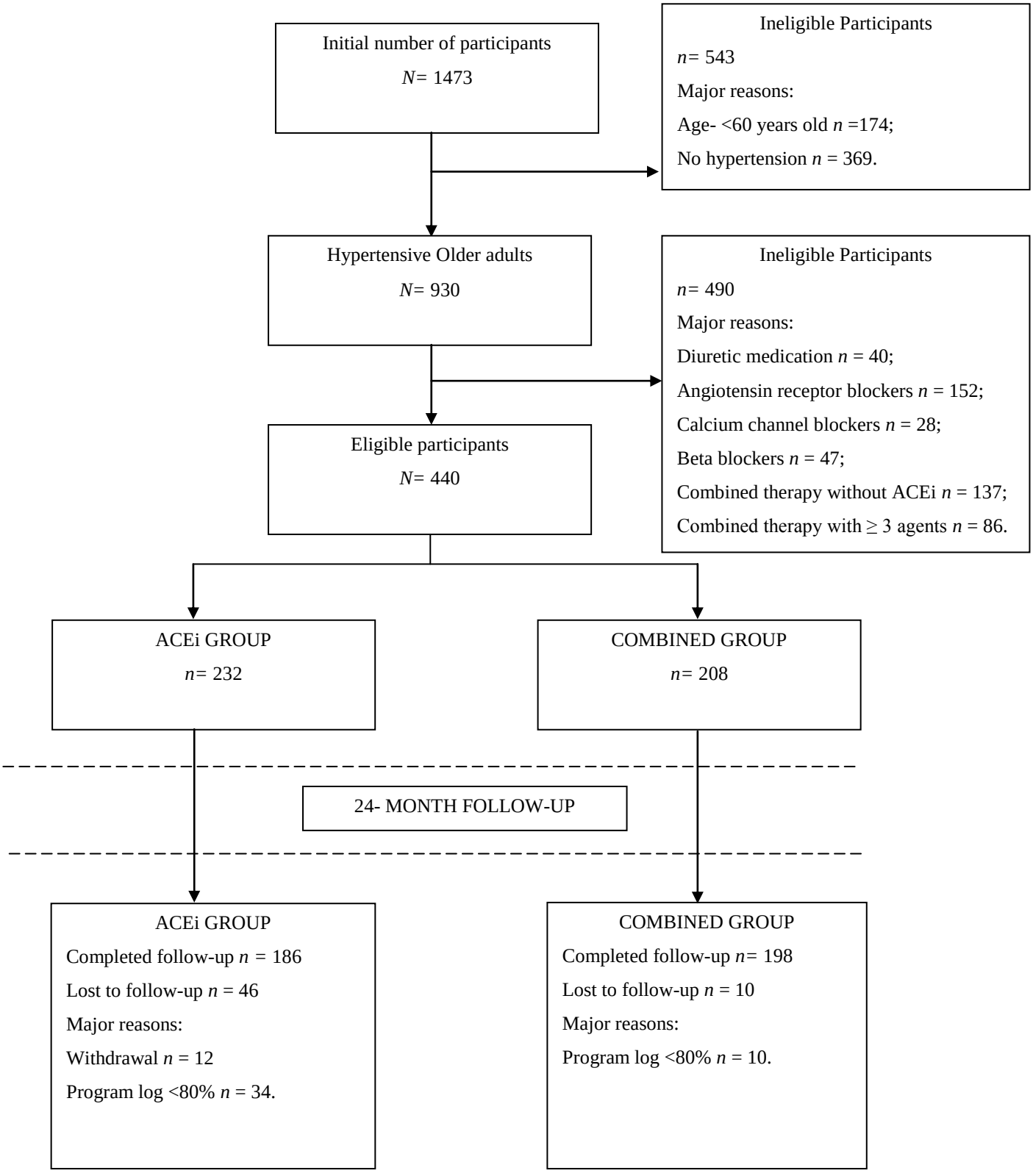

Figure 4.5.1. Cohort flux diagram

Table 4.5.1 – Descriptive baseline characteristics using *t*- Test student and ANCOVA (N=440)

Variables	Total (N=440)	ACEi (n=232)	Combined (n=208)	Group Effect (*P* Values)	Group Effect Adjusted [a] (*P* Values)	Effect Size
Female (%)	76	78	72	0.111	0.078	-
Age, years	68.9 (7.3)	67.9 (7.1)	70.2 (7.4)	<0.001**	-	0.318
Comorbidity, n	2.6 (1.6)	2.4 (1.6)	2.8 (1.7)	0.014*	-	0.243
Systolic BP, mmHg	142 (17)	139 (14)	147 (19)	<0.001**	<0.001**	0.483
Diastolic BP, mmHg	79 (12)	78 (11)	80 (12)	0.133	0.031*	0.174
Waist circumference, cm	93.4 (9.5)	92.5 (9.1)	94.6 (10.1)	0.034*	0.084	0.219
Body mass, kg	74.8 (12.2)	74.1 (11.6)	75.8 (13.0)	0.178	0.095	0.138
Body mass Index, kg/m2	29.6 (4.4)	29.4 (4.1)	30.0 (4.8)	0.148	0.120	0.135
Waist-to-hip ratio	0.90 (0.07)	0.90 (0.07)	0.91 (0.07)	0.204	0.408	0.143
Glycaemia, mg/dL	107 (28)	104 (24)	112 (32)	0.013*	0.046*	0.285
Total cholesterol, mg/dL	194 (36)	198 (38)	190 (33)	0.030*	0.080	-0.224
Triglycerides, mg/dL	122 (56)	124 (57)	120 (53)	0.572	0.482	-0.073
Lower body strength, n	14 (5)	14 (5)	14 (5)	0.627	0.185	0.000
Upper body strength, n	17 (5)	17 (5)	17 (4)	0.548	0.043*	0.000
Lower body flexibility, cm	1.0 (8.6)	0.6 (8.5)	1.5 (8.7)	0.315	0.496	0.105
Upper body, flexibility, cm	17.9 (10.2)	17.4 (10.3)	18.7 (10.1)	0.213	0.933	0.127
Agility/dynamic balance, s	5.8 (1.7)	5.6 (1.4)	6.2 (1.9)	0.001*	0.071	0.362
Aerobic endurance, m	435 (121)	444 (116)	420 (126)	0.063	0.523	-0.199
Physical Functioning	80 (20)	82 (19)	78 (20)	0.049*	0.397	-0.205
Role Physical	74 (23)	75 (23)	74 (24)	0.683	0.633	-0.043
Bodily Pain	67 (24)	67 (25)	67 (24)	0.809	0.292	0.000
General Health	57 (18)	57 (18)	58 (19)	0.773	0.281	0.054
Physical Component Score	70 (17)	70 (17)	69 (17)	0.665	0.440	-0.059

Data are expressed as mean (SD).). [a] Group effect adjusted to age and comorbidities number. *Differences between evaluations ($p \leq 0.05$). ** Differences between evaluations ($p \leq 0.001$).

Table 4.5.2- Differences within groups from baseline to 24 month evaluation, using a two-way ANOVA (*n*= 384)

Variables	ACEi (n=186)				Combined (n=198)			
	Baseline	24-months	*P* Value	Effect Size	Baseline	24-month	*P* Value	Effect Size
Systolic BP, mmHg	139 (14)	128 (16)	<0.001**	0.687	149 (19)	131 (15)	<0.001**	1.200
Diastolic BP, mmHg	78 (10)	74 (10)	<0.001**	0.400	79 (11)	73 (10)	<0.001**	0.600
Waist circumference, cm	92.8 (8.9)	90.4 (9.6)	<0.001**	0.250	94.4 (10.1)	91.7 (10.0)	<0.001**	0.270
Body mass, kg	74.5 (11.0)	73.6 (11.1)	<0.001**	0.081	75.9 (13.2)	75.8 (12.8)	0.687	0.008
Body mass Index, kg/m2	29.4 (3.8)	29.0 (3.8)	<0.001**	0.105	30.0 (4.7)	30.0 (4.7)	0.896	0.000
Waist-to-hip ratio	0.90 (0.07)	0.89 (0.07)	0.054	0.143	0.91 (0.07)	0.90 (0.07)	0.018*	0.143
Glycaemia, mg/dL	109 (27)	110 (29)	0.497	0.034	116 (35)	118 (41)	0.510	0.049
Total cholesterol, mg/dL	197 (38)	192 (35)	0.069	0.143	189 (35)	185 (36)	0.243	0.111
Triglycerides, mg/dL	131 (59)	132 (63)	0.845	-0.016	119 (51)	122 (63)	0.610	0.048
Lower body strength, n	14 (5)	18 (5)	<0.001**	0.800	14 (5)	18 (4)	<0.001**	1.000
Upper body strength, n	16 (4)	19 (6)	<0.001**	0.500	17 (5)	22 (5)	<0.001**	1.000
Lower body flexibility, cm	0.9 (8.3)	-2.8 (8.5)	<0.001**	0.435	1.4 (9.0)	-1.9 (9.2)	<0.001**	0.359
Upper body, flexibility, cm	17.7 (10.2)	14.0 (9.8)	<0.001**	0.378	18.0 (10.2)	15.2 (9.2)	<0.001**	0.326
Agility/dynamic balance, s	5.5 (1.4)	5.1 (1.5)	<0.001**	0.267	6.1 (1.9)	5.4 (1.9)	<0.001**	0.368
Aerobic endurance, m	445 (111)	563 (106)	<0.001**	1.113	425 (122)	538 (108)	<0.001**	1.046
Physical Functioning	83 (18)	88 (12)	<0.001**	0.417	79 (20)	86 (13)	<0.001**	0.538
Role Physical	75 (23)	80 (21)	<0.001**	0.238	75 (23)	79 (22)	0.033*	0.182
Bodily Pain	67 (24)	71 (23)	0.007*	0.174	67 (23)	73 (22)	0.003*	0.273
General Health	58 (19)	59 (16)	0.180	0.063	58 (18)	61 (17)	0.041*	0.176
Physical Component Score	71 (17)	75 (14)	<0.001**	0.286	70 (16)	75 (14)	<0.001**	0.357

Data are expressed as mean (SD). *Differences between evaluations ($P \leq 0.05$). ** Differences between evaluations ($P \leq 0.001$).

4.5.4.3. Differences between groups after 24 month intervention

After the 24-mouths of intervention period, and adjustment for covariates, groups did not presented significant statistical differences ($P > 0.05$), for primary and secondary outcomes; small effect size exceptions were observed for BM, BMI and PF domains (Table 4.5.3).

Table 4.5.3- Differences between and within groups from baseline to 24-month evaluation

Variables	Differences within groups		Differences between groups		
	ACEi Mean Change; Confidence Intervals	Combined Mean Change; Confidence Intervals	Mean Change; Confidence Intervals	*P Values*	*Effect Size*
Systolic BP, mmHg	-11.5 (-13.9: -9.1)	-15.7 (-18.5: -12.8)	-0.1 (-3.4: 3.1)	0.938	0.423
Diastolic BP, mmHg	-4.0 (–5.5: -2.5)	-6.6 (–8.5: -4.8)	1.9 (-0.2: 3.9)	0.072	0.191
Waist circumference, cm	-2.4 (–3.0: -1.9)	-2.7 (-3.4: -2.0)	0.1 (-0.8: 1.0)	0.793	0.032
Body mass, kg	-0.8 (–1.2: -0.4)	-0.1 (-0.6: 0.4)	-0.8 (-1.5: -0.2)	0.013*	0.066
Body mass Index, kg/m2	-0.3 (–0.5: -0.2)	-0.0 (-0.2: 0.2)	-0.4 (-0.6: -0.1)	0.011*	0.094
Waist-to-hip ratio	-0.01 (–0.01: 0.00)	-0.01 (-0.02: -0.00)	0.0 (-0.0: 0.0)	0.427	0.000
Glycaemia, mg/dL	1.1 (-2.0: 4.1)	1.6 (-3.2: 6.4)	-1.2 (-6.7: 4.2)	0.660	0.032
Total cholesterol, mg/dL	-5.3 (–11.0: 0.4)	-3.8 (-10.3: 2.6)	3.0 (-4.6: 10.6)	0.432	0.027
Triglycerides, mg/dL	0.9 (–7.9: 9.6)	2.9 (-8.2:13.9)	3.2 (-10.0: 16.4)	0.634	0.036
Lower body strength, n	4.5 (4.0: 5.1)	4.6 (3.5: 4.8)	-0.1 (-0.9: 0.7)	0.781	0.000
Upper body strength, n	5.1 (4.5: 5.7)	5.1 (4.4: 5.7)	-0.4 (-1.2: 0.4)	0.328	0.439
Lower body flexibility, cm	-3.7 (-4.9: -2.6)	-3.3 (-4.5: -2.1)	-0.4 (-2.0: 1.2)	0.615	0.046
Upper body, flexibility, cm	-3.7 (-4.5: -2.8)	-2.8 (-3.8: -1.7)	-0.8 (-2.1: 0.4)	0.192	0.088
Agility/dynamic balance, s	-0.4 (-0.6: -0.3)	-0.7 (-0.9: -0.5)	0.2 (-0.0: 0.5)	0.055	0.178
Aerobic endurance, m	118.2 (102.1: 134.2)	112.1 (90.7: 133.6)	7.2 (-13.9: 28.4)	0.501	0.043
Physical Functioning	4.8 (2.8: 6.7)	7.3 (5.0: 9.5)	-0.1 (-2.0: 1.9)	0.002*	0.105
Role Physical	5.6 (2.6: 8.5)	3.9 (0.3: 7.6)	0.6 (-3.4: 4.6)	0.766	0.000
Bodily Pain	4.3 (1.2: 7.3)	5.6 (2.0: 9.2)	-1.6 (-5.8: 2.5)	0.434	0.085
General Health	1.4 (-0.6: 3.5)	2.9 (0.1: 5.8)	-2.2 (-5.1: 0.7)	0.132	0.108
Physical Component Score	4.2 (2.4: 5.9)	5.0 (3.0: 7.1)	-0.9 (-3.3: 1.4)	0.439	0.061

Data are expressed as mean (SD). *Differences between evaluations ($P \leq 0$ .05). ** Differences between evaluations ($P \leq 0.001$).

4.5.5. Discussion

The recent literature has pointed out the inconsistent evidence about the standard prescription practice to reduce the rate of physical disability among hypertensive older adults. To our knowledge, the present study is the first to compare the ACEi therapy with ACEi combined with other antihypertensive class medication on functional status, revealing two novel and important findings. Firstly, it demonstrates the benefic effect of the chronic use of exercise training combined with antihypertensive medication in the improvement of physical functional status in a sample of hypertensive older adults with comorbidities. Secondly, it demonstrates that the functional status was improved in both therapies independently of the drug therapy.

The few previous studies conducted with the combination of ACEi and exercise training showed controversial results, including improvements in functional status (Buford et al., 2012), but also unchanged exercise response (Sumukadas et al., 2014). Nevertheless, both investigations have experimental design flaws that reduce their explanatory capacities. In fact, while in the first study (Buford et al., 2012), the therapy categorization may have included participants with mono and combined ACEi therapy in the same group, in the second study (Sumukadas et al., 2014), the exercise program that was not designed to specifically improve the aerobic capacity, beyond the low adherence in the unsupervised home-based exercise regimen, probably may have mitigated the benefic effect of exercise training jointly with ACEi use. The well characterized sample therapy groups of the current study confirm that exercise training combined with ACEi medication may produce significant improvements in the functional status of hypertensive older adults. Furthermore, the eclectic design of the supervised community multicomponent exercise program of the present study, targeting different components of skeletal muscle function (Simon et al., 2015), have improved the physiologic reserve, increasing the lower and upper body strength, the agility and dynamic balance, the upper and lower body flexibility, and the cardiorespiratory endurance.

The literature has reported that the ACEi acts through the vasodilatation achieved by blockade of the renin–angiotensin–aldosterone system (Sever & Messerli, 2011), blocking Angiotensin I to Angiotensin II conversion by inhibiting ACE activity, preventing the constriction of blood vessels, and lowering blood pressure (Simon et al., 2015).

However, the exact physiological mechanism of ACEi in physical function remains somewhat unclear. It has been suggested that the ACEi together with exercise training mechanisms, involving inhibition of pro-inflammatory and stimulation of anti-inflammatory pathways (Pedersen & Saltin, 2015), might activate a virtuous cycle (Buford, 2016; Matteo Cesari et al., 2010), through a reduction in angiotensin II, resulting in decreased oxidative stress and improved endothelial function (Buford, 2016; Simon et al., 2015). These effects may act in the preservation of the muscle strength, endurance, and body composition (Simon et al., 2015). Actually, this rationale seems to be supported by the results of the present study. Indeed, while in the monotherapy group the improvements of the functional status may be the result of the pronounced hemodynamic (SBP and DBP) and anthropometric (WC, BM and BMI) benefits, within the Combined therapy group it seems to have benefits not just with better hemodynamic profile but also with better redistribution of the fat mass, by reducing the WHR.

Another source of variation may be the different pharmacodynamics properties of each therapy (Mancia et al., 2013) which may explain the results of the present study. While in the monotherapy, the ACEi act primordially in the renin–angiotensin–aldosterone system (Sever & Messerli, 2011), in the Combined therapy, the synergetic effect of the ACEi combined with a diuretic or calcium channel blocker agent, not only act in the renin-angiotensin system but also add the effect of a different target organ (Digne-malcolm et al., 2016). In fact, whereas diuretic therapy (in our sample, Indapamide and Hydrochlorothiazide), promotes a vasodilation effect (Shih et al., 2014) through the inhibition of different sodium reabsorption mechanisms in the renal tubule, except for the Indapamide use, that acts mainly via inhibition of tubular reabsorption, analogous to the action of the non-selective β-blockers (Digne-malcolm et al., 2016), in the Lercanidipine, a calcium channel blocker, the inhibition of the movement of calcium ions into cardiac and vascular smooth muscles reduces arterial blood pressure and peripheral vascular resistance (Azizi et al., 2016), which could led to the improvements in functional status.

Of note, in the current study the improved functional status, hemodynamic and anthropometric profiles were also self-perceived as enhanced physical empowerment, expressing the improvements in the physical HRQoL in both groups, particularly in PF, RP and PCS, similarly as in the previous studies with ACEi (Kurklinsky & Levy, 2013; Sumukadas et al., 2007). One surprising result, however, was the increased small effect of

the BP sub-scale observed in both groups which could have several explanations including post-exercise muscle soreness. Moreover, the increased BP may also be the consequence of disease burden, including severity and related comorbidity (Buford, 2016).

Another surprising result was the inexistence differences between groups on functional status variables after the follow-up. It seemed logical that due to the added effect of the Combined therapy that ensemble the use of ACEi and other agent, this therapy would provide larger benefits than those offered by a monotherapy, especially due to the synergetic effect of the physiological and pharmacological characteristics of the different classes of agents (Mancia et al., 2013), which did not occurred. This result may indicate that even though these agents exert a protective effect in target organs in the treatment of hypertension (Mancia et al., 2013), leading to a final similar action through different mechanisms, it seems that other underlying agent might have a more substantial contribution in this relationship(Buford, 2016). In fact, even though both therapies have agents that directly act as vasodilators, or through indirect effects (Digne-malcolm et al., 2016), exercise training, the common element in both groups, may be the key concept to the inexistence of between groups differences. Additionally, the results also seem to suggest that using different types of ACEi therapy, in the presence of exercise training, is irrelevant to this relationship. Nevertheless, this rationale could not be confirmed by our study due to the inexistence of control group without exercise training; therefore future researches should be designed incorporating this previous concern.

The longitudinal design of the present study has several strengths, including the large community sample exclusively composed by well characterized hypertensive older adults with mono or combined ACEi therapy, long-term supervised exercise training intervention, the use of well-validated instruments and the range of outcomes measuring different aspects of physical function. However, the non-randomized methodological design and the lack of information about the duration of the disease could introduce a bias in how ACEi use and comorbidities affect functional independence. Actually, individuals taking higher ACEi doses for longer might have more severe hypertension which could be confounder variables. Additionally, even though the baseline blood pressure comparisons between those taking mono and Combined ACEi were different, being more severe in the Combined therapy group, at the end of the follow-up, no differences between groups were registered, presenting both improved functional status, indicating that this limitation might

has been mitigated. Furthermore, the inclusion of a control group without exercise training would have allowed to have a direct comparison of the effects of ACEi therapy and exercise training, and therefore, to strengthen the generalization to other hypertensive older adult populations. Future studies on this topic should also use a randomized controlled trial design, testing for other comorbidities, and long-standing hypertension.

Regardless of the limitations, the present study has important clinical implications, being the first step and evidence to a more fully-powered randomized control trial, demonstrating important public health implications because better functional status increases the ability to perform functional movements and everyday activities including personal care, shopping, or housework (Jones, J., Rikli, 2002), preventing physical disability, and ultimately augmenting HRQoL (Buford, 2016).

It should be also noted that the promotion of exercise training programs seems to be valuable, as exercise appears to be effective not only for functional status preservation, but also for the enhancement of the pharmacodynamics properties of the ACEi medications, to improve blood pressure and overall cardiovascular risk factors management (Piepoli et al., 2016), regardless the use of mono or combined ACEi therapy.

In summary, the current study provides evidence that exercise training benefits hypertensive older adults with independently functional status, regardless the ACEi therapy, in physical functioning, blood pressure and cardiovascular risk factors management, and ultimately HRQoL. Exercise training plus ACEi antihypertensive therapy should be recommended into the standard prescription practice to reduce the rate of physical disability among hypertensive older adults.

4.6. Study VI- Functional status improves in hypertensive older adults: the long-term effects of antihypertensive therapy combined with multicomponent exercise intervention

Functional status improves in hypertensive older adults: the long-term effects of antihypertensive therapy combined with multicomponent exercise intervention

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4.6.1. Abstract

Purpose: This study aims to compare the effects of multicomponent exercise and different pharmacological treatments on functional status and cardiovascular risk outcomes in hypertensive older adults with comorbidities.

Methods: Participants (n = 96) underwent a multicomponent exercise training program and one of the following 3 conditions: i) thiazide-related diuretics (TDs; n = 33, 69.9 ± 9.5 years); ii) calcium channel blockers (CCBs; n = 23, 67.0 ± 9.0 years); iii) and β-blockers (βBs; n = 40, 65.6 ± 7.2 years) medication. Baseline and 2-year follow-up evaluations included the *Senior Fitness Test battery*, anthropometrics and hemodynamic profile, health-related quality of life (HRQoL; *Short Form Health Survey 36*) and health history questionnaires.

Results: All groups have significantly improved the physical functional status; particularly upper and lower body strength and aerobic endurance and systolic blood pressure. The TDs and βBs groups have significantly diminished the waist circumference and body mass. The CCBs significantly decreased total cholesterol (P = 0.028), perceived better physical functioning, physical component score but also augmented bodily pain ($P < 0.05$). The βB group decreased triglycerides (P = 0.013). No group differences were found.

Conclusion: Multicomponent exercise training has improved functional status regardless of the antihypertensive medication options. Hypertensive older adults should add exercise training to pharmacological antihypertensive therapy to reduce the rate of physical disability.

***Keywords*:** Diuretics; Calcium channel blockers; β- blockers; Exercise; Functional Status; Older adults

4.6.2. Introduction

Functional independence during the aging process is determinant for the health-related quality of life (HRQoL) and hypertension management (Buford, 2016; Mancia et al., 2013). However, the increasing prevalence of functionally-limited hypertensive individuals (Hajjar et al., 2016) highlights the need for interventions to reduce the burden of hypertension-aging-disability (Buford, 2016) and to maximize the chances of healthy aging (Sumukadas et al., 2014). Indeed, hypertensive older adults are a specific high risk group for falls and fractures (Berlowitz et al., 2016), physical disability (Buford, 2016), hospitalization, surgical outcomes and mortality (Dumurgier et al., 2009), comparatively with normotensive counterparts (Dumurgier et al., 2009, 2010; Hajjar et al., 2016).

The recent literature, both from animal and human studies, has suggested that antihypertensive medication may play an important role to reduce functional decline (Buford et al., 2012; Christy S. Carter et al., 2012; Rosenberg et al., 2008; Shih et al., 2014), especially due to the blood pressure lowering properties and the pleiotropic effect on cardiovascular outcomes (Mancia et al., 2013; Sica, 2011). It seems that antihypertensive medication may have a beneficial effect on skeletal muscle through the stimulation of a virtuous cycle on the physiological responses, including improvements in body composition, inflammatory status, insulin resistance and oxidative stress (Matteo Cesari et al., 2010), that ultimately prevent physical functional health decline. To date, inconsistent results were reported in the literature on the effect of first-line antihypertensive therapies, which include positive associations between functional status with the use of angiotensin converting enzyme inhibitors (Buford et al., 2012; Christy S. Carter et al., 2012), βBs (Belenkov et al., 2003; Zhubrina et al., 2009), and TDs (Shih et al., 2014), and negative associations between functional status and the use of angiotensin converting enzyme inhibitors, CCBs, and TDs (Rosenberg et al., 2008). This suggests that the efficacy of antihypertensive medication as a therapeutic option for physical function may vary considerably according to select circumstances (Sica, 2011), drugs and/or specific populations with varying characteristics. However, no studies have examined the effect of calcium channel blockers (CCBs), thiazide diuretics (TDs) and β- blockers (βBs) on functional status in hypertensive older adults.

Earlier studies with angiotensin converting enzyme inhibitors (Buford, 2016; Buford et al., 2012) proposed to use exercise to stimulate certain adaptations to pharmacological treatments which may not be observed in response to the drug alone (Christy S. Carter et al., 2012; Kritchevsky et al., 2005). Exercise interventions, by themselves, showed promising results in the prevention of functional decline (C. K. Liu et al., 2014; Pahor et al., 2006). Therefore, the aims of the present study are: *i)* to compare the effects of exercise training and three different types of antihypertensive pharmacological treatments (i.e. TDs, CCBs, βBs) on functional status in independently hypertensive older adults with comorbidities; and *ii)* to assess overall cardiovascular risk outcomes including blood chemistry, anthropometric profile, and self-perception of physical HRQoL of the three interventions groups.

4.6.3. Methods

4.6.3.1. *Study design and procedures*

Study design has been previously described (Baptista, Machado-Rodrigues, Verissimo, & Martins, 2017). Briefly, this non-randomized cohort study is part of a larger research involving community dwelling older adults, addressed to the effect of long-term multicomponent exercise training on several variables, which were referred to the study by their physician or self-referred from flyers distributed at community centers, media or word of mouth advertising. The baseline interviews, clinical examination and the follow up testing occurred between September 2013 and September 2015 and were performed by the same order at the baseline and at the end of the follow-up.

The methods and procedures were approved by the Institutional Scientific Board of the University of Coimbra, the local institution (Santa Maria da Feira County) and national ethics committees Data Protection Authority-CNPD; Health Administration from North Ethics Committee-ARS/Norte.

In the preliminary meeting, participants were informed about the nature, benefits and risks of the study, and gave their written informed consent, consistent with the ethical procedures of the Declaration of Helsinki for human studies by the World Medical Association (World Health Organisation, 2013). Additionally, participants completed the health history questionnaire and the Medical Outcomes Study 36-item Short-form Health Study questionnaire (SF-36). A second meeting was then scheduled for the assessment of the following measures: anthropometric, hemodynamic profile and the Senior Fitness Test battery. For all the measurements that were considered to be affected by tester technique, the same investigator took the measurements at baseline and at the end-point, and were periodically supervised to minimize any systematic error associated with variation in measurement techniques, and to ensure the precision and accuracy of the measurements (American College of Sports Medicine, 2010). Stature, body mass (BM), waist and hip circumferences, blood pressure and hemodynamic profile were assessed by trained nurses and the other variables were examined by study staff.

During the intervention period, all participants were encouraged to maintain the same nutritional pattern and held trimester consultations with their primary care physician,

to control medication treatment. Additionally, all participants engage in a three sessions/week of multicomponent exercise in local centers of Santa Maria da Feira over the 24-months intervention period.

Several safety procedures were taken to ensure participants' safety. Firstly, communication with participants' primary care physician was the key factor to maintain safety. Additionally, potential adverse effects were explained in the preliminary meeting and if participants experienced any abnormal symptom with medication, hypertension or exercise training, they were encouraged to notify study staff immediately. Subsequently, study staff was instructed to notify physicians that ultimately decided the appropriate course of action.

Physicians had full discretion to manage therapy regimen, doing all the necessary dose or drug changes prescription in order to maintain a medically supervised symptom-limited, to prevent hypokalemia, cardiac dysrhythmias, hypoglycemia, heat intolerance or other common symptoms associated with exercise like: shakiness, weakness, abnormal sweating, nervousness, anxiety, tingling of the mouth and fingers, hunger, headache, visual disturbances, mental dullness, confusion, amnesia, seizures, or coma. Resting systolic blood pressure (SBP) above 200 mm Hg and/or diastolic blood pressure (DBP) higher than 110 mm Hg was a contra-indication to perform exercise training and a criterion to communicate with the primary care physician. Nevertheless, no serious adverse event (life-threatening event, inpatient hospitalization or clinically significant abnormal laboratory or diagnostic test) was registered during the intervention period, except for soreness.

4.6.3.2. Participants

Participants were eligible if they were aged 60 or more years, presented the *European Society of Hypertension* and of the *European Society of Cardiology* (Mancia et al., 2013) criteria for hypertension and presented physically independent functional status, determined by responses to the 12-item of Composite Physical Functioning Scale (Roberta E. Rikli & Jones, 2013). Independent functional status was defined if participants were able to perform all basic and all instrumental activities of daily living without assistance (Roberta E. Rikli & Jones, 2013). Exclusion criteria included: (a) unstable angina; (b) uncontrolled symptomatic heart failure; (c) uncontrolled cardiac dysrhythmias; (d) symptomatic aortic stenosis; (e) participants who were not under regular supervision of the

treating physician for the period of the study evaluation; (f) known cancer or limited life expectancy, acute emergencies; (g) Parkinson's disease; (h) Alzheimer's disease; (i) dementia; (j) severe visual impairment; (k) further reasons that made it impossible or highly problematic to participate and come to the follow-up visits, completing baseline and follow-up testing (program log ≥ 80 %) and (l) using angiotensin receptor blockers, angiotensin converting enzyme inhibitors medication or combined therapy.

A sub-group of 96 hypertensive older adults that fulfilled all the conditions exposed was retained as participants and was divided according with 3 oral antihypertensive therapy criteria (figure 1): i) TDs (*n*=33 ; 76% females); ii) CCBs (*n* = 23; 78% female); iii) and βBs (*n* = 40; 75% female). The inclusion criteria in each group was the used of mono-dose daily pharmacological therapy according to the preceding type of antihypertensive medication for at least 1 year. Additionally, all participants engage in a local multicomponent exercise program during intervention follow-up.

After the 24-months intervention, 8 participants were lost to follow-up due to: the drop-out (1 from CCBs); and the exercise program adherence under 80% (3 from TDs, and 4 from βBs). The trial was completed by 92% of the participants (*n* = 88): TDs (*n* = 30); CCBs (*n* = 22) and βBs group (*n* = 36). Participants lost to follow-up did not differ significantly in baseline characteristics from those completing the study. Completeness of data was 100%, having no missing responses.

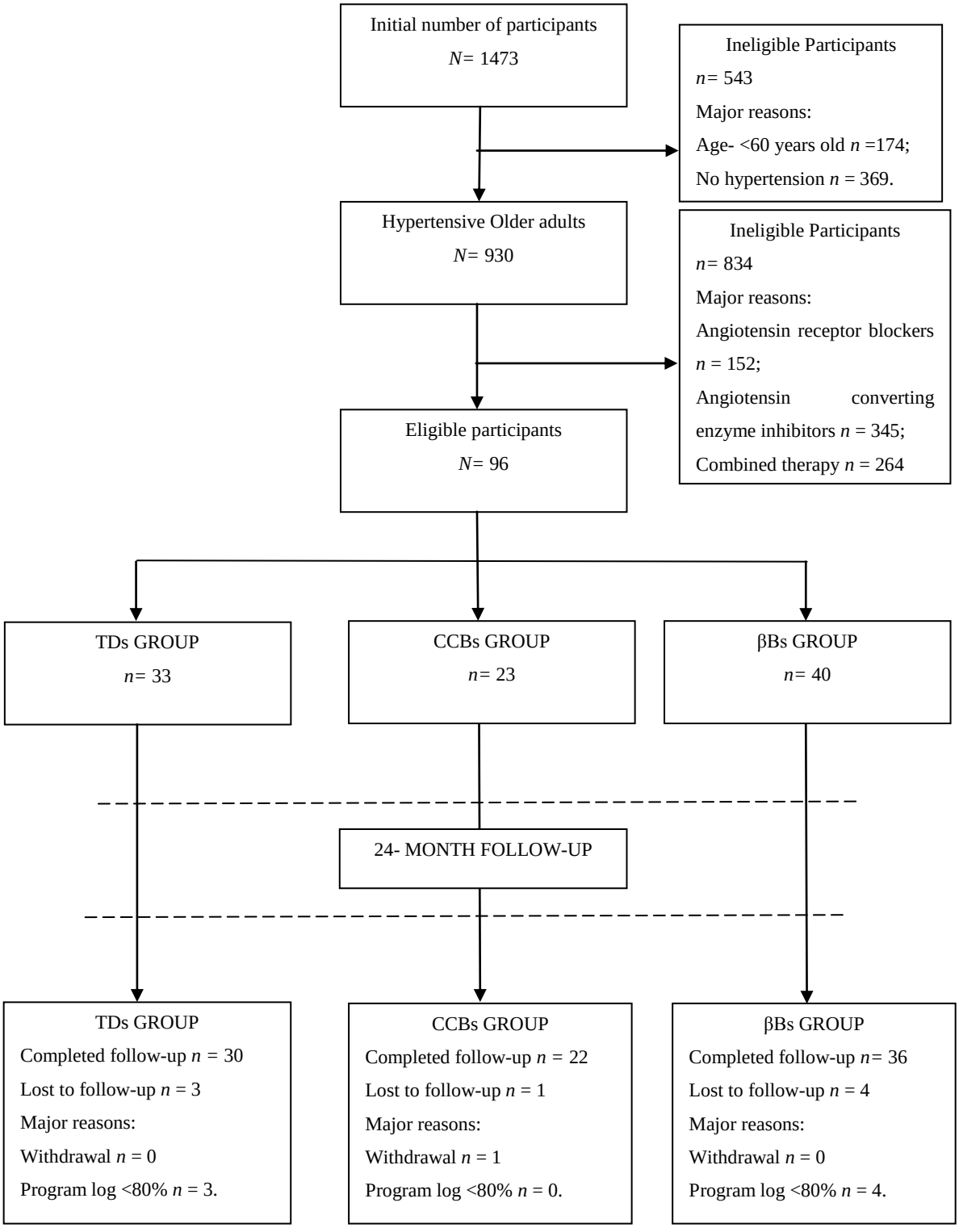


Figure 4.6.1- Flow chart of participants. TDs: thiazide-related diuretics intervention group; calcium channel blockers intervention group; β-blockers intervention group.

4.6.3.3. Interventions

Multicomponent exercise program

This exercise training program was designed to meet the exercise and physical activity guidelines for older adults with hypertension established by *American College of Sport Medicine* (American College of Sports Medicine, 2010). Exercise sessions were planned and adjusted according to the safety limits (American College of Sports Medicine, 2010) and intensity was monitored using an perceived exertion scale (Borg, 1988). Exercise modifications such as duration, number of repetitions, or use of an exercise auxiliary were recommended by the group instructor when needed.

The supervised multi-component exercise program consisted in three 60-min sessions/week, on three non-consecutive days. Aerobic, resistance, balance and flexibility were trained accordingly with these items: 5-10 minutes of warm-up, 20-30 minutes of aerobic, 15-20 minutes of resistance training, 10 minutes of balance, 10 minutes of stretching, and 5-10 minutes of cool down exercises. Aerobic exercise started with participants in a standing position (e.g., walking in place with arm movements), and progressively involved continuous movement of major muscles of the upper-extremity, performed alternately with movement of the lower-extremity. Time and intensity of aerobic exercise was increased from 20 minutes per session at 50% HR_{max} (maximum heart rate) to 30 minutes at 60% HR_{max} per session (American College of Sports Medicine, 2010).

Resistance training involved a set of 5-8 exercises from the large muscle groups, with 1-3 sets of 8-12 repetitions for each upper and lower body muscle group and came from participants' own BM or with light free weights. Intensity was set at 50% to 70% 1-repetition maximum (1-RM), with 90 to 120 seconds of rest between sets.

Balance training was also based on functional tasks required by older adults. Prior to cool down, participants performed stretching exercises designed to improve flexibility of the major muscle groups; each stretch was sustained between 15 and 30 seconds to the point of tightness, and repeated three times.

Over the 24-months intervention, exercise progression increased every 6 weeks through augments on duration, repetitions, resistance, and/or difficulty (e.g., transition from sitting to standing to complete exercises).

Pharmacological procedure

Participants from each group used individualized mono-dose daily prescriptions of antihypertensive drugs prescribed by their primary care physician, according with the presence or not of others comorbidities and blood pressure levels. All the necessary dose prescription adjustments were made throughout the intervention period by the primary care physician to maintain a medically supervised symptom-limited, reducing the risk of hypotension, hypokalemia, cardiac dysrhythmias and hyperglycemia/hypoglycemia (American College of Sports Medicine, 2010). In the TDs sample group participants used Indapamide- 2,5mg. In the CCBs group all participants used Amlodipine- 5mg. In the βBs group 57.5% used Bisoprolol- 5mg; 24.0% used Nebivolol- 5mg; and 18.5% used Carvedilol-25 mg.

4.6.3.4. *Outcomes Measures*

The primary outcome in our study was the change in functional status measured by the *Senior Fitness Test battery* (R.E. Rikli & Jones, 1999) and the secondary end-points included changes in the anthropometric, hemodynamic profile and physical subjective HRQoL outcomes.

Functional Status

The Senior Fitness Test battery (R.E. Rikli & Jones, 1999), develop to measure the underlying parameters associated with functional ability of older adults to perform the normal everyday activities (Roberta E. Rikli & Jones, 2013) was employed due to the strong psychometric properties (validity and test-retest reliability between 0.80 and 0.98), (Roberta E. Rikli & Jones, 2013) ease and safe use with a wide range of physical abilities, and his continuous scale allows a gradual assessment of changes over time (improvements or decline) (Roberta E. Rikli & Jones, 2013). This test battery includes measures of strength, aerobic endurance, flexibility, and agility/dynamic balance. The individual´s upper/lower body strength was measured by the number of repetitions in 30-second arm curl and chair stand test; the back scratch and the chair sit-and-reach test was used to measure the upper/lower body flexibility; the agility/dynamic balance was measured by the 8-foot up-and-go; and the aerobic endurance was measured by the 6-minutes' walk test. To

minimize intraday variability, temperature effects, and biological rhythms, this test battery was performed between 8am and 10am. Participants were told to avoid vigorous exercise in the 2 hours prior to testing, to wear comfortable clothes and appropriate walking shoes, and to continue their usual medication. Recommended reasons for immediately stopping the Senior Fitness Test evaluation and to ensure participants safety include chest pain, intolerable dyspnea, leg cramps, staggering, diaphoresis, and pale or ashen appearance.

Anthropometric Profile

Stature was measured using a standard stadiometer to 0.1cm in the upright position, with the participant´s back square against the wall and eyes looking straight ahead, without shoes. Body mass (BM) was measured by a calibrated digital balance-beam scale (SECA 770, Germany) with a precision nearest to 100 grams, with barefoot participants and in light clothing. Waist circumference (WC) was measured at the midpoint between the lowest rib and the top of the iliac crest at minimal respiration, and hip circumference was taken in a horizontal plan along pubic symphysis. Body mass index (BMI) and Waist-to-hip ratio (WHR) were calculated according to standard methods (American College of Sports Medicine, 2010).

Hemodynamic profile

Resting blood pressure was measured three times using a sphygmomanometer (Aneroid Sphygmomanometer-HICO HM 1001, Germany) and stethoscope (Nurse Type Professional Stethoscope-HICO HM-3005, Germany), in the seated position, after 5 minutes rest; the measurements were performed with 2 minutes intervals (American College of Sports Medicine, 2010). The mean of the measurements was used for systolic (SBP) and diastolic blood pressure (DBP). Trained nurses collected venous blood in the morning after 12 hours fasting. Glycaemia, triglycerides (TG) and total cholesterol (TC) were determined by standard methods (American College of Sports Medicine, 2010) by an accredited laboratory.

Subjective physical health-related quality of life

Perceived physical HRQoL was assessed using the SF-36 questionnaire, adapted and validated for the Portuguese population (Ferreira, 1998). This instrument, with high internal consistency and reliability (between 0.80 and 0.86) (Ferreira, 1998), was developed to measure generic health status and HRQoL (Anderson et al., 1996). In our study, only the 4 physical health-related subscales were utilized: Physical Functioning (PF); Role-Physical limitations (RP); Bodily Pain (BP); General Health (GH); and the summary dimension Physical Component Score (PCS), calculated using the methods set out by Ware and colleagues (Ware. Jr, 2000). Scores range from 0 to 100, with higher values indicating better functional health and well-being.

Health history

Demographic, medical and lifestyle data were obtained by questionnaire and included the following information: age, gender, education level, living situation, smoking status and the presence of several conditions like heart disease, hypertension, stroke, diabetes, dyslipidemia, osteoarthritis, pulmonary diseases, liver diseases, thyroid diseases, visual and audio problems, cancer, Parkinson's disease, Alzheimer disease, dementia or other comorbidities. Medication type and dosage were also assessed by detailed questionnaire with visual confirmation of prescription drugs recorded by the study staff.

4.6.3.5. *Statistical analysis*

Normality of distribution, skewness and homoscedastic variance were verified with Shapiro- Wilks, skewness coefficient and Levene´s tests. Baseline participant's characteristics were carried out with measures of central tendency and dispersion – mean and standard deviation (SD), for the following variables: age, BM, BMI, WHR, SBP, DBP, TC, TG, glycaemia, upper/lower body strength, upper/ lower body flexibility, agility/dynamic balance, aerobic endurance and physical HRQoL domains PF, RP, BP, GH and PCS.

Baseline demographic, physical performance and subjective HRQoL were compared using a one-way analysis of variance (ANOVA) test followed by Gabriel post-hoc for comparisons between groups. Longitudinal changes within groups were tested

using a two-way ANOVA for repeated measures. Differences between groups after 24-month intervention were performed using the analysis of covariance (ANCOVA), adjusting for baseline score values. To test responsiveness at baseline and after 24-months intervention, it was calculated the Hedges´s *g* effect size, providing a measure of the effect size weighted according to the relative different sample size within our study population (Hedges & Olkin, 1985). Standardized effects sizes were classified as small (<0.20), moderate (0.20-0.79) and large (>0.80) (Cohen, 1988). Data analysis was performed using Statistical Package for the Social Sciences for Windows (IBM-SPSS, Inc. Chicago, IL, USA), software version 24. Statistical tests were 2-tailed and significance was set at 5%.

4.6.4. Results

4.6.4.1. Baseline characteristics

Complete data were available for 96 hypertensive older adults (76% females) at baseline and after 24-months follow-up. Baseline demographic, medical, physical functional status and HRQoL characteristics and differences between groups are presented in Table 4.6.1 and Table 4.6.2. The most prevalent comorbidities of the TDs group were: hypercholesterolemia (33%), cancer (18%) and osteoarthritis (18%); in the CCBs group were diabetes (30%), osteoporosis and osteoarthritis (30%) and hypercholesterolemia (15%); and in the βBs were hypercholesterolemia (35%), osteoarthritis (23%) and osteoporosis (20%). At baseline, there were no significant differences between groups, except for SBP. Differences in SBP were more pronounced between βBs and CCBs groups (-13.7 mmHg; $P = 0.008$) and between TDs and βBs groups (11.5 mmHg; $P = 0.017$).

4.6.4.2. Differences within and between groups from baseline to 24-months follow-up

After the 24-months intervention, all groups improved the physical functional status, with large effects sizes in the upper and lower body strength and aerobic endurance ($P < 0.05$) (Table 4.6.3). Additionally, the SBP significantly decreased in all the groups ($P < 0.05$). The TDs and βBs groups have also significantly improved the anthropometric profile, specifically the WC and BM ($P < 0.05$). The CCBs decreased TC ($P = 0,028$), presented better physical HRQoL, not just in the PF and PCS but have also increased BP ($P < 0.05$) comparatively to the other two groups which had no significant change in physical HRQoL. The βBs group decreased TG ($P = 0.013$).

After the intervention period, and adjustment for covariates, there were no differences between groups in primary and secondary outcomes.

Table 4.6.1 – Descriptive baseline characteristics of the intervention groups, using one- way ANOVA (N=96)

Variables	Total (N=96)	TDs (n=33)	CCBs (n=23)	βBs (n=40)	Group Effect *P* Value
Female (%)	76	76	78	75	0.959
Age, years	67.4 (8.6)	69.9 (9.5)	67.0 (9.0)	65.6 (7.2)	0.106
Comorbidity, n	2.3 (1.6)	1.9 (1.7)	2.9 (1.5)	2.4 (1.5)	0.096
Systolic BP, mmHg	142 (16)	146 (17)	149 (16)	135 (13)	0.003*
Diastolic BP, mmHg	78 (11)	79 (10)	77 (13)	79 (11)	0.737
Waist circumference, cm	90.6 (8.6)	91.5 (8.4)	91.8 (9.5)	88.9 (8.0)	0.385
Body mass, kg	71.7 (8.9)	72.9 (9.6)	73.2 (7.3)	69.7 (9.1)	0.280
Body mass Index, kg/m2	28.3 (3.2)	28.8 (3.3)	28.6 (2.7)	27.5 (3.4)	0.267
Waist-to-hip ratio	0.89 (0.07)	0.90 (0.06)	0.91 (0.08)	0.87 (0.07)	0.156
Glycaemia, mg/dL	102 (24)	101 (22)	95 (11)	108 (32)	0.181
Total cholesterol, mg/dL	202 (47)	207 (42)	203 (40)	196 (58)	0.734
Triglycerides, mg/dL	123 (47)	125 (48)	112 (48)	130 (47)	0.483
Lower body strength, n	14 (5)	13 (4)	15 (5)	14 (5)	0.633
Upper body strength, n	17 (4)	16 (4)	18 (4)	17 (5)	0.120
Lower body flexibility, cm	-1.3 (8.9)	0.0 (8.0)	-1.5 (7.1)	-2.5 (10.7)	0.569
Upper body, flexibility, cm	15.9 (10.8)	16.2 (9.3)	16.8 (12.8)	14.9 (10.9)	0.817
Agility/dynamic balance, s	5.7 (1.7)	5.9 (1.7)	5.7 (2.0)	5.5 (1.6)	0.684
Aerobic endurance, m	434 (118)	430 (118)	435 (132)	438 (113)	0.974
Physical Functioning	81 (21)	82 (18)	79 (21)	81 (23)	0.893
Role Physical	76 (24)	75 (24)	70 (29)	81 (21)	0.224
Bodily Pain	67 (24)	72 (20)	60 (28)	67 (24)	0.170
General Health	61 (19)	66 (20)	56 (18)	59 (19)	0.116
Physical Component Score	71 (17)	74 (15)	66 (19)	72 (19)	0.239

TDs- Thiazide Diuretics; CCBs- Calcium Channel Blockers; βBs- Beta Blockers; Data are expressed as mean (SD); *Differences between evaluations ($p \leq 0.05$).

Table 4.6.2- Differences between groups at baseline in functional status and physical HRQoL outcomes

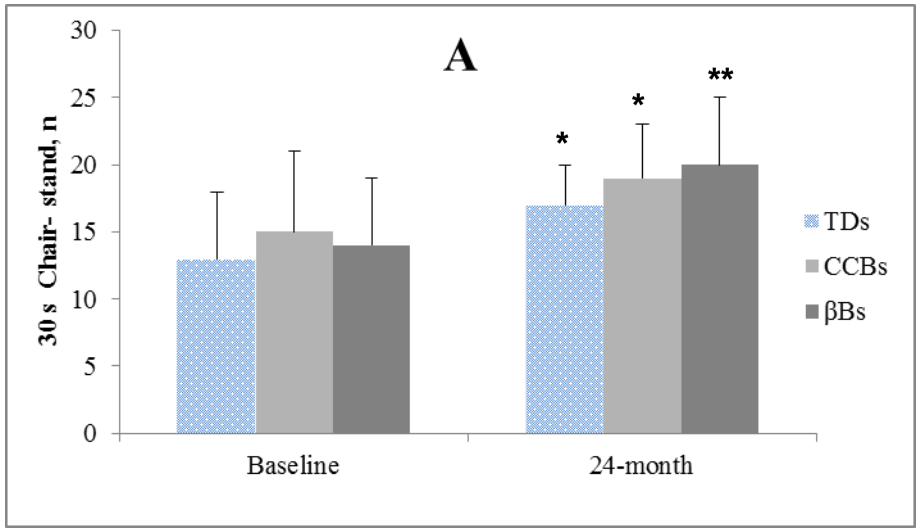
Variables	TDs vs CCBs	*P* Value	Effect Size	βBs vs CCBs	*P* Value	Effect Size	TDs vs βBs	*P* Value	Effect Size
Age, years	2.8 (-2.8 to 8.4)	0.531	-0.312	-1.4 (-6.8 to 3.9)	0.883	0.177	4.3 (-0.6 to 9.1)	0.102	-0.517
Comorbidity, n	-0.9 (-2.0 to 0.1)	0.088	0.617	-0.5 (-1.5 to 0.5)	0.492	0.333	-0.4 (-1.3 to 0.5)	0.603	0.314
Systolic BP, mmHg	-2.2 (-13.3 to 8.9)	0.947	0.181	-13.7 (-24.5 to -3.0)	0.008*	0.989	11.5 (1.7 to 21.4)	0.017*	-0.736
Diastolic BP, mmHg	2.3 (-5.8 to 10.3)	0.865	-0.177	2.3 (-5.5 to 10.1)	0.857	-0.170	0.0 (-7.1 to 7.2)	1.000	0.000
Waist circumference, cm	-0.3 (-5.3 to 4.7)	0.905	0.034	-2.9 (-7.9 to 2.0)	0.238	0.338	2.6 (-1.8 to 7.1)	0.245	-0.318
Body mass, kg	-0.3 (-6.6 to 6.0)	0.999	0.034	-3.5 (-9.7 to 2.7)	0.432	0.412	3.2 (-2.5 to 8.8)	0.439	-0.343
Body mass Index, kg/m2	0.2 (-2.1 to 2.5)	0.994	-0.065	-1.1 (-3.3 to 1.2)	0.561	0.348	1.3 (-0.8 to 3.4)	0.331	-0.387
Waist-to-hip ratio	-0.01 (-0.06 to 0.04)	0.946	0.145	-0.03 (-0.08 to 0.01)	0.200	0.542	0.03 (-0.02 to 0.07)	0.389	-0.457
Glycaemia, mg/dL	6.4 (-11.6 to 24.3)	0.769	-0.327	13.6 (-4.2 to 31.4)	0.184	-0.492	-7.2 (-24.4 to 11.6)	0.769	0.251
Total cholesterol, mg/dL	4.0 (-31.6 to 39.6)	0.990	-0.097	-6.8 (-43.1 to 29.5)	0.955	0.134	10.8 (-23.0 to 44.7)	0.819	-0.214
Triglycerides, mg/dL	12.2 (-23.6 to 48.0)	0.787	-0.271	17.8 (-18.4 to 53.9)	0.545	-0.380	-5.5 (-38.7 to 27.7)	0.968	0.105
Lower body strength, n	-1.4 (-4.8 to 2.1)	0.716	0.451	-0.6 (-4.0 to 2.8)	0.958	0.200	-0.7 (-3.8 to 2.4)	0.918	0.219
Upper body strength, n	-2.7 (-5.8 to 0.4)	0.113	0.500	-1.5 (-4.5 to 1.6)	0.569	0.214	-1.2 (-4.0 to 1.6)	0.639	0.219
Lower body flexibility, cm	1.5 (-5.0 to 8.0)	0.920	-0.196	-1.0 (-7.4 to 5.4)	0.974	0.105	2.5 (-3.3 to 8.3)	0.641	-0.261
Upper body, flexibility, cm	-0.6 (-8.4 to 7.1)	0.996	0.055	-1.9 (-9.5 to 5.7)	0.905	0.163	1.3 (-5.7 to 8.3)	0.959	-0.127
Agility/dynamic balance, s	0.2 (-1.0 to 1.4)	0.976	-0.109	-0.2 (-1.4 to 1.0)	0.965	0.114	0.4 (-0.7 to 1.5)	0.765	-0.243
Aerobic endurance, m	-4.7 (-91.5 to 82.2)	0.999	0.040	2.7 (-81.4 to 86.7)	1.000	-0.025	-7.3 (-85.7 to 71.1)	0.994	0.069
Physical Functioning	2.7 (11.0 to 16.3)	0.950	-0.156	1.6 (-11.5 to 14.5)	0.987	-0.090	1.1 (-10.8 to 12.9)	0.995	-0.048
Role Physical	5.3 (-10.6 to 21.1)	0.804	-0.191	10.8 (-4.4 to 25.9)	0.237	-0.455	-5.5 (-19.3 to 8.2)	0.696	0.268
Bodily Pain	12.2 (-3.4 to 27.8)	0.168	-0.509	7.6 (-7.3 to 22.5)	0.523	-0.274	4.6 (-8.9 to 18.1)	0.790	-0.224
General Health	9.9 (-2.5 to 22.3)	0.155	-0.521	2.7 (-9.2 to 14.5)	0.929	-0.161	7.3 (-3.5 to 18.0)	0.281	-0.360
Physical Component Score	7.6 (-3.4 to 18.6)	0.264	-0.478	5.7 (-4.8 to 16.3)	0.469	-0.316	1.9 (-7.7 to 11.4)	0.951	-0.116

TDs- Thiazide Diuretics; CCBs- Calcium Channel Blockers; βBs- Beta Blockers; Data are expressed as mean (SD); *Differences between evaluations ($p \leq 0.05$).

Table 4.6.3- Differences within and between groups from baseline to 24 month evaluation, using a two-way ANOVA for repeated measures and ANCOVA (n=88)

	TDs (n=30)				CCBs (n=22)				βBs (n=36)				Differences between groups [a]
Variables	Baseline	24-months	*P* Value	Effect Size	Baseline	24-month	*P* Value	Effect Size	Baseline	24-months	*P* Value	Effect Size	*P* Value
Systolic BP, mmHg	149 (17)	131 (14)	<0.001**	1.286	150 (17)	134 (23)	0.003*	0.696	132 (13)	124 (14)	0.037*	0.571	0.898
Diastolic BP, mmHg	78 (10)	72 (8)	0.006*	0.750	74 (13)	72 (13)	0.400	0.154	79 (11)	72 (6)	0.027*	1.167	0.815
Waist circumference, cm	91.3 (8.8)	88.5 (9.0)	0.001*	0.311	91.0 (10.3)	88.6 (7.8)	0.074	0.308	88.1 (9.1)	83.9 (8.8)	0.001*	0.477	0.144
Body mass, kg	72.7 (10.2)	70.6 (10.2)	0.001*	0.206	72.0 (7.3)	71.4 (7.3)	0.249	0.082	69.6 (10.4)	68.4 (9.7)	0.038*	0.124	0.212
Body mass Index, kg/m2	28.5 (3.3)	27.8 (3.1)	0.004*	0.226	28.1 (3.1)	28.0 (3.4)	0.455	0.029	27.4 (3.9)	26.9 (3.8)	0.085	0.132	0.269
Waist-to-hip ratio	0.90 (0.06)	0.90 (0.07)	0.477	0.000	0.92 (0.08)	0.90 (0.08)	0.231	0.250	0.86 (0.06)	0.85 (0.07)	0.178	0.143	0.171
Glycaemia, mg/dL	101 (23)	95 (14)	0.264	0.429	96 (11)	102 (15)	0.130	-0.400	110 (34)	110 (37)	0.951	0.000	0.280
Total cholesterol, mg/dL	208 (48)	192 (59)	0.147	0.271	208 (41)	191 (31)	0.028*	0.548	205 (62)	179 (38)	0.055	0.684	0.648
Triglycerides, mg/dL	138 (48)	120 (35)	0.120	0.514	110 (44)	107 (46)	0.616	0.065	134 (46)	103 (38)	0.013*	0.816	0.323
Lower body strength, n	13 (5)	17 (3)	0.001*	1.333	15 (6)	19 (4)	0.002*	1.000	14 (5)	20 (5)	<0.001**	1.200	0.161
Upper body strength, n	16 (4)	22 (4)	<0.001**	1.500	19 (4)	23 (3)	0.001*	1.333	17 (5)	23 (4)	<0.001**	1.500	0.543
Lower body flexibility, cm	-0.1 (8.8)	-2.3 (8.3)	0.025*	0.265	-2.9 (7.4)	-5.4 (5.0)	0.119	0.500	-1.3 (10.4)	-4.9 (11.8)	0.027*	0.305	0.666
Upper body, flexibility, cm	16.0 (10.6)	13.3 (9.8)	0.024*	0.276	15.9 (12.8)	12.3 (10.6)	0.035*	0.340	13.2 (8.8)	11.0 (10.9)	0.013*	0.202	0.773
Agility/dynamic balance, s	5.8 (1.8)	5.7 (2.6)	0.786	0.038	5.3 (1.0)	4.7 (0.5)	0.022*	1.200	5.4 (1.5)	4.8 (0.9)	0.037*	0.667	0.297
Aerobic endurance, m	419 (126)	551 (118)	<0.001**	1.119	478 (114)	557 (94)	0.013*	0.840	426 (108)	576 (85)	<0.001**	1.765	0.351
Physical Functioning	82 (19)	86 (20)	0.405	0.200	80 (21)	89 (13)	0.017*	0.692	85 (18)	88 (11)	0.348	0.273	0.803
Role Physical	75 (23)	83 (23)	0.094	0.348	70 (30)	79 (24)	0.187	0.375	83 (17)	85 (18)	0.431	0.111	0.955
Bodily Pain	71 (20)	75 (22)	0.241	0.182	63 (25)	76 (23)	0.050*	0.565	71 (22)	73 (21)	0.716	0.095	0.470
General Health	65 (20)	66 (16)	0.742	0.063	59 (18)	57 (13)	0.633	0.154	59 (18)	62 (16)	0.084	0.188	0.260
Physical Component Score	73 (16)	78 (18)	0.198	0.278	68 (18)	75 (16)	0.014*	0.438	74 (14)	77 (14)	0.257	0.214	0.829

TDs- Thiazide Diuretics; CCBs- Calcium Channel Blockers; βBs- Beta Blockers; Data are expressed as mean (SD); *Differences between evaluations ($p \leq 0.05$). ** Differences between evaluations ($P \leq 0.001$). [a] Differences between groups adjusted to baseline score values.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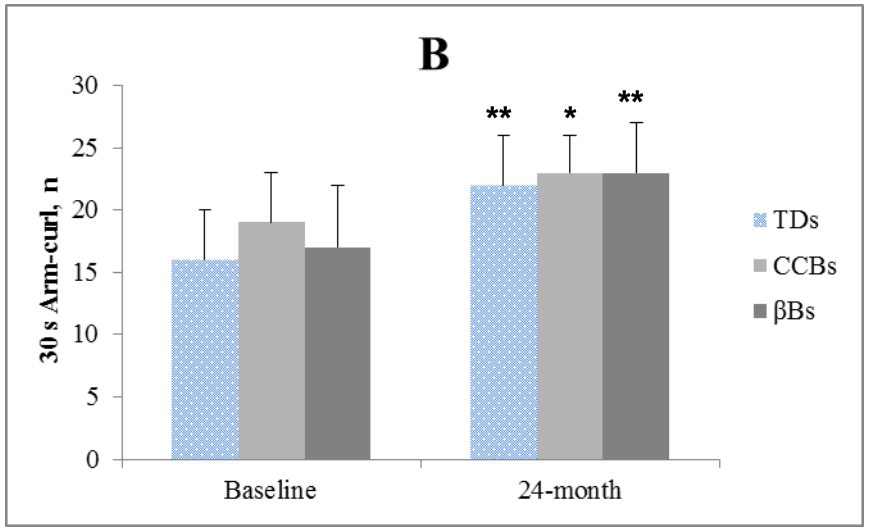
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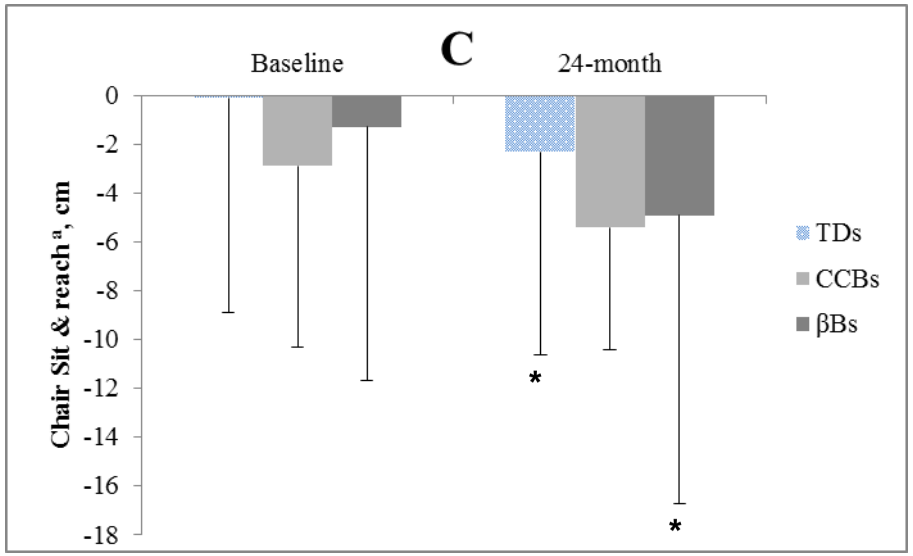
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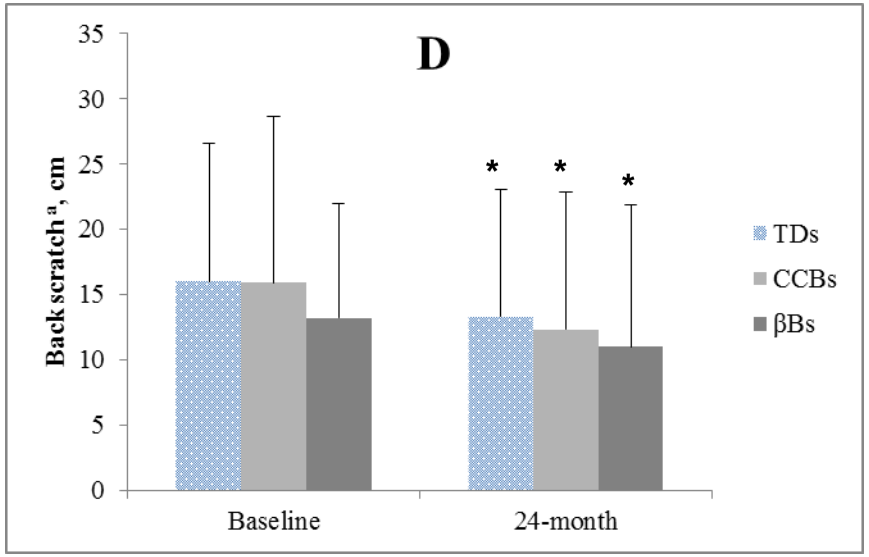
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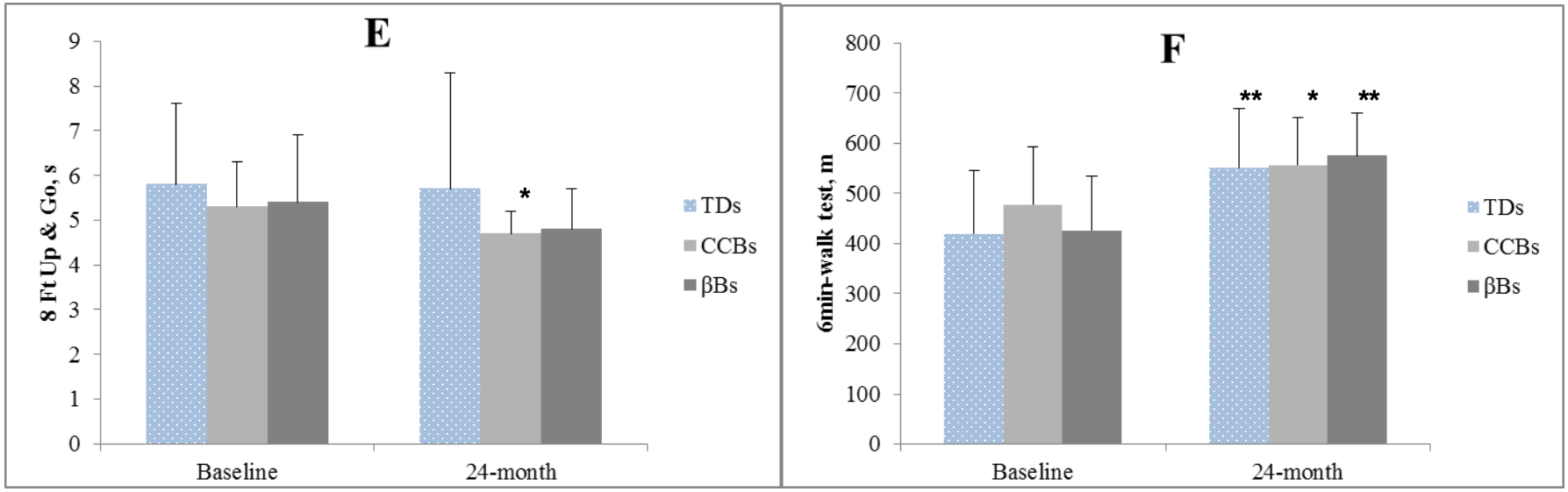

Figure 4.6.2- Values of lower body strength (Panel A), upper body strength (Panel B), lower body flexibility (Panel C), upper body flexibility (Panel D), agility/dynamic balance (Panel E) and aerobic endurance (Panel F) at baseline and after 24 month intervention. [a] Decrease means improvements. * Differences between evaluations ($p \leq 0.05$). ** Differences between evaluations ($p \leq 0.001$).

4.6.5. Discussion

The recent literature has reported inconsistent evidence about the standard prescription practice to reduce the rate of physical disability among hypertensive older adults. Longitudinal data analyses are essential to evaluate the impact of long-term first-line therapies and exercise on physical function of hypertensive older people. To our knowledge, this study is the first to compare the functional status among the three first-line antihypertensive treatments. The major findings of the present study were the evidence of the beneficial effect of the chronic use of exercise training plus antihypertensive medication in the improvement of functional status in independently hypertensive older adults, regardless the type of antihypertensive therapy. Therefore, exercise training plus antihypertensive therapy should be recommended into the standard prescription practice to reduce the rate of physical disability among hypertensive older adults.

The similarities of action that follow chronic administration of antihypertensive drugs should not necessarily be taken to imply similarities of mechanism (Digne-malcolm et al., 2016). In fact, this rationale may be the central aspect to the inexistence of differences between our groups after the follow-up. Despite the protective effects exerted on the target organs in treating hypertension, leading to a final similar action, some agents act as direct vasodilators, whilst others may had indirect effects, which mediated by exercise training may reduce physical decline (Buford, 2016).

In the present study, consistent with previous studies (Belenkov et al., 2003; Shih et al., 2014; Zhubrina et al., 2009), the βBs Bisoprolol, the third generation βBs- Nebivolol and Carvedilol, the TDs drug Indapamide and the CCBs Amlodipine, all improved physical function outcomes. This was particularly noted in the upper and lower body strength and aerobic endurance capacity, regardless the individual pharmacodynamics properties; even though, agility and dynamic balance and lower body flexibility outcomes, didn´t reach statistical significance in TDs and CCBs group, respectively.

These afore-mentioned improvements may be associated with the differentiated underlying biologic pathways that jointly with exercise training benefits may create a differentiated pleiotropic effect on the cardiovascular outcomes (Mancia et al., 2013; Sica, 2011), with improvements in endothelial function, in oxidative stress (particularly the third generation of βBs Nebivolol (Weber, 2005)) and inflammation, leading to a final similar result within each group, through different pathways. Of note, even though we did not

measure it, the βBs have been linked to the: *i*) the inhabitation of the renin-angiotensin system, decreasing renin release (Simon et al., 2015; Weber, 2005); *ii*) central inhabitation of the sympathetic nervous activity and increased vagal activity (Weber, 2005) that have been implicated in the cardioprotective benefits of exercise (J. B. Carter, Banister, & Blaber, 2003); *iii*) improve neuro-hormonal modulation (Lambert, Jonsdottir, Gavin, & Influ-, 1998); *iv*) decrease heart rate and cardiac output (Weber, 2005), leading to improved contractile capacity and enhanced cardiac electrical stability, which were linked with exercise training contributions in autonomic regulation and with decreased risk of future functional decline in older adults (Soares-miranda, Sattelmair, Chaves, Siscovick, & Stein, 2014). The TDs drug Indapamide, acts mainly via inhibition of tubular reabsorption, similar to the action of the non- selective β-blockers (Digne-malcolm et al., 2016) and the CCBs Amlodipine, inhibits the movement of calcium ions into cardiac and vascular smooth muscles, reducing arterial blood pressure and peripheral vascular resistance, presenting important autonomic adjustments associated with sympathetic autonomic modulation reduction (Azizi et al., 2016). Furthermore, in a macro-perspective, the medication and exercise training physiological benefits may acted in the improvement of body composition, reduction of the inflammatory status, reduction of insulin resistance, resulting in an improved cardiovascular system (Buford, 2016; Matteo Cesari et al., 2010; Simon et al., 2015), acting into the muscle cell, and ultimately, preventing physical functional decline. Findings of the present study, particularly related to the anthropometric, lipid and hemodynamic profile, seem to support this rationale, once all groups improved SBP. Additionally the TDs and βBs groups decreased their central obesity with reductions on WC and BM and the CCBs and βBs groups improved their lipid profile, with improved TC and TG, respectively. Contrary to our expectations and other previous studies (Kurklinsky & Levy, 2013) was the lack of statistical significance within groups in the perceived physical HRQoL, except for the higher scores in PF, BP and PCS, in the CCBs group. Potential explanations may be related with the small sample within each group which may reduce the statistical robustness, once even though they did not reach statistical significance, both groups improved their physical HRQoL outcomes.

The improvements observed in the CCBs group in the physical HRQoL, are in line with previous studies with other antihypertensive medications (Kurklinsky & Levy, 2013; Sumukadas et al., 2007). On the other hand, potential explanations to the higher BP sub-scale in CCBs group may be related with muscle soreness caused by the adaptation to the exercise training because the introduction of the exercise training regimen resulted in a

more “active” therapy requiring that individuals participate actively for an extended period of time and could require significant behavioral changes (Ambrose & Golightly, 2015); In turn, for some individuals, it could be more difficult to accomplish, but as confirmed by the results of the present study, they are the most empowering, yielding the in symptoms and overall quality of life (Ambrose & Golightly, 2015).

The present study has several strengths including its longitudinal design, a sample group composed by hypertensive older adults using antihypertensive mono-dose therapy, long-term supervised exercise training intervention; furthermore, the use of well-validated instruments and the range of outcomes measuring different aspects of physical function were important methodological issues in the present scientific field. In contrast, the small group sample size and the non- randomized methodological design represent some drawbacks that may have limited some results in the perceived physical HRQoL. Additionally, the inclusion of one control group (receiving no exercise or antihypertensive TDs, CCBs and βBs) would have allowed a direct comparison of these antihypertensive therapy types and exercise training. Thus, future studies on this topic should use a randomized controlled trial design with a similar sample size, testing for other comorbidities, long-standing hypertension and use a control group to strengthen the generalization to other hypertensive older adult populations.

These findings have important clinical implications, since they were the first step of evidence to a more fully-powered randomized control trial, to demonstrate that mono-pharmacological antihypertensive therapy should be used combined with exercise training to prevent aging hypertension functional impairment (Buford, 2016), to improve blood pressure and overall cardiovascular risk factors management (Mancia et al., 2013). Furthermore, these data suggests that independently of the first-line antihypertensive therapies choice, exercise training prescription should be added into the standard pharmacological care of hypertension to reduce the increasingly higher rate of physical disability among hypertensive older adults (Dumurgier et al., 2010). These gains increase the ability to perform functional movements such as walking, stair climbing and standing up, which in turn augments the capacity to perform everyday activities (e.g. personal care, shopping, housework)(Roberta E. Rikli & Jones, 2013), and ultimately prevents physical disability (Buford, 2016).

In summary, in order to maintain the functional status hypertensive older adults should add exercise training into the standard prescription practice, independently of the antihypertensive pharmacological choice, to reduce the rate of physical disability.

4.7. Study VII- Exercise training is more effective than statins to improve functional status: the longitudinal effect in dyslipidemic older adults

Exercise training is more effective than statins to improve functional status: the longitudinal effect in dyslipidemic older adults

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4.7.1. Abstract

Purpose: This study aims to analyze the effect of exercise training and statins on functional status, cardiovascular risk (CVR), and physical health-related quality of life (HRQoL) in dyslipidemic older adults with comorbidities.

Methods: Participants (*n* = 981) underwent one of the following 3 conditions: i) multicomponent exercise training (MEX; *n* = 298; 74% females); ii) oral statins (ST; *n* = 178; 65% females); iii) combined therapy - exercise plus ST therapy (MEX+ST; *n* = 505; 79% females). Functional fitness, anthropometry, hemodynamic and lipid profiles, and HRQoL were evaluated at baseline and at 2-year follow-up.

Results: MEX and MEX+ST participants improved all the functional status variables, whereas ST participants aggravated all the outcomes. In terms of HRQoL, MEX and MEX+ST groups augmented physical functioning (PF), role physical (RP), physical component score (PCS), Total SF-36, but also augmented bodily pain (BP); reversely, the ST group decreased PF, BP, PCS and Total SF-36. Triglycerides and HDL-cholesterol maintained unchanged and total cholesterol decreased in the three groups, whereas LDL-cholesterol (LDL-C) decreased in MEX and MEX+ST groups but not in ST group. MEX and MEX+ST groups decreased body mass index (BMI), systolic and diastolic blood pressure; contrarily, ST group increased these variables.

Conclusion: Exercise alone, or combined with statins, improves functional status, physical HRQoL, BMI and hemodynamics, whereas isolated statin treatment deteriorates these variables. Furthermore, only exercising groups decreased LDL-C. Exercise training should be prescribed for all dyslipidemic older adults with comorbidities, particularly for those who present statins adverse effects.

***Keywords*:** Statins; Exercise; Functional Status; Older adults

4.7.2. Introduction

Statins (ST) are the first-line pharmacologic antidyslipidemic therapy to decrease low-density lipoprotein cholesterol (LDL-C) levels for primary and secondary prevention of cardiovascular disease (CVD) (Catapano et al., 2016; Gui et al., 2017). Actually, recent guidelines (Catapano et al., 2016) increased the number of eligible people for ST therapy, including almost three quarters of older adults (Pencina et al., 2014). Unfortunately, ST have been also associated with an increased likelihood of diabetes (Sattar et al., 2017), elevated liver enzyme levels and musculoskeletal conditions, ranging from mild myalgia to rhabdomyolysis (Catapano et al., 2016) that seems to be aggravated with high-doses of ST (Bruckert, Hayem, Dejager, Yau, & Begaud, 2005; Parker Beth A, Capizzi Jeffrey A, Grimaldi Adam S, Clarkson Priscilla M, 2013), high levels of exercise (Williams & Thompson, 2017), and with increasing age (Bruckert et al., 2005).

The effects of ST therapy on physical activity (PA) function and health related quality of life (HRQoL) presents some controversy. In fact, a negative impact has been found leading to decreased PA and increased sedentary behavior (Lee et al., 2014), but others did not found association between ST and the rate of functional decline (Gray et al., 2012), or differences in muscle strength and exercise capacity (Parker Beth A, Capizzi Jeffrey A, Grimaldi Adam S, Clarkson Priscilla M, 2013). Moreover, ST use was associated with poor physical functioning and poor self-rated health related with muscle pain (Peeters, Tett, Conaghan, Mishra, & Dobson, 2015). Nevertheless, positive associations between ST treatment and functional status (Magaly Villafrádez-Díaz, Yesenia Santiago-Casas Mariely Nieves-Plaza, Rodríguez, Ríos, David Martínez, & Vilá, 2014), lower decline in walking speed (Dumurgier et al., 2014) and greater response to resistance training (Riechman et al., 2007) also exist.

Combining ST therapy with exercise training also presents inconsistent results, including impaired exercise training adaptations (Mikus et al., 2013), maintenance of muscle damage following exercise (Panayiotou et al., 2013) and exercise-related injuries (tendon, ligament, and muscle) (Bakker et al., 2017), but also benefits from PA intervention (Henderson et al., 2016), and higher efficacy in terms of insulin sensitivity, inflammation and exercise capacity (Gui et al., 2017); and improving fitness could potentially modulate the diabetogenic effects of the ST use (P. Kokkinos et al., 2017). Therefore, the present study aims to analyze the effect of three types of treatment

(multicomponent exercise training – MEX; oral ST; combined therapy including ST plus exercise training – MEX+ST) on functional status, on physical self-perception of HRQoL, and on CVR factors including the anthropometric, lipid and hemodynamic profiles, in independently dyslipidemic older adults with comorbidities. It is hypothesized that the combined therapy would promote significant benefits due to the synergetic effects of both therapies (Gui et al., 2017).

4.7.3. Methods

4.7.3.1. *Study design and procedures*

This research occurred between September 2013 and September 2015. Methodological design was previously described (Baptista, Machado-Rodrigues, Verissimo, et al., 2017). Briefly, this non-randomized cohort study is part of a larger research addressed to analyze the effect of long-term MEX in community dwelling older adults, in terms of functional status, physical self-perception of HRQoL, and CVR factors including the anthropometric, lipid and hemodynamic profiles. Participants' allocation was made by self-referencing through flyers that were distributed at community centers, media, word-of-mouth advertising or through physician counseling. The methods and procedures were approved by the Institutional Scientific Board of the University of Coimbra, the local institution (Santa Maria da Feira County) and national ethics committees Data Protection Authority-CNPD; Health Administration from North Ethics Committee-ARS/Norte. Informed consent was obtained from all the participants, consistent with the ethical procedures of the 1964 Helsinki declaration and its later amendments for human studies by the World Medical Association (World Health Organisation, 2013).

After the recruitment period, in the preliminary meeting, participants were informed about the nature, benefits and risks of the study, and those that volunteered gave their written informed consent, completed the health history questionnaire and the Medical Outcomes Study 36-item Short-form Health Study questionnaire (SF-36). In the second meeting, it was assessed the anthropometric outcomes, the hemodynamic profile and the functional status by the Senior Fitness Test (SFT) battery (R.E. Rikli & Jones, 1999). Baseline evaluation, clinical examination and the follow up testing were performed by the same order at the baseline and at the end of the follow-up.

Stature, body mass (BM), waist and hip circumferences, blood pressure and hemodynamic profile were assessed by trained nurses. All the other variables were examined by exercise specialists (degree in physical education and/ or sport sciences). For all the measurements that were considered to be affected by tester technique, the same investigator performed the measurements at baseline and at the end of the study. All study staff was periodically supervised to minimize any systematic error associated with

variation in measurement techniques, and to ensure the precision and accuracy of the measurements (American College of Sports Medicine, 2010) by the study coordinator.

During the intervention period, all participants were encouraged to maintain the same nutritional pattern. Participants of the MEX and MEX+ST groups met three times a week for one hour over the 24-months intervention period to perform the multicomponent exercise program in 32 local centers of Santa Maria da Feira, while the participants of the ST and MEX+ST held trimester consultations with their primary care physician, to control medication treatment. Several procedures were taken to ensure participants' safety: *i*) communication with participants' primary care physician was the key factor to maintain safety; *ii*) potential adverse effects were explained in the preliminary meeting and participants were encouraged to notify study staff if experienced any abnormal symptom with medication or exercise training; *iii*) physicians had full discretion to manage therapy regimen, doing all the necessary dose or drug changes prescription to maintain a medically supervised symptom-limited.

4.7.3.2. Participants

Eligibility criteria included: *i*) aged above 60 years; *ii*) presented the *European Society of Cardiology* and *European Atherosclerosis Society* (Catapano et al., 2016) criteria for dyslipidaemia; *iii*) and be physically independent, determined by responses to the 12-item of Composite Physical Functioning Scale (Roberta E. Rikli & Jones, 2013). Participants were considered independent if they were able to perform all the basic and all the instrumental activities of daily living without assistance (Rikli & Jones, 2013). Exclusion criteria included: (a) unstable angina; (b) uncontrolled symptomatic heart failure; (c) uncontrolled cardiac dysrhythmias; (d) symptomatic aortic stenosis; (e) participants who were not under regular supervision of the treating physician for the period of the study evaluation; (f) known cancer or limited life expectancy, acute emergencies; (g) Parkinson's disease; (h) Alzheimer's disease; (i) dementia or mild/severe cognitive impairment; (j) severe visual impairment; (k) further reasons that made it impossible or highly problematic to participate and come to the follow-up visits, completing baseline and follow-up testing (program log $\geq$ 80 %); (l) using bile acid sequestrate, cholesterol absorption inhibitors, PCSK9 inhibitors, nicotinic acid or other drug combination. A sub-group of 981 inactive (American College of Sports Medicine, 2014) dyslipidemic older adults that fulfilled all the conditions exposed was retained as participants and divided

according with 3 therapy criteria: *i*) MEX (n = 298; 74% females); *ii*) ST (n = 178; 65% females); *iii*) MEX+ST (n = 505; 79% females).

4.7.3.3. Interventions

Multicomponent exercise program

The supervised exercise training program was designed, planned and adjusted to meet the exercise and PA guidelines and the safety limits for older adults as stated by the *American College of Sport Medicine* (American College of Sports Medicine, 2010). The intensity was monitored using a perceived exertion scale (Borg, 1988) and a heart rate monitor (Polar, SWE).

Exercise modifications such as duration, number of repetitions, or use of an exercise auxiliary were recommended by the group instructor when needed. The multicomponent exercise training consisted in three 60-min sessions/week, on three non-consecutive days and included aerobic, resistance, balance and flexibility components according with these items: 5-10 minutes (min) of warm-up, 20-30 min of aerobic, 15-20 min of resistance training, 10 min of balance, 10 min of stretching, and 5-10 min of cool down exercises. Aerobic exercise started with participants in a standing position (e.g., walking in place with arm movements), and progressively involved continuous movement of major muscles of the upper-extremity, performed alternately with movement of the lower-extremity. Time and intensity of aerobic exercise was increased from 20 to 30 min at 50-70% maximum heart rate (HR_{max}) per session (American College of Sports Medicine, 2010).

Resistance training involved a set of 5-8 exercises from the large muscle groups, with 1-3 sets of 8-12 repetitions for each upper and lower body muscle group and came from participants' own BM or with free weights. Intensity was set at 50-70% 1-repetition maximum (1-RM), with 90 to 120 seconds of rest between sets. Balance training was also based on functional tasks required by older adults. Prior to cool down, participants performed stretching exercises designed to improve flexibility of the major muscle groups; each stretch was sustained between 15 and 30 seconds to the point of tightness, and repeated three times.

Exercise progression increased every 6 weeks through augments on duration, repetitions, resistance, and/or difficulty (e.g., transition from sitting to standing to complete exercises). All training sessions were carefully supervised by 34 experienced exercise specialists (ratio of supervision was 1 professor for 9 participants) who were regularly supervised by the general study coordinator. To minimize any systematic error associated with variation in training sessions (American College of Sports Medicine, 2014), monthly meetings were conducted by the general study coordinator.

Pharmacological procedure

The participants of the ST and MEX+ST groups used daily ST monotherapy, prescribed by their primary care physician according to their lipid profile, during at least one year prior to the study initiation. Furthermore, trimester medical consultations were held by the participants with their physician to control blood lipid levels and antidyslipidemic medications doses, and all abnormal symptoms detected were discussed with the primary care physician that decided the appropriate course of action. The ST drugs prescribed to these groups included: Atorvastatin (10mg), Pravastatin (20mg), Pitavastatin (2mg), Rosuvastatin (20mg) and Simvastatin (20mg).

4.7.3.4. *Outcomes Measures*

Functional Status

To assess the underlying parameters associated with functional ability of older adults to perform the normal everyday activities (Roberta E. Rikli & Jones, 2013) it was used the SFT battery (R.E. Rikli & Jones, 1999), a performance-based measure. This battery possesses strong psychometric properties (validity and test-retest reliability between 0.80 and 0.98) (Roberta E. Rikli & Jones, 2013), ease and safe use, with a wide range of physical abilities, and his continuous scale allows a gradual assessment of changes over time (improvement or decline) (Roberta E. Rikli & Jones, 2013).

Functional status assessment includes measures of strength, aerobic endurance, flexibility, and agility/dynamic balance. The individual´s upper/lower body strength was measured by the 30-second arm curl and chair stand test; the back scratch and the chair sit-

and-reach test was used to measure the upper/lower body flexibility; the agility/dynamic balance was measured by the 8-foot up-and-go; and the cardiorespiratory fitness (CRF) was measured by the 6-minutes-walk test.

To minimize intraday variability, temperature effects, and biological rhythms, this test battery was performed between 8-10 am and participants were instructed to avoid vigorous exercise in the 2 hours prior to testing, to wear comfortable clothes and appropriate walking shoes, and to continue their usual medication. Recommended reasons for immediately stopping the SFT evaluation and to ensure participants safety included chest pain, intolerable dyspnea, leg cramps, staggering, diaphoresis, and pale or ashen appearance.

Anthropometric Profile

Stature was measured using a standard stadiometer to 0.1 cm in the upright position, with the participant´s back square against the wall and eyes looking straight ahead, without shoes. Body mass (BM) was measured by a calibrated digital balance-beam scale (SECA 770, Germany) with a precision nearest to 100 grams, with barefoot participants and in light clothing. Waist circumference (WC) was measured at the midpoint between the lowest rib and the top of the iliac crest at minimal respiration, and hip circumference was taken in a horizontal plan along pubic symphysis. Body mass index (BMI) and Waist-to-hip ratio (WHR) were calculated according to standard methods (American College of Sports Medicine, 2010).

Hemodynamic and lipid profile

Resting blood pressure was taken three times using a sphygmomanometer (Aneroid Sphygmomanometer-HICO HM 1001, Germany) and stethoscope (Nurse Type Professional Stethoscope-HICO HM-3005, Germany), in the seated position, after 5 minutes rest; the measurements were performed with 2 minutes intervals (American College of Sports Medicine, 2014). The mean of the measurements was used for systolic (SBP) and diastolic blood pressure (DBP). Blood lipid outcomes were determined from venous blood collected in the morning after 12 hours fasting. Total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C) and triglycerides (TG) were carried out in plasma and determined by standard methods

(American College of Sports Medicine, 2014) by the same accredited laboratories at baseline and at the end of the study.

Subjective health-related quality of life

Self-perception of HRQoL was assessed using the SF-36 questionnaire, adapted and validated for the Portuguese population (Ferreira, 1998). This instrument with high internal consistency and reliability (between 0.80 and 0.86) (Ferreira, 1998) was developed to measure generic health status and HRQoL. In this study attention was placed on physical body perception through the evaluation of 4 health-related subscales: Physical Functioning (PF), Role-Physical limitations (RP), Bodily Pain, General Health (GH) and one summary measure Physical Component Score (PCS). A Total SF-36 Score was also calculated. The standardized summary scores for physical was calculated using the methods set out by Ware and colleagues (Ware. Jr, 2000). The scores range from 0 to 100, with higher values indicating better functional health and well-being. For the purpose of the present study, the sub-scales of the PF, RP and bodily pain assume as important self-perception outcomes of treatments effects (Gray et al., 2012).

Health history

Participants demographic, medical and lifestyle data were obtained by questionnaire and included the following information: age, gender, education level, living situation, smoking status and the presence of several conditions like heart disease, hypertension, stroke, diabetes, dyslipidemia, osteoarthritis, pulmonary diseases, liver diseases, thyroid diseases, visual and audio problems, cancer, Parkinson's disease, Alzheimer disease, dementia or other comorbidities. Medication type and dosage were also assessed by detailed questionnaire with visual confirmation of prescription drugs recorded by the study staff.

4.7.3.5. *Statistical analysis*

Baseline characteristics were compared across the 3 groups with measures of frequency, central tendency and dispersion – mean and standard deviation (SD), for the following variables: sex, age, comorbidity number, WC, BM, BMI, WHR, SBP, DBP, TC, HDL-C, LDL-C, TG, 30-s chair-stand, 30-s arm-curl, chair sit-and-reach, back scratch, 8

foot up-and-go, 6-min-walk test, and physical HRQoL domains PF, RP, bodily pain, GH, PCS and Total SF-36. Furthermore, for all continuous variables, normality of distribution and homoscedastic variance were verified through numeric (Kolmogorov-Smirnov and Levene´s tests) and graphical methods.

One-way analysis of variance (ANOVA) followed by Gabriel *post-hoc* was used for comparisons between groups on the baseline demographic, anthropometric, hemodynamic, lipid, physical performance and subjective HRQoL outcomes. To assess the longitudinal changes within and between groups, a two-way ANOVA for repeated measures was used. These models examined whether the mean scores on these outcome measures differ at baseline or with respect to mean change over 24-months intervention. In additional analyses and to minimize potential confounding, important covariates were included on the basis of clinical relevance as factors that could influence the outcomes, thus differences between groups after 24-months intervention were also assessed using the analysis of covariance (ANCOVA), adjusting for age, sex and comorbidity number. Additionally, we also conducted several sensitivity analyses to minimize the possibility of reverse causation, with adjustment to baseline mean scores.

To test the magnitude of changes within each group from baseline to 24-months intervention, we calculated Hedges´s *g* effect size, which provides a measure of the effect size weighted according to the relative different sample size within each group and the respective 95% confidence intervals (Hedges & Olkin, 1985). Standardized effects sizes were classified as small (<0.20), moderate (0.20-0.79) and large (>0.80) (Cohen, 1988). The equation $\underline{\Delta}$% [(Post-pre follow-up/Total Test) x 100] was used to a more simple interpretation to determine the percentage difference within each group across all variables analyzed from baseline to final 24-months evaluation.

Data analysis was performed using Statistical Package for the Social Sciences for Windows (IBM-SPSS, Inc. Chicago, IL, USA), software version 24. Statistical tests were 2-tailed and significance was set at 5%.

4.7.4. Results

The most prevalent pharmacologic drugs prescribed to our study participants were Simvastatin and Atorvastatin. More specifically, 68% of the MEX+ST participants used Simvastatin, 15% Atorvastatin, 13% Pravastatin, 9% Pitavastatin, and 6% Rosuvastatin. In the ST group, 62% of the participants used Simvastatin, 15% Atorvastatin, 11% Pravastatin, 4% Rosuvastatin, and 3% used Pitavastatin. There were no significant differences in drug treatments and doses maintained throughout the intervention period.

After the 24-months intervention, 5.8% (n = 57) of our participants withdrawn and 9.9% (n = 97) were lost to follow-up due to an exercise training adherence under 80%. The trial was completed by 84% of the participants (n = 827): MEX group (n = 251; 84%); ST (n = 161; 91%) and MEX+ST group (n = 415; 82%) – Figure 1. The baseline characteristics of the participants lost to follow-up did not differ significantly from those who completed the study.

No serious adverse event (life-threatening event, inpatient hospitalization or clinically significant abnormal laboratory or diagnostic test) was registered during the intervention period, except for occasional soreness in the MEX and MEX+ST groups.

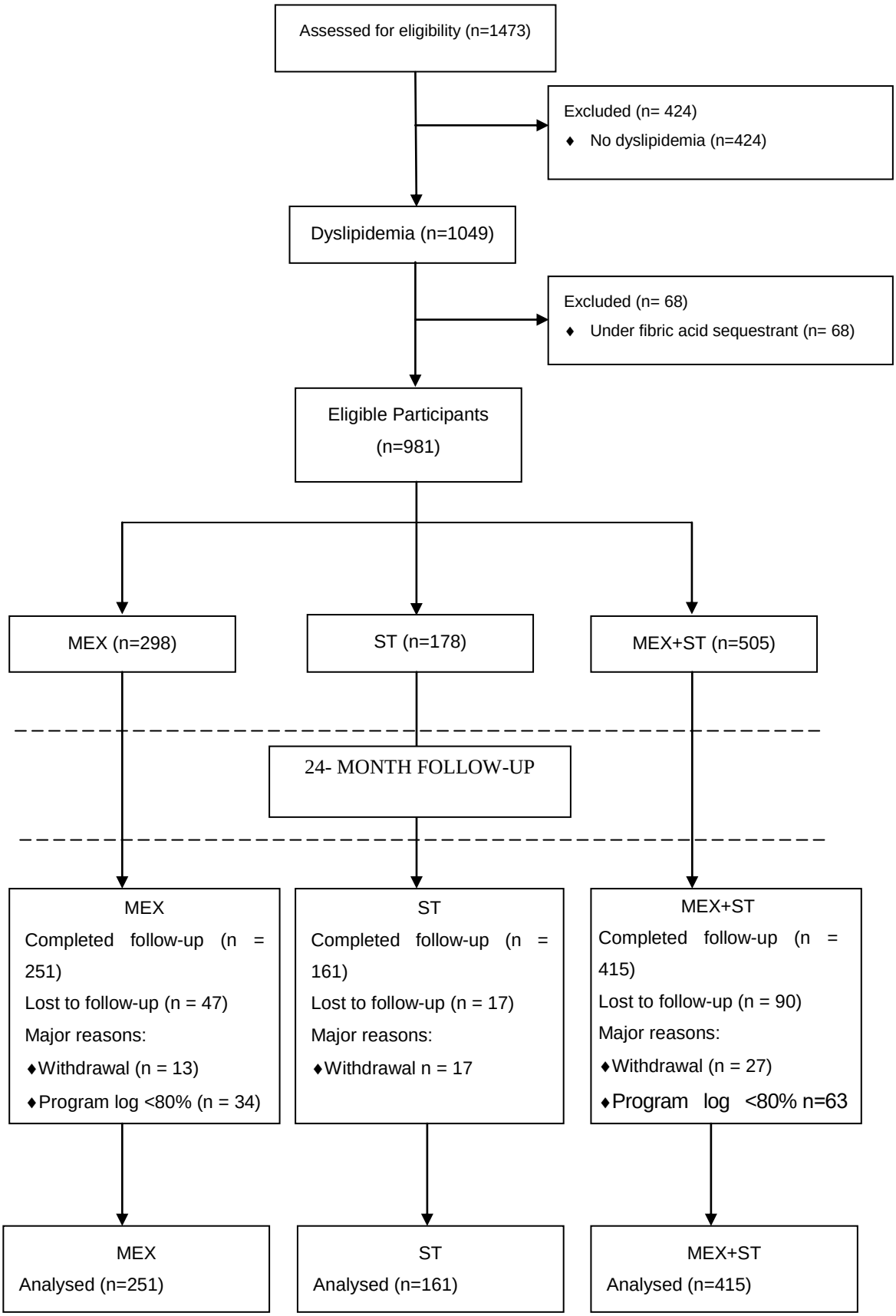

Figure 4.7.1- Flow chart of participants.MEX- Multicomponent exercise; ST- Statins; MEX+ST- Multicomponent exercise plus Statins

4.7.4.1. Baseline characteristics

Baseline demographic, medical, physical functional status and HRQoL characteristics are presented in Table 4.7.1 and Supplemental Table 4.7.1. Overall, 74% were women, with mean (±SD) age of 67(7.8) years, with 2.3(1.6) comorbidities.

Overall, the most prevalent comorbidities were hypertension (46%), osteoarthritis (27%), osteoporosis (23%), and diabetes (19%). In the MEX group, 44% had hypertension, 27% osteoarthritis, 25% osteoporosis and 12% T2D. In the combined MEX+ST group, 47% of the participants had hypertension, 29% osteoarthritis, 24% T2D, and 24% osteoporosis. In the ST group, 47% had hypertension, 22% osteoarthritis, 18% T2D and 16% osteoporosis. Some differences between-groups appeared in age, SBP, DBP, LDL-C, TG, upper/lower body strength, upper/lower body flexibility, RP and Total SF-36. At baseline, MEX participants had less comorbidity (2.1±1.5), WHR and TG, and higher LDL-C and better body flexibility, comparatively with the other two groups. The MEX+ST group was older (68.4±7.4) (p <0.001), had higher SBP, TG, upper strength, RP, Total SF-36 but had less strength than the other two groups. The ST participants were younger (64.1±7.2), had more comorbidities (2.5±1.6) and WHR, but had less SBP, DBP, lower and upper strength, lower and upper flexibility, RP, and Total SF-36 than the other groups.

4.7.4.2. Differences between groups after the 24-month intervention

After the intervention period, the differences between groups occurred in all variables (p<0.05), except for the BMI and TG (Table 4.7.2 and Supplemental Table 4.7.2). Nevertheless, after adjusting for age, sex, comorbidity and baseline values scores covariates, the differences between the 3 groups in the lipid profile disappeared (p> 0.05), but increased in all the other outcomes (p<0.001). The MEX participants enhance their functional status (p<0.001), and revealed better HRQoL (p<0.001) than the ST group, despite the higher bodily pain augment (9.8; p=0.004). Furthermore, the MEX participants presented less WC (-3.7 cm; p<0.001), BM (-3.2 kg; p=0.018), WHR (-0.04; p<0.001), SBP (-10.3 mmHg; p<0.001) and DBP (-3.8 mmHg; p<0.001) than the ST group. Likewise, MEX+ST group presented improved functional status (p<0.001) and better HRQoL (p<0.001) than the ST group, despite the increase in bodily pain scale (10.1; p<0.001) (Table 3). Similarly, the MEX+ST group also presented less WC (-2.9 cm; p= 0.004), BM (-4.0 kg; p<0.001), WHR (-0.03; p<0.001), SBP (-9.4 mmHg; p<0.001) and DBP (-4.1 mmHg; p<0.001) than the ST group.

4.7.4.3. Differences within groups from baseline to 24-month intervention

Despite the differences between groups at baseline, both MEX and MEX+ST participants improved all physical functional status variables (p<0.001), particularly upper/lower body strength and CRF with large effect sizes (> 0.80) (Table 4.7.3, and Figure 4.7.2). Moreover, the MEX group also showed moderately changes specifically in the WC (-3%), SBP (-10%), DBP (-7%), PF (8%), RP (6%), PCS (6%), Total SF-36 (5%), LDL-C (-5%), but also revealed small effects in BM (-1%), BMI (-1%), WHR (-1%) and in TC (-3%). However, MEX participants moderately increased bodily pain (7%). Similarly, the MEX+ST participants decreased WC (-3%), BM (-1%), BMI (-1%) and WHR (-1%), SBP (-10%) and DBP (-9%). This group also revealed a small decrease in LDL-C (-5%). In terms of subjective perception of physical HRQoL, MEX+ST participants presented moderately improvements in PF (5%), RP (6%), PCS (5%) and Total SF-36 (4%), and small effect size in GH (4%) but augmented bodily pain (6%). Reversely, the ST group reduced all the functional status outcomes, particularly upper/lower body strength and CRF (p<0.001), and augmented SBP (5%), DBP (2%), WC (2%), BM (1%), BMI (1%), WHR (2%), and TC (12%). Additionally, the ST participants decreased their self-perception of HRQoL, particularly PF (-6%), GH (-9%), PCS (-7%) and Total SF-36 (-7%), and augmented bodily pain (-9%).

Table 4.7.1-Baseline Characteristics using one-way ANOVA (*N*= 981)

Variables	Total (N=981)	MEX+ST (n=505)	ST (n=178)	MEX (n= 298)	Group Effect *P* Value
Female, %	74	79	65	74	<0.001**
Age, years	67.0 (7.8)	68.6 (7.4)	64.1 (7.2)	66.1 (8.1)	<0.001**
Comorbidity, n	2.3 (1.6)	2.4 (1.7)	2.5 (1.6)	2.1 (1.5)	0.041*
Waist circumference, cm	91.4 (9.6)	92.4 (10.0)	91.2 (10.3)	90.6 (8.9)	0.097
Body Mass, kg	74.0 (12.0)	73.5 (12.4)	75.9 (11.6)	73.5 (10.9)	0.082
Body mass index, kg/m^2	28.8 (4.0)	29.2 (4.2)	28.5 (3.2)	28.5 (4.0)	0.060
Waist-to-hip ratio	0.90 (0.07)	0.90 (0.07)	0.91 (0.08)	0.89 (0.07)	0.024*
Systolic blood pressure, mmHg	139 (17)	141 (17)	131 (17)	140 (17)	<0.001**
Diastolic blood pressure, mmHg	79 (11)	79 (11)	76 (9)	80 (11)	0.002*
Total cholesterol, mg/dL	202 (39)	201 (42)	202 (39)	205 (35)	0.374
HDL cholesterol, mg/dL	52 (15)	53 (16)	52 (13)	52 (12)	0.061
LDL cholesterol, mg/dL	124 (34)	120 (36)	123 (33)	132 (28)	<0.001**
Triglycerides, mg/dL	124 (59)	130 (61)	129 (71)	113 (47)	0.001*
30-s chair stand, n	13 (4)	14 (4)	12 (3)	13 (4)	0.001*
30-s arm curl, n	16 (4)	17 (4)	14 (3)	17 (4)	<0.001**
Chair sit-and-reach, cm	0.5 (8.5)	0.2 (7.9)	2.4 (8.8)	-0.5 (8.9)	0.003*
Back scratch, cm	16.2 (11.1)	17.6 (10.4)	15.6 (11.8)	14.1 (11.3)	0.001*
8 foot up- and- go, s	5.7 (1.5)	5.8 (1.6)	5.7 (1.4)	5.6 (1.4)	0.288
6 min walk test, m	444 (108)	436 (116)	450 (65)	455 (117)	0.079
Physical Functioning	80 (20)	81 (19)	78 (22)	80 (19)	0.136
Role Physical	75 (24)	76 (23)	69 (28)	75 (23)	0.006*
Bodily Pain	68 (25)	68 (24)	68 (27)	67 (25)	0.723
General Health	58 (18)	58 (19)	55 (18)	59 (18)	0.077
Physical Component Score	70 (17)	71 (17)	67 (20)	70 (17)	0.064
Total SF-36	73 (16)	74 (16)	70 (18)	73 (15)	0.015*

Data are expressed as mean (SD). *Differences between evaluations ($P \leq 0.05$). ** Differences between evaluations ($P \leq 0.001$).

Supplemental Table 4.7.1 -Differences between groups at baseline using one- way ANOVA (*N*=981)

Variables	MEX+ST vs ST	P Value	MEX vs ST	P Value	MEX+ST vs MEX	P Value
Age, years	4.8 (3.3: 6.4)	<0.001**	1.9 (0.2: 3.6)	0.019	2.5 (1.1: 3.8)	<0.001**
Comorbidity, n	-0.1 (-0.4: 0.3)	0.980	-0.3 (-0.7 : 0.1)	0.115	0.3 (-0.0: 0.5)	0.060
Waist circumference, cm	2.2 (0.1: 4.3)	0.042*	0.4 (-2.0: 2.7)	0.987	1.8 (-0.1: 3.7)	0.077
Body Mass, kg	-2.4 (-4.9: 0.2)	0.088	-2.3 (-5.2: 0.6)	0.160	-0.0 (-2.4: 2.3)	1.000
Body mass index, kg/m^2	0.7 (-0.2: 1.6)	0.158	-0.1 (-1.0: 0.9)	0.999	0.8 (-0.0: 1.6)	0.069
Waist-to-hip ratio	-0.01 (-0.02: -0.01)	0.610	-0.02 (-0.04: -0.00)	0.026*	0.01 (-0.00: 0.03)	0.122
Systolic blood pressure, mmHg	9.9 (6.1 : 13.6)	<0.001**	9.4 (5.3: 13.6)	<0.001**	0.4 (-3.0: 3.8)	0.986
Diastolic blood pressure, mmHg	3.2 (0.8: 5.6)	0.004*	3.5 (0.9: 6.2)	0.004*	-0.4 (-2.5: 1.8)	0.968
Total cholesterol, mg/dL	-1.8 (-10.9: 7.3)	0.954	2.6 (-7.4: 12.5)	0.902	-4.3 (-11.6: 3.0)	0.402
HDL cholesterol, mg/dL	1.7 (-0.7: 6.2)	0.167	-0.0 (-3.8: 3.7)	1.000	1.7 (0.0: 5.5)	0.057
LDL cholesterol, mg/dL	-3.0 (-11.1: 5.2)	0.766	8.6 (-0.2: 17.4)	0.057	-11.5 (-17.4: 0.2)	<0.001**
Triglycerides, mg/dL	1.6 (-12.2: 15.5)	0.989	-15.6 (-30.7: -0.5)	0.040*	17.2 (6.2 : 28.3)	0.001*
30-s chair stand, n	1.3 (0.5: 2.2)	0.001*	1.2 (0.2: 1.2)	0.010*	0.2 (-0.6: 0.9)	0.946
30-s arm curl, n	2.2 (1.3: 3.1)	<0.001**	2.7 (1.7: 3.7)	<0.001**	-0.5 (-1.3: 0.3)	0.366
Chair sit-and-reach, cm	-2.3 (-4.1: -0.4)	0.011*	-2.9 (-5.0: -0.8)	0.003*	0.6 (-1.0: 2.3)	0.745
Back scratch, cm	2.0 (-0.4: 4.4)	0.140	-1.5 (-4.2: 1.2)	0.448	3.5 (1.3: 5.7)	0.001*
8 foot up- and- go, s	0.1 (-0.2: 0.4)	0.794	-0.1 (-0.4: 0.3)	0.935	0.2 (-0.1: 0.5)	0.316
6 min walk test, m	-14.7 (-38.4: 9.0)	0.360	4.5 (-22.0: 31.0)	0.968	-19.2 (-40.8 : 2.3)	0.096
Physical Functioning	3.4 (-0.6: 7.5)	0.126	1.9 (-2.6: 6.5)	0.667	1.5 (-1.9: 4.9)	0.650
Role Physical	6.8 (1.9 : 11.7)	0.003*	5.2 (-0.2: 10.7)	0.063	1.6 (-2.5: 5.7)	0.730
Bodily Pain	0.1 (-4.9: 5.2)	1.000	-1.3 (-6.9: 4.4)	0.930	1.4 (-2.8: 5.7)	0.814
General Health	3.3 (-0.4: 7.1)	0.099	3.8 (-0.4: 7.9)	0.093	-0.4 (-3.6: 2.7)	0.984
Physical Component Score	3.6 (0.1: 7.1)	0.045*	2.6 (-1.4: 6.5)	0.315	1.0 (-1.9: 4.0)	0.794
Total SF-36	4.1 (0.8: 7.4)	0.008*	3.4 (-0.3: 7.0)	0.003*	0.8 (-2.0: 3.5)	0.885

Data are expressed as mean (SD). * Differences between evaluations ($p \leq 0.05$). ** Differences between evaluations ($p \leq 0.001$).

Table 4.7.2-Differences between groups in anthropometric, hemodynamic, functional status and health related quality of life after 24-month intervention, using ANOVA and ANCOVA adjusted to age, sex, comorbidity number and baseline value score

Variables	MEX+ST (n=415)	ST (n=161)	MEX (n= 251)	Unadjusted *P* Value	Adjusted *P* Value
Waist circumference, cm	89.0 (9.4)	91.9 (99)	88.0 (10.1)	<0.001**	<0.001**
Body Mass, kg	72.6 (11.2)	76.6 (11.7)	73.4 (11.3)	0.001*	<0.001**
Body mass index, kg/m^2	28.7 (3.7)	28.8 (3.8)	28.4 (4.1)	0.489	<0.001**
Waist-to-hip ratio	0.89 (0.08)	0.92 (0.08)	0.88 (0.08)	<0.001**	<0.001**
Systolic blood pressure, mmHg	128 (15)	137 (17)	127 (17)	<0.001**	<0.001**
Diastolic blood pressure, mmHg	73 (9)	77 (9)	74 (10)	<0.001**	<0.001**
Total cholesterol, mg/dL	191 (45)	181 (47)	197 (34)	0.024*	0.076
HDL cholesterol, mg/dL	54 (12)	50 (11)	51 (12)	0.020*	0.626
LDL cholesterol, mg/dL	114 (35)	112 (24)	122 (29)	0.021*	0.160
Triglycerides, mg/dL	130 (87)	126 (65)	118 (50)	0.266	0.969
30-s chair stand, n	18 (4)	12 (2)	18 (4)	<0.001**	<0.001**
30-s arm curl, n	22 (4)	13 (3)	23 (4)	<0.001**	<0.001**
Chair sit-and-reach, cm	-3.8 (8.0)	4.2 (9.0)	-2.9 (9.1)	<0.001**	<0.001**
Back scratch, cm	13.3 (9.3)	17.2 (11.4)	10.9 (10.4)	<0.001**	<0.001**
8 foot up- and- go, s	5.0 (1.3)	5.8 (1.4)	5.0 (1.4)	<0.001**	<0.001**
6 min walk test, m	561 (103)	430 (51)	571 (102)	<0.001**	<0.001**
Physical Functioning	87 (14)	74 (23)	87 (13)	<0.001**	<0.001**
Role Physical	81 (22)	66 (26)	80 (20)	<0.001**	<0.001**
Bodily Pain	73 (22)	63 (26)	73 (23)	<0.001**	<0.001**
General Health	62 (17)	51 (16)	60 (16)	<0.001**	<0.001**
Physical Component Score	76 (15)	64 (18)	75 (15)	<0.001**	<0.001**
Total SF-36	77 (14)	65 (17)	76 (14)	<0.001**	<0.001**

Data are expressed as mean (SD). *Differences between evaluations ($P \leq 0.05$). ** Differences between evaluations ($P \leq 0.001$).

Supplemental Table 4.7.2-Differences between groups in anthropometric, hemodynamic, functional status and health related quality of life after 24-month intervention using ANOVA and Gabriel *post-hoc* test.

Variables	MEX+ST vs ST	P Value	MEX vs ST	P Value	MEX+ST vs MEX	P Value
Waist circumference, cm	-2.9 (-5.0: -0.7)	0.004*	-3.7 (-6.2: -1.5)	<0.001**	1.0 (-0.9: 2.0)	0.499
Body Mass, kg	-4.0 (-6.5: -1.5)	<0.001**	-3.2 (-5.9: -0.4)	0.018*	-0.8 (-3.0: 1.4)	0.770
Body mass index, kg/m^2	-0.2 (-1.0: 0.7)	0.963	-0.4 (-1.4: 0.5)	0.593	0.3 (-0.5: 1.0)	0.730
Waist-to-hip ratio	-0.03 (-0.05: -0.02)	<0.001**	-0.04 (-0.06: -0.02)	<0.001**	0.00 (-0.01: 0.02)	0.636
Systolic blood pressure, mmHg	-9.4 (-12.8: -6.0)	<0.001**	-10.3 (-14.1: -6.5)	<0.001**	0.9 (-2.1: 4.0)	0.854
Diastolic blood pressure, mmHg	-4.1 (-6.2: 2.0)	<0.001**	-3.8 (-6.1: -1.5)	<0.001**	-0.3 (-2.1: 1.6)	0.981
Total cholesterol, mg/dL	10.0 (-2.6: 22.6)	0.166	16.1 (2.2: 30.0)	0.017*	-6.2 (-15.8: 3.5)	0.332
HDL cholesterol, mg/dL	3.5 (-0.2: 7.2)	0.067	0.9 (-3.2: 4.9)	0.941	2.6 (-0.1: 5.4)	0.061
LDL cholesterol, mg/dL	2.9 (-7.5: 13.2)	0.880	10.8 (-0.5: 22.2)	0.067	-7.8 (-15.6: -0.3)	0.038*
Triglycerides, mg/dL	3.9 (-19.3: 27.0)	0.970	-7.9 (-33.3: 17.4)	0.837	11.8 (-5.4: 29.0)	0.274
30-s chair stand, n	6.7 (5.9: 7.5)	<0.001**	6.7 (5.8: 7.7)	<0.001**	-0.0 (-0.8: 0.8)	1.000
30-s arm curl, n	8.9 (8.1: 9.8)	<0.001**	9.3 (8.3: 10.2)	<0.001**	-0.4 (-1.1: 0.4)	0.615
Chair sit-and-reach, cm	-7.9 (-9.8: -6.1)	<0.001**	-7.1 (-9.2: -5.0)	<0.001**	-0.9 (-2.5: 0.8)	0.527
Back scratch, cm	-4.0 (-6.2: -1.8)	<0.001**	-6.3 (-8.8: -3.8)	<0.001**	2.3 (0.4: 4.3)	0.015*
8 foot up- and- go, s	-0.8 (-1.1: -0.5)	<0.001**	-0.9 (-1.2: -0.5)	<0.001**	0.0 (-0.2: 0.3)	0.982
6 min walk test, m	131.3 (110.6: 151.9)	<0.001**	141.6 (118.6: 164.7)	<0.001**	-10.4 (-28.9: 8.1)	0.449
Physical Functioning	12.7 (9.3: 16.1)	<0.001**	12.4 (8.6: 16.2)	<0.001**	0.3 (-2.8: 3.3)	0.995
Role Physical	15.3 (10.4: 20.1)	<0.001**	13.9 (8.5: 19.3)	<0.001**	1.4 (-2.9: 5.7)	0.826
Bodily Pain	10.1 (5.1: 15.2)	<0.001**	9.8 (4.2: 15.4)	<0.001**	0.4 (-4.1: 4.9)	0.996
General Health	10.6 (7.0: 14.2)	<0.001**	9.6 (5.6: 13.6)	<0.001**	1.0 (-2.2: 4.3)	0.830
Physical Component Score	12.2 (8.9: 15.6)	<0.001**	11.5 (7.8: 15.3)	<0.001**	0.7 (-2.3: 3.7)	0.924
Total SF-36	12.0 (8.8: 15.2)	<0.001**	11.2 (7.6: 14.7)	<0.001**	0.8 (-2.0: 3.7)	0.862

*Differences between evaluations ($P \leq 0.05$). ** Differences between evaluations ($P \leq 0.001$).

Table 4.7.3- Differences within groups in anthropometric, hemodynamic, functional status and health-related quality of life from baseline to 24-month intervention using ANOVA for repeated measures, Δ percentage difference and Cohen *d* effect size

	MEX+ST				ST				MEX			
Variables	**Mean Difference (95% CI)**	**Δ Difference (%)**	***P* Value**	**Effect size**	**Mean Difference (95% CI)**	**Δ Difference (%)**	***P* Value**	**Effect Size**	**Mean Difference (95% CI)**	**Δ Difference (%)**	***P* Value**	**Effect Size**
Waist circumference, cm	-2.6 (-3.1: -2.1)	-2.9	<0.001**	0.272	1.6 (1.2: 2.0)	1.7	<0.001**	0.161	-2.9 (-3.5: -2.3)	-3.3	<0.001**	0.333
Body mass, kg	-0.7 (-1.0: -0.3)	-0.9	<0.001**	0.059	0.7 (0.4: 0.9)	0.9	<0.001**	0.057	-0.9 (-1.4: -0.4)	-1.2	<0.001**	0.080
Body mass index, kg/m^2	-0.3 (-0.4: -0.2)	-1.0	<0.001**	0.075	0.3 (0.2: 0.4)	1.0	<0.001**	0.075	-0.3 (-0.5: -0.1)	-1.0	0.002*	0.071
Waist-to-hip ratio	-0.01 (-0.01: -0.00)	-0.8	0.002*	0.103	0.01 (0.01: 0.02)	1.5	<0.001**	0.169	-0.01 (-0.01: -0.00)	-1.0	0.004*	0.123
Systolic blood pressure, mmHg	-12.7 (-14.6: -11.0)	-10.0	<0.001**	0.794	6.2 (4.4:8.0)	4.5	<0.001**	0.372	-12.5 (-14.8: -10.2)	-9.8	<0.001**	0.760
Diastolic blood pressure, mmHg	-6.3 (-7.4:-5.2)	-8.7	<0.001**	0.645	1.4 (0.3: 2.5)	1.8	0.014*	0.154	-5.2 (-6.7: -3.8)	-7.1	<0.001**	0.483
Total cholesterol, mg/dL	-9.9 (-15.6: -4.3)	-5.2	0.001*	0.222	-21.0 (-33.1: -8.9)	-11.6	0.001*	0.471	-6.2 (-11.0: -1.4)	-3.1	0.012*	0.189
HDL cholesterol, mg/dL	-0.5 (-1.8: 0.7)	-0.9	0.412	0.040	-0.8 (-2.7: 1.1)	-1.5	0.422	0.066	0.7 (-0.4: 1.8)	1.4	0.184	0.064
LDL cholesterol, mg/dL	-6.0 (-10.7: -1.3)	-5.3	0.012*	0.165	-9.4 (-20.4: 1.6)	-8.5	0.093	0.319	-6.4 (-11.1: -1.6)	-5.2	0.009*	0.231
Triglycerides, mg/dL	-2.0 (-11.6: 7.7)	-1.5	0.686	0.026	-8.3 (-22.1: 5.6)	-6.5	0.236	0.117	0.3 (-7.1: 7.8)	0.3	0.935	0.006
30-s chair stand, n	4.6 (4.2: 5.1)	25.4	<0.001**	1.112	-0.7 (-0.9: -0.4)	-5.7	<0.001**	0.292	4.9 (4.4: 5.4)	26.3	<0.001**	1.166
30-s arm curl, n	5.5 (5.0: 5.9)	24.5	<0.001**	1.304	-1.1 (-1.4: 0.8)	-8.1	<0.001**	0.349	5.2 (4.7: 5.7)	23.0	<0.001**	1.286
Chair sit-and-reach, cm	-3.5 (-4.3: -2.7)	-109.0	<0.001**	0.444	1.8 (1.3: 2.2)	42.0	<0.001**	0.197	-3.0 (-4.0: -2.1)	-105.6	<0.001**	0.349
Back scratch, cm	-3.7 (-4.3: -3.0)	-27.3	<0.001**	0.384	1.6 (1.0: 2.3)	9.5	<0.001**	0.141	-2.8 (-3.9: -1.8)	-25.7	<0.001**	0.257
8 foot up- and- go, s	-0.6 (-0.8: -0.5)	-12.6	<0.001**	0.444	0.2 (0.1: 0.3)	2.9	0.006*	0.126	-0.5 (-0.7: -0.4)	-10.8	<0.001**	0.407
6 min walk test, m	115.1 (102.1: 128.1)	20.5	<0.001**	1.067	-21.1 (-27.4: -14.9)	-4.9	<0.001**	0.362	109.1 (92.4: 125.8)	19.1	<0.001**	1.006
Physical Functioning	4.5 (2.9: 6.2)	5.2	<0.001**	0.278	-4.1 (-7.6: -0.6)	-5.5	0.021*	0.183	6.6 (4.4: 8.7)	7.6	<0.001**	0.398
Role Physical	4.5 (2.2: 6.7)	5.5	<0.001**	0.203	-3.7 (-7.9: 0.6)	-5.5	0.093	0.137	5.0 (2.1: 7.9)	6.3	0.001*	0.230
Bodily Pain	4.6 (2.4: 6.7)	6.2	<0.001**	0.202	-5.4 (-10.1: -0.7)	-8.5	0.026*	0.201	5.2 (2.2: 8.3)	7.2	0.001*	0.221
General Health	2.7 (1.0: 4.3)	4.3	0.002*	0.146	-4.5 (-7.3: -1.7)	-8.8	0.002*	0.269	1.5 (-0.5: 3.5)	2.5	0.142	0.088
Physical Component Score	4.1 (2.8: 5.4)	5.4	<0.001**	0.265	-4.2 (-6.9: -1.5)	-6.6	0.002*	0.221	4.7 (2.9: 6.4)	6.2	<0.001**	0.299
Total SF-36	3.3 (2.0: 4.6)	4.3	<0.001**	0.226	-4.5 (-6.8: -2.1)	-6.8	<0.001**	0.253	3.5 (1.7: 5.2)	4.6	<0.001**	0.238

* Differences between evaluations ($p \leq 0.05$). ** Differences between evaluations ($p \leq 0.001$). Effects sizes were classified as small (<0.20), moderate (0.20-0.79) and large (>0.80).

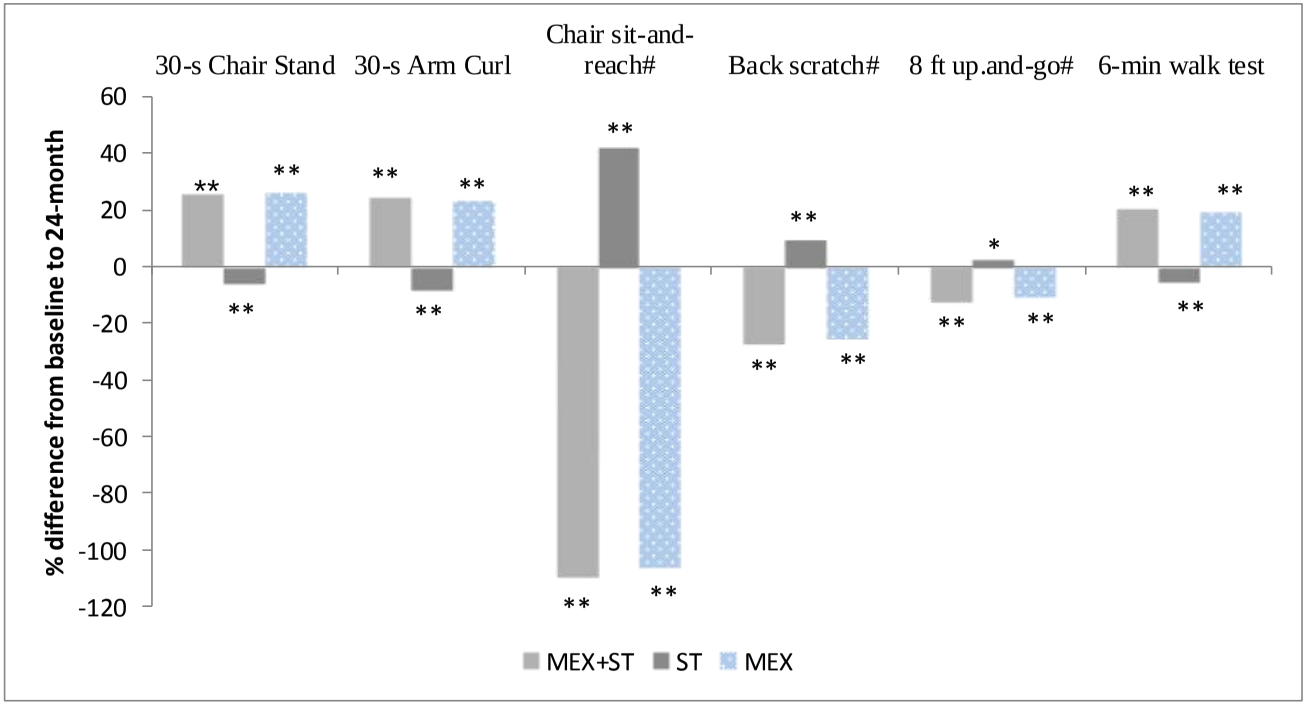

Figure 4.7.2- Percentage difference within groups in functional status from baseline to 24-month follow-up; #- Decrease means improvement. * Differences between evaluations ($p \leq 0.05$). ** Differences between evaluations ($p \leq 0.001$).

4.7.5. Discussion

The prescription of ST therapy among older adults is increasing (Gui et al., 2017), despite the potential adverse effects that may hinder older adults' ability to participate in exercise training, and may limit numerous exercise-associated metabolic and functional benefits (Henderson et al., 2016). Thus, it is fundamental to find effective interventions to reduce physical decline and HRQoL (Anton et al., 2015). Therefore, we intended to analyze the efficacy of the two first-line treatments recommended to manage LDL-C – ST and/or MEX combination therapies (Catapano et al., 2016) on functional status, CVR and physical HRQoL in dyslipidemic older adults with comorbidities.

Our study prove that chronic MEX *per se* is an effective strategy to reach dyslipidemic and functional status goals, and may counteract the age and ST-induced adverse effect in the deterioration of the functional status (Auer, Sinzinger, Franklin, & Berent, 2016), highlighting MEX as an important goal of health status and independent functional status (Anton et al., 2015), even in those under ST therapy. Furthermore, to our knowledge, this study is the first to demonstrate that the combination of MEX and ST therapy present more pronounced effects in the maintenance and improvement of physical functioning than the isolated ST therapy. Moreover, it was demonstrated that the MEX and MEX+ST therapies have an antagonist effect, comparing with the ST monotherapy, on the functional status, CVR factors and HRQoL. Our findings are consistent with some previous studies (Bahls et al., 2017; Dumurgier et al., 2014; Gray et al., 2012; Gui et al., 2017; Henderson et al., 2016; P. Kokkinos et al., 2017; Lee et al., 2014; Loenneke & Loprinzi, 2016; Magaly Villafrádez-Díaz, Yesenia Santiago-Casas Mariely Nieves-Plaza et al., 2014; Mikus et al., 2013; Panayiotou et al., 2013) but not with others (Parker Beth A, Capizzi Jeffrey A, Grimaldi Adam S, Clarkson Priscilla M, 2013). These inconsistent previous results may be due to the use of mixed age samples including adults and older adults (Bakker et al., 2017; Bruckert et al., 2005; Gray et al., 2012; Magaly Villafrádez-Díaz, Yesenia Santiago-Casas Mariely Nieves-Plaza et al., 2014) with heterogeneous characteristics.

On the other hand, the few randomized controlled trials with exclusively older adults (Dumurgier et al., 2014; Henderson et al., 2016; P. Kokkinos et al., 2017; Lee et al., 2014; Parker Beth A, Capizzi Jeffrey A, Grimaldi Adam S, Clarkson Priscilla M, 2013)

used extensive exclusion criteria, small sample sizes, relative youth of the study participants, low levels of comorbidity, indirect measurements (questionnaires), different pathologies profiles with different active arm comparators (placebo, control, EX and MEX+ST), with short-time length and different primary outcomes, limiting the external validity and the generalizability of the findings in elderly with comorbidities (Noaman, Ibrahim, & Grenfell, 2014).

Our study, exclusively with dyslipidemic older adults with comorbidities, during a long-term period, and using direct objectively measurements, confirms that MEX training preserves functional status, increasing the lower and upper body strength, the agility and dynamic balance, the upper body flexibility, and the CRF, even in older adults under ST therapy.

The mechanism by which MEX promotes functional status improvement may be related with the cumulative benefits of MEX training in mitochondrial biogenesis (increase in number or content) and mitochondrial oxidative capacity (improved function) that lead to greater capacity for skeletal muscle oxygen consumption, which is a key component of exercise-mediated improvements in CRF (Bouaziz et al., 2017; Eijsvogels et al., 2016; Mann et al., 2014; Mikus et al., 2013; J. Myers et al., 2015; Sharman et al., 2015). CRF gains reduce inflammation and improve cardio metabolic parameters (P. Kokkinos et al., 2017), that combined with the ST therapy in the lipid profile, synergistically promoted positive anti-inflammatory effects and reduced oxidative stress that lead to an improved cardiometabolic system with important functional status gains in the combined MEX+ST group (P. Kokkinos et al., 2017). In fact, our results seem to support these rationales due to the improvements that both, MEX and MEX+ST groups presented in the secondary outcomes, particularly the reduction in the adiposity (-3% WC; -1% BM, BMI and WHR), in the hemodynamic profile (-10% SBP; -9% in the MEX+ST and -8% in the MEX, in terms of DBP), and in the lipid profile (-5% in TC and LDL-C in the MEX+ST; -3% in TC and -5% in LDL-C in the MEX group), despite the worst hemodynamic and lipid profile that both groups presented at baseline. In the opposite, ST participants aggravated their CVR profile, increasing SBP in 5%, WC, WHR and DBP in 2%, and BM and BMI in 1%, despite the 12% reduction in TC. These results seem to suggest that after 24-months intervention with ST therapy, participants were only able to manage their lipid profile (TC), but not the other CVR factors.

Collectively, our results have important implications once the enhancement of functional ability improves the capacity to perform everyday activities including personal care, shopping, or housework (Jones, J., Rikli, 2002), leading to a more fulfilling independent functional status and ultimately prevent physical disability (Buford, 2016). Furthermore, the benefits of the MEX and MEX+ST therapies on the lipid profile, blood pressure, adiposity, and CRF seem to have important additive/synergetic effects on the reduction of CVD morbidity and mortality events (Bouaziz et al., 2017; Catapano et al., 2016).

While some have not associated ST therapy with decreased muscle strength or exercise performance (Parker Beth A, Capizzi Jeffrey A, Grimaldi Adam S, Clarkson Priscilla M, 2013), or decreased eccentric strength (Panayiotou et al., 2013), others have found that ST therapy reduces the knee extensor force, which could relate with increase in muscle pain (Loenneke & Loprinzi, 2016). Surprisingly, our results are quite different once the ST therapy decreased upper/ lower body strength, but also decreased 9% in subjective bodily pain, despite the reduction in overall HRQoL. Possible explanations may be related with the initiation time of ST therapy, once it seems that there is a 10-fold rate ratio of developing myalgia or myopathy between the treatment initiation until 12-months of ST therapy (Bhardwaj, Selvarajah, & Schneider, 2013). Furthermore, some selected statins are more likely to be associated with adverse muscle symptoms than others (e.g. Fluvastatin has been highly recommended because of its relatively low incidence of myalgia due to the assumed reduced lipophilicity, which may contribute to its slower rate of passage into muscle cells and thus, creating less myotoxicity, but there is also evidence that statin-induced myopathy seems to be less frequently with the use of Rosuvastatin and Pravastatin)(Auer et al., 2016). Additionally, lower doses vs higher dose of ST use (Auer et al., 2016; Bhardwaj et al., 2013) are also negatively associated with ST muscle adverse effects. Thus, although our participants used different ST therapies (lipophilic and hydrophilic drugs), the majority used low-dose and had at least one year of ST use, passing the critical phase of ST adaptation, which could explain, at least in part, the inexistence of ST adverse effects in this group.

Likewise, in terms of ST effects on CRF, previous evidence also present mixed results. While some previous studies showed that walking speed declined less with ST use (Dumurgier et al., 2014), others, consistent with our results, reported that ST use blunted

CRF and skeletal muscle mitochondrial content when combined with exercise training (Mikus et al., 2013). Bahls and colleagues (Bahls et al., 2017), on the other hand, reported that ST effects on CRF impairment is sex-specific related, impairing males but not females. Similarly, our results showed that ST therapy group, with higher prevalence of males, decreased 5% CRF, reversely to the MEX+ST and MEX groups that improved 20% CRF.

One surprising result was the bodily pain augment in MEX and MEX+ST participants after the 24-months intervention. Even though ST usage has been related to muscle adverse effects (Auer et al., 2016), it seems more appropriate to associate our increase in the bodily pain with the exercise training, instead of the ST therapy, once only those who performed the multicomponent exercise (MEX+ST and MEX) experienced occasional soreness. Previous evidence support that exercise induces muscle injury, with myalgia and creatine kinase concentrations peaking 2-3 days after the activity (Bosomworth, 2016). In our participants, this occasional soreness was reported during 1-2 days after MEX training, leading us to relate the results in bodily pain outcome with the increases in MEX load and to the normal exercise body adaptation (Bosomworth, 2016). Furthermore, in our perception, the introduction of a more gradual "active" therapy, with the exercise training regimen, for inactive participants at baseline, requiring additional behavior changes, could imply augment of bodily pain self-perception because, for some individuals, these gradual increments could be more difficult to accomplish. Another possible explanations might be related with age criteria, or characteristics of the disease and related comorbidities (Catapano et al., 2016), once both MEX and MEX+ST groups were older, and MEX+ST participants had more comorbidities than the ST, which may have impacted participants' self-perception. However, despite this increase, our results confirmed that MEX and MEX+ST therapies were the most empowering treatments, yielding the largest improvements of symptoms, with enhancement of PF, RP, GH and PCS and overall HRQoL (Ambrose & Golightly, 2015).

The present study has several strengths including the longitudinal design, the large sample group composed by dyslipidemic older adults using ST monotherapy, and/or long-term supervised exercise training intervention; furthermore, the use of well-validated instruments and the wide range of outcomes objectively measuring different aspects of physical function (performance-based measures, CVR factors and physical self-perception)

were important methodological issues in the present scientific field. In contrast, the non-randomized methodological design and the relative heterogeneous sample represent some drawbacks that may have limited some results. Nevertheless, the penalizing variables were worst to MEX+ST and MEX participants that as demonstrated by our results achieved the largest improvements in all the outcomes after the intervention, which limits in part this drawback. However, the causality relationship should be carefully interpreted once the different sample sizes within each study group and the non-randomized methodological design might have caused some bias in our results.

We tried to mitigate these limitations adopting specific statistical procedures to counteract these effects, particularly controlling for several covariates that were available and evaluated as potential confounders and also measuring the magnitude of the results out-weighting to the different samples sizes with the Hedges *g* effect size. Unfortunately, residual confounding factors due to unknown or incompletely measured factors cannot be excluded. Thus, future studies on this topic should use a randomized controlled trial design with a similar sample size, testing for other comorbidities.

Regardless of the limitations, these results have important clinical implications once chronic MEX training or combined with ST therapy emerged as effectives therapies to manage functional status in dyslipidemic older adults. Furthermore, as demonstrated by our "holistic" treatment, reducing overall CVD risk (anthropometric, hemodynamic and lipid profile) seems to be more effective and present more pronounced effects to manage several pathologies than isolated ST pharmacological treatment that had only a significant reduction in one risk factor. Moreover, this rationale is extremely important due to ST increased risk of unfavorable glycemic homeostasis and T2D development (P. Kokkinos et al., 2017) that in our sample of comorbid older adults will translate into the aggravation of the existent disease, for those suffering of T2D. Thus, the long-term accumulation of several CVD risk factors will lead to an additive/synergistic deleterious effect, that ultimately will increase overall CVD and associated morbidities (Catapano et al., 2016).

Finally, for those with confirmed myalgia, clinicians follow several therapeutic options including adjusting ST therapy by changing the type and dose, utilizing a hydrophilic ST, or recommending a drug holiday followed by a re-challenge (Gui et al., 2017). However, our study showed that MEX training *per se* is more effective than the isolated ST therapy

to improve functional status, to manage CVR factors including adiposity, hemodynamic and lipid profile, and HRQoL.

4.7.6. Conclusion

The findings of the present study suggest that chronic MEX training is more effective than ST treatment to improve functional status, the management of cholesterol levels, overall CVR and to improve physical HRQoL in dyslipidemic older adults with comorbidities. Furthermore, current results proved that the negative effects of the isolated ST therapy on the functional status and on the HRQoL may be significantly attenuated/ counterbalance by the inclusion of MEX training regimen.

These results provide further support and may guide health care professionals and health organizations in the prescription process, according with two types of patients: *i*) in asymptomatic dyslipidemic older adults with comorbidities, MEX programs should be prescribed as the first non-pharmacological choice to counterbalance the negative effects that age and dyslipidemia promotes; *ii*) for those asymptomatic dyslipidemic older adults under ST treatment, MEX training should be added to mitigate the negative effects of statins therapy.

4.8. Study VIII- Effectiveness of exercise training comparing with first-line antidiabetic, antihypertensive and antidyslipidemic therapies in older adults with comorbidities

Effectiveness of exercise training comparing with first-line antidiabetic, antihypertensive and antidyslipidemic therapies in older adults with comorbidities

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4.8.1. Abstract

Purpose: This study aims to analyze the longitudinal effectiveness of multicomponent exercise training comparing with first-line pharmacologic therapies in the management of type 2 diabetes (metformin – MET), hypertension (angiotensin converting enzyme inhibitors – ACEi) and dyslipidemia (statins – ST) in older adults with comorbidities.

Methods: A total sample of 1473 community-dwelling older adults comprises sub-groups with pharmacologic therapy, with exercise, and with combined therapy including exercise training plus pharmacologic treatment. The evaluations occurred at baseline and at 24-months follow-up and included anthropometrics, hemodynamic and lipid profiles, medication consumption, cardiorespiratory fitness (CRF) and health-related quality of life (HRQoL).

Results: After the 24-months intervention, the effectiveness of exercise training alone, to reduce the cardiovascular risk factors and increase HRQoL, was higher in T2D (OR 7.1, 95%CI: 3.3-15.3 – taking 0-1 medicines; OR 2.2, 95%CI: 1.0-5.0 – taking 2-3 medicines), hypertension (OR 6.8, 95%CI: 2.6-17.8 – taking 0-1 medicines; OR 1.7, 95%CI: 0.7-4.2 – taking 2-3 medicines), and dyslipidemia (OR 6.1, 95%CI: 4.0-9.5 – taking 0-1 medicines; OR 1.9, 95%CI: 1.2-2.9 – taking 2-3 medicines), comparing with the isolated pharmacological treatments.

Conclusion: Long-term exercise training is more effective than first-line pharmacological drugs (MET, ACEi or ST) to manage multifactorial cardiovascular risk factors, to improve medication consumption, CRF and HRQoL in older adults with comorbidities. Furthermore, isolated pharmacological therapies decrease hemodynamic profile along with HRQoL and may be significantly attenuated/counterbalance by the inclusion of a multicomponent exercise training regimen. In fact, the combined therapy (pharmacological treatment plus exercise) is more effective than isolated pharmacologic therapy to manage these outcomes.

Keywords: Exercise; Metformin; Angiotensin converting enzyme inhibitors; Statins; Cardiovascular risk factors; Medication consumption; Older adults

4.8.2. Introduction

Exercise has significant cardiometabolic benefits (Sharman et al., 2015) being one of the most important activities for primary and secondary prevention of many chronic diseases (Pedersen & Saltin, 2015). Unfortunately, inactivity by the opposite, is a major risk factor to the development and aggravation of cardiovascular diseases (CVD) like hypertension and dyslipidemia, and type 2 diabetes (T2D), particularly among older adults (Lim et al., 2017; World Health Organization, 2014). Actually, almost a quarter of European adults are inactive and half of elderly Europeans does not fulfill physical activity (PA) guidelines (World Health Organization, 2014). Furthermore, in the elderly population the high prevalence of multiple chronic health conditions increase the likelihood of multiple use of medicines (Charlesworth, Smit, Lee, Alramadhan, & Odden, 2015b). Nevertheless, heavy use of pharmaceuticals in comorbid elderly individuals rise new concerns regarding adverse side effects of drug–drug interactions, drug–disease interactions, therapeutic competition, poor adherence, adverse drug events, hospitalization, and ultimately mortality, not only related to the number of medications, but also to the regimen (Charlesworth et al., 2015b; Fabbri et al., 2015). Additionally, the rise of prescription drugs also results in higher health care costs (Bloom et al., 2015) highlighting the need for cost-effective treatment plans in the elderly population as a valuable aspiration within the several international guidelines (Catapano et al., 2016; Colagiuri et al., 2014; Mancia et al., 2013), with major health and economic gains (Davis et al., 2014).

A patient-centered treatment approach based on the weight assessment of risk-benefits, the patient preferences, cost, and potential side effects of each class has been suggested (Catapano et al., 2016; Colagiuri et al., 2014; Mancia et al., 2013). Normally, a stepwise treatment plan is recommended in a first stage of these diseases (Catapano et al., 2016; Colagiuri et al., 2014; Mancia et al., 2013), starting with lifestyle modification, including nutritional and exercise habits, and/or introducing a first-line oral pharmacological therapy (antidiabetic, antihypertensive or antidyslipidemic) for those that not adhere/comply with this form of treatment, or according with the disease severity and concurrent comorbid risk factors. However, the majority of the previous recommendations are based in expert consensus and clinical experience, due to the lack of evidence and clinical trials comparing the efficacy of both forms of treatments (non-pharmacological

and pharmacological) in the elderly population, particularly in patients with morbidities (Fabbri et al., 2015). Moreover, there is a lack of clinical trials comparing the isolated exercise training effects with first-line pharmacological drugs in cardiovascular risk (CVR) factors, medicine use, cardiorespiratory fitness (CRF) and health related quality of life (HRQoL). In fact, to date, only one systematic review (Naci & Ioannidis, 2013) was addressed to compare the isolated effectiveness of drugs and exercise interventions even though the main focus was on the mortality risk. Nevertheless, recently has been suggested that the combination of drugs and exercise training may be more effective to diminish CVR factors, medicine use and disability than each treatment alone due to the synergetic effects in the heart, vascular and musculoskeletal systems (Anton et al., 2015; Bamman et al., 2014; Buford, 2016; Gui et al., 2017), but lacks more evidence supporting this rationale. Therefore, the aim of the present study is to analyze the longitudinal effectiveness of three types of treatment (exercise training; pharmacologic treatment; combined therapy including drug plus exercise training) on CVR factors, medicine use, CRF and HRQoL in older adults with T2D, hypertension and dyslipidemia, and with comorbidities. It is hypothesized that the combined therapy would promote significant benefits over the pharmacologic treatment due to the synergetic effects between both therapies (Anton et al., 2015; Bamman et al., 2014; Buford, 2016; Gui et al., 2017).

4.8.3. Methods

4.8.3.1. *Study design and procedures*

This longitudinal cohort study involved community-dwelling adults of the local community of Santa Maria da Feira, Portugal and occurred between September 2013 and September 2015. Methodological design has been previously described (Baptista, Dias, et al., 2017). Briefly, this study intended to analyze the effect of long-term multicomponent exercise training in terms of CVR factors, CRF, medication use and costs and HRQoL comparatively with first-line pharmacological drugs in community dwelling older adults. Participants' allocation was made by self-referencing through flyers that were distributed at community centers, media, word-of-mouth, advertising, or through physician counseling.

After the allocation period, in the preliminary meeting, participants were informed about the nature, benefits and risks of the study, and those that volunteered gave their written informed consent consistent with the ethical procedures of the 1964 Helsinki declaration and its later amendments for human studies by the World Medical Association (World Health Organisation, 2013). Moreover, participants also completed the health history questionnaire and the Medical Outcomes Study 36-item Short-form Health Study questionnaire (SF-36). In the second meeting, it was assessed the anthropometric, hemodynamic and lipid profile, and the CRF by the 6-minutes-walk test (R.E. Rikli & Jones, 1999).

Baseline evaluation, clinical examination and the follow up testing were performed by the same order at the baseline and at the end of the follow-up. Stature, body mass (BM), blood pressure, hemodynamic and lipid profile, and medication use were assessed by trained nurses. All the other variables were examined by exercise specialists (degree in physical education and/or sport sciences).

For all the measurements that were considered to be affected by tester technique, the same investigator performed the measurements at baseline and at the end of the study. All study staff was periodically supervised to minimize any systematic error associated with variation in measurement techniques, and to ensure the precision and accuracy of the measurements (American College of Sports Medicine, 2010) by the study coordinator.

During the intervention period, all the participants were encouraged to maintain the same nutritional pattern. Groups of the multicomponent exercise training (MEX) and the combined therapies (exercise training plus metformin – MEX+MET; exercise training plus angiotensin converting enzyme inhibitor – MEX+ACEi; exercise training plus statins – MEX+ST) met three times a week for one hour over the 24-months intervention period to perform the multicomponent exercise program in 32 local centers.

The participants in the pharmacological groups (MET; ACEi; ST) and in the combined therapies (MEX+MET; MEX+ACEi; MEX+ST) held trimester consultations with their primary care physicians to control the medication treatments. Several procedures were taken to ensure participants' safety: *i*) communication with participants' primary care physician was the key factor to maintain safety; *ii*) potential adverse effects were explained in the preliminary meeting and the participants were encouraged to notify study staff if experienced any abnormal symptom with medication or exercise training; *iii*) physicians had full discretion to manage therapy regimen, doing all the necessary dose or drug changes prescription in order to maintain a medically supervised symptom-limited.

The methods and procedures were approved by the Institutional Scientific Board of the University of Coimbra, the local institution (Santa Maria da Feira County) and national ethics committees Data Protection Authority-CNPD; Health Administration from North Ethics Committee-ARS/Norte.

4.8.3.2. Participants

This project involved 1473 inactive community-dwelling adults aged 60 and over. At baseline, it was given the opportunity that all participants engaged in a multicomponent exercise program but 252 participants' preferred to maintain only in the standard care (control group). All the others agree to participate in the exercise program (experimental group).

Afterwards, participants were divided according to the presence of several morbidities and medication used namely for T2D, hypertension and dyslipidemia. The inclusion criteria for the definition of the participants' pathologies were: *i)* T2D according with the criteria of the *International Diabetes Federation* (Aschner et al., 2014): self-report clinical history of the pathology confirmed by the primary care physician and/or

pharmacological treatment; or HbA1c ≥ 6,5%/ 48 mmol/mol; or fasting plasma glucose (FPG) ≥ 126 mg/dl (7.0 mmol/l); 75 g oral glucose tolerance test (OGTT) with FPG ≥ 126 mg/dl (7.0 mmol/l) and/or 2 hour plasma glucose ≥ 200 mg/dl (11.1 mmol/l); *ii)* Hypertension was defined according with *European Society of Hypertension* and of the *European Society of Cardiology* (Mancia et al., 2013): self-reported diagnosis of the pathology confirmed by the health professional and/or pharmacological treatment; or blood pressure values above 140 mmHg for systolic blood pressure (SBP) and/or 90 mmHg for diastolic blood pressure (DBP); *iii*) Dyslipidemia was defined according to the *European Society of Cardiology* and *European Atherosclerosis Society* (Catapano et al., 2016): previous clinical diagnosis confirmed by the health professional and/or pharmacological treatment; and/or LDL cholesterol (LDL-C) ≥ 115 mg/dl (3.0 mmol/l); or HDL cholesterol (HDL-C) values ≤ 40 mg/dl in men and 45 mg/dl in women; and/or triglycerides (TG) ≥ 150 mg/dl (1.7 mmol/l). Exclusion criteria included: (a) unstable angina; (b) uncontrolled symptomatic heart failure; (c) uncontrolled cardiac dysrhythmias; (d) symptomatic aortic stenosis; (e) participants who were not under regular supervision of the treating physician for the period of the study evaluation; (f) known cancer or limited life expectancy, acute emergencies; (g) Parkinson's disease; (h) Alzheimer's disease; (i) dementia or mild/severe cognitive impairment; (j) severe visual impairment; (k) further reasons that made it impossible or highly problematic to participate and come to the follow-up visits, completing baseline and follow-up testing (program log ≥ 80 %). Furthermore, participants were also excluded if they were under thiazide diuretic medication, calcium channel blockers, angiotensin receptor blockers medication or combined therapy in the hypertensive group; and were using bile acid sequestrate, cholesterol absorption inhibitors, PCSK9 inhibitors, nicotinic acid or other drug combination in the dyslipidemic participants. Three sub-groups of T2D, hypertensive and dyslipidemic older adults were divided according with 3 therapy criteria: *i)* isolated MEX; *ii)* isolated oral pharmacological therapies – MET, ACEi, and ST; *iii)* combined therapy – MEX+MET, MEX+ACEi, and MEX+ST. The sub-group of 284 older adults with T2D included 59 participants (71% female) in the MEX group, 30 (40% female) in oral hypoglycemic therapy with MET, and 195 (68% female) combined both forms of therapy- MEX plus oral MET. The sub-group of 418 hypertensive older adults included 116 participants (79% females), in the MEX group, 70 (68% females), using oral ACEi medication, and 232

participants (77% females), combining MEX plus ACEi. The sub-group of 981 dyslipidemic older adults was composed by 298 participants (74% females) in the MEX group, 178 participants (65% females) using oral ST, and 505 participants (79% females) combining MEX plus oral ST. The inclusion criteria in the MEX group was engagement in the isolated multicomponent exercise training; in the pharmacologic therapies participants used only daily oral medication; and in the combined groups participants used both forms of treatment – multicomponent exercise training and oral pharmacologic therapy.

4.8.3.3. Interventions

Multicomponent exercise program

The multicomponent exercise training program was designed to meet the exercise and physical activity guidelines for older adults, and the sessions were planned, supervised and adjusted according to the safety limits (American College of Sports Medicine, 2010). Intensity was monitored using both the Borg perceived exertion scale (Borg, 1988) and a heart rate monitor (Polar, SWE). Exercise modifications such as duration, number of repetitions, or use of an exercise auxiliary were recommended by the group instructor when needed.

Exercise training sessions consisted in three 60-min sessions/week, on three non-consecutive days and included aerobic, resistance, balance and flexibility components according with these items: 5-10 minutes (min) of warm-up, 20-30 min of aerobic, 15-20 min of resistance training, 10 min of balance, 10 min of stretching, and 5-10 min of cool down exercises. Aerobic exercise started with participants in a standing position (e.g., walking in place with arm movements), and progressively involved continuous movement of major muscles of the upper-extremity, performed alternately with movement of the lower-extremity. Time and intensity of aerobic exercise increased from 20 to 30 min at 50% to 70% maximum heart rate (HRmax) per session (American College of Sports Medicine, 2010).

Resistance training involved a set of 5-8 exercises from the large muscle groups, with 1-3 sets of 8-12 repetitions for each upper and lower body muscle group and came

from participants' own BM or with free weights. Intensity was set at 50% to 70% 1-repetition maximum (1-RM), with 90 to 120 seconds of rest between sets.

Balance training was also based on functional tasks required by older adults. Prior to cool down, participants performed stretching exercises designed to improve flexibility of the major muscle groups; each stretch was sustained between 15 and 30 seconds to the point of tightness, and repeated three times.

Exercise progression increased every 6 weeks through augments on duration, repetitions, resistance, and/or difficulty (e.g., transition from sitting to standing to complete exercises). All training sessions were carefully supervised by 34 experienced exercise specialists (ratio of supervision 1:9- 1 professor for 9 participants) who were regularly supervised by the general study coordinator. To minimize any systematic error associated with variation in training sessions (American College of Sports Medicine, 2014), monthly meetings were conducted by the general study coordinator.

Pharmacological procedure

The participants of isolated pharmacologic therapy (MET, ACEi and ST) and the combined groups (MEX+MET, MEX+ACEi and MEX+ST) used daily doses during at least one year prior to this study initiation, prescribed by their primary care physician, according with the presence or not of others comorbidities and disease specific criteria. Trimester medical consultations were held by these participants with their physician to control their diseases and medications doses, and all abnormal symptoms detected were discussed with their physician that decided the appropriate course of action. The MET and MEX+MET groups used pharmacological therapy with oral hypoglycemic metformin (850 mg twice daily) to manage their disease; the ACEi and MEX+ACEi groups used mono-dose daily of ACEi medication and included: Enalapril- 10-20 mg; Perindopril-2, 4, 10 mg; Lisinopril- 5-20 mg; Ramipril- 2,5-5 mg; and Captopril- 25 mg; and the participants of the ST and MEX+ST groups used daily ST monotherapy and included: Atorvastatin (10mg), Pravastatin (20mg), Pitavastatin (2mg), Rosuvastatin (20mg) and Simvastatin (20mg).

4.8.3.4. *Outcomes Measures*

Anthropometric Profile

Stature was measured using a standard stadiometer to 0.1 cm in the upright position, with the participant´s back square against the wall and eyes looking straight ahead, without shoes. BM was measured by a calibrated digital balance-beam scale (SECA 770, Germany) with a precision nearest to 100 grams, with barefoot participants and in light clothing. Body mass index (BMI) was calculated dividing BM in kilograms by stature in meters squared (American College of Sports Medicine, 2010).

Hemodynamic and lipid profiles

Blood pressure was measured three times, after 5 minutes rest and the measurements were performed with 2 minutes intervals, using a sphygmomanometer (Aneroid Sphygmomanometer-HICO HM 1001, Germany) and stethoscope (Nurse Type Professional Stethoscope-HICO HM-3005, Germany). The mean of the measurements was used for SBP and DBP (American College of Sports Medicine, 2014). Blood lipid outcomes were collected in the morning after 12 hours fasting from venous blood.

Glycaemia, total cholesterol (TC), HDL-C, LDL-C and TG were carried out in plasma and determined by standard methods (American College of Sports Medicine, 2014) by the same accredited laboratories at baseline and at the end of the study.

Health history

Participants demographic, medical and lifestyle data were obtained by questionnaire including the following information: age, gender, education level, living situation, smoking status and the presence of several conditions like heart disease, hypertension, stroke, diabetes, dyslipidemia, osteoarthritis, pulmonary diseases, liver diseases, thyroid diseases, visual and audio problems, cancer, Parkinson's disease, Alzheimer disease, dementia or other comorbidities. Medication type and dosage were also assessed by detailed questionnaire with visual confirmation of prescription drugs recorded by the study staff. Medication cost was annually calculated to each participant according to the chronic medication use monthly, with the retail price of 2015 using a national web site (http://www.infarmed.pt).

Health-related quality of life

HRQoL was assessed using the SF-36 questionnaire, adapted and validated for the Portuguese population (Ferreira, 1998). This instrument with high internal consistency and reliability (between 0.80 and 0.86) (Ferreira, 1998) was developed to measure generic health status and HRQoL through the evaluation of eight health-related subscales. However, in this study was only used the total summary score, Total SF-36, that was calculated using the methods set out by Ware and colleagues (Ware. Jr, 2000). The scores range from 0 to 100, with higher values indicating better functional health and well-being.

Cardiorespiratory fitness

CRF was evaluated using the 6-minute-walk test (6MWT) performed on a flat 50-m rectangular course, marked off in five-meter segments (R.E. Rikli & Jones, 1999). This test derived from the *Senior fitness Test* battery (R.E. Rikli & Jones, 1999) which has strong psychometric properties (validity and test-retest reliability between 0.80 and 0.98) (Roberta E. Rikli & Jones, 2013), ease and safe use, and measures a wide range of physical abilities. Furthermore, his continuous scale allows a gradual assessment of changes over time (improvements or decline) (Roberta E. Rikli & Jones, 2013). To minimize intraday variability, temperature effects, and biological rhythms, this test was performed between 8-10 am and participants were instructed to avoid vigorous exercise in the 2 hours prior to testing, to wear comfortable clothes and appropriate walking shoes, and to continue their usual medication. Recommended reasons for immediately stopping this test and to ensure participants safety included chest pain, intolerable dyspnea, leg cramps, staggering, diaphoresis, and pale or ashen appearance.

4.8.3.5. *Statistical analysis*

Descriptive demographic and medical characteristics of the sample were presented as weighted percentages at baseline. Moreover, baseline anthropometric, hemodynamic, lipid, medication number and cost, CRF and HRQoL outcomes were compared in total sample and across disease and medication use with measures of frequency, central tendency and dispersion – mean and standard deviation (SD), for the following variables:

sex, age, comorbidity number, BMI, SBP, DBP, glycaemia, TC, HDL-C, LDL-C, TG, medicines number and annual cost, 6MWT, and HRQoL-Total SF-36. Furthermore, for all continuous variables, normality of distribution and homoscedastic variance were verified through numeric (Kolmogorov-Smirnov and Levene´s tests) and graphical methods.

One-way analysis of variance (ANOVA) followed by Gabriel *post-hoc* and a T-Student test were used for comparisons between groups on the baseline demographic, anthropometric, hemodynamic, medication number and annual cost, CRF and HRQoL outcomes.

To assess the longitudinal changes within and between groups, a two-way ANOVA for repeated measures was performed. Additional analyses to minimize potential confounding covariates were included as factors that could influence the outcomes, thus differences between groups after 24-months intervention were also assessed using the analysis of covariance (ANCOVA), adjusting for age, sex and comorbidity number. Additionally, we also conducted several sensitivity analyses to minimize the possibility of reverse causation, with adjustment to baseline mean scores. To test the magnitude of changes within each group from baseline to 24-months intervention, Cohen´*d* effect size was calculated. Standardized effects sizes were classified as small (<0.20), moderate (0.20-0.79) and large (>0.80) (Cohen, 1988).

The equation $\underline{\Delta}$% [(Post-pre follow-up/Total Test) x 100] was used to a more simple interpretation to determine the percentage difference within each group across all variables analyzed from baseline to final 24-months evaluation.

We then explored the independent variables association of participant characteristics at baseline and after the 24-months intervention, in total sample and in each disease with a linear regression modeling. A stepwise, backward conditional model was used with the continuous variables BMI, SBP, DBP, glycaemia, TC, HDL-C, LDL-C, TG, HRQoL, and CRF, with $p<0.100$ as the threshold for inclusion in the model. Medication number was then divided into 3 categories (0-1; 2-3; and ≥4 medications) to test treatments effectiveness (the odds ratio) on the continuous variables, using the multinomial logistic regression modeling with backward method. The referent category was more than 4 for medicines, comparing isolated exercise training with pharmacologic treatments.

Data analysis was performed using Statistical Package for the Social Sciences for Windows (IBM-SPSS, Inc. Chicago, IL, USA), software version 24. Statistical tests were 2-tailed and significance was set at 5%.

4.8.4. Results

After the 24-months intervention, 7.2% (*n* = 106) of our participants withdrawn and 9.6% (*n* = 141) were lost to follow-up due to a program adherence under 80%. The trial was completed by 83% of the participants (*n* = 1226): EX group (*n* = 986; 81%); CO (*n* = 240; 95%) (Figure 4.8.1). In the T2D group, 217 participants completed the trial: 80% in the MEX group (*n* = 47); 97 % in MET group (*n* = 29) and 72% in the MEX+MET group (*n* = 141). In the hypertensive group, the trial was completed by 82% of the participants (*n* = 342); 78 % in the MEX group (*n* = 90); 94% in the ACEi group (*n* = 66) and 80 % in the MEX+ACEi group (*n* = 186). Relatively, to the dyslipidemic participants, the trial was completed by 84% of the participants (*n* = 827): 84 % in the MEX group (*n* = 251); 91% in ST group (*n* = 161) and 82% in the MEX+ST group (*n* = 415).

Participants characteristics lost to follow-up did not differ significantly from those who completed the study. Completeness of data was of 100%, having no missing responses.

No serious adverse event (life-threatening event, inpatient hospitalization or clinically significant abnormal laboratory or diagnostic test) was registered during the intervention period, except for occasional soreness in the isolated multicomponent exercise group and in the combined therapy groups.

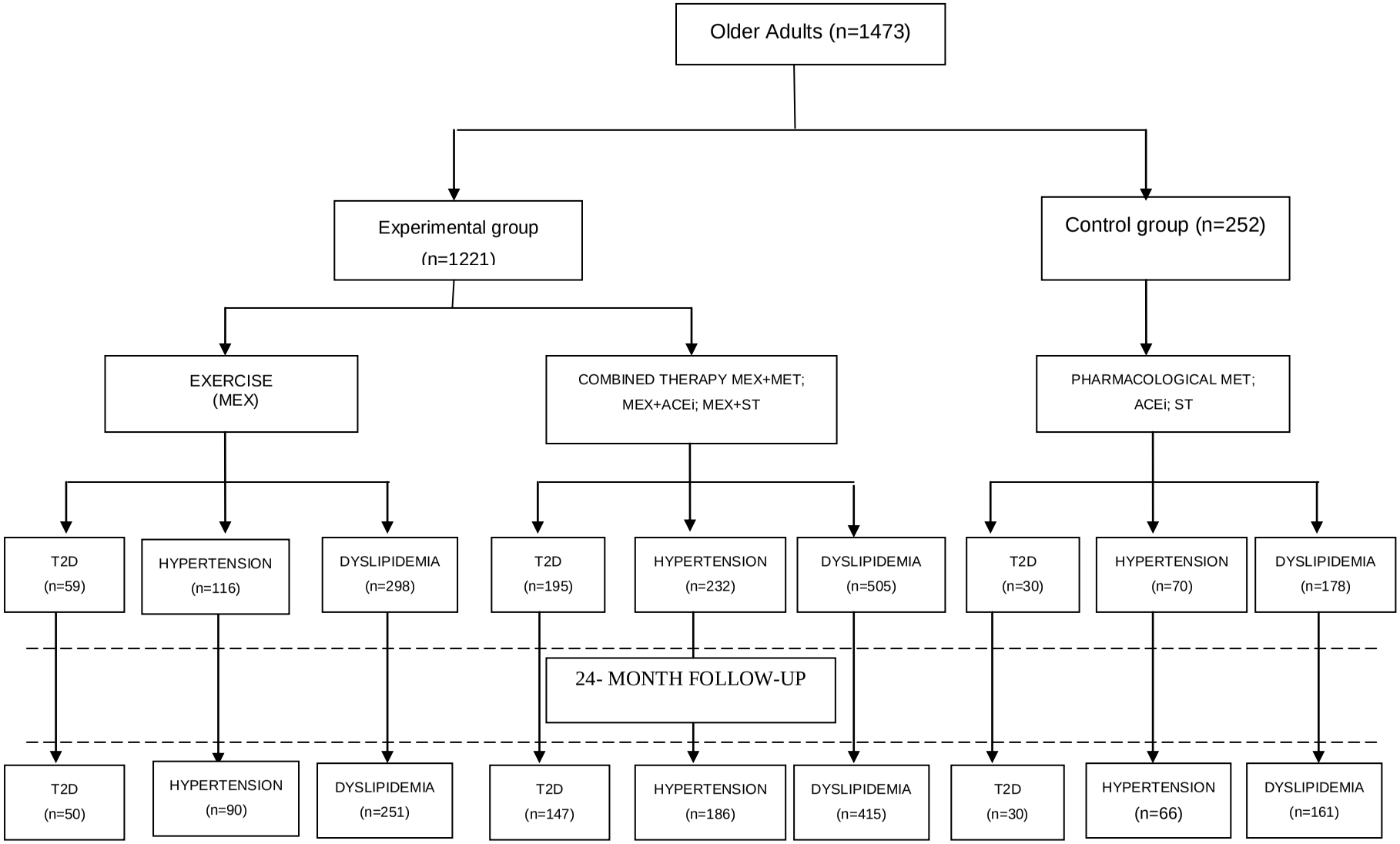

Figure 4.8.1- Cohort flux diagram

4.8.4.1. Baseline characteristics

Baseline demographic, medical, medication use, anthropometric, hemodynamic, lipid, CRF and HRQoL characteristics, and differences between groups are presented in the Tables 4.8.1 and 4.8.2. Overall, 75% were women, with mean (±SD) age of 67 (7.9) years, with 2.2 (1.6) comorbidities. Dyslipidemia (71%), hypertension (63%), osteoarthritis (26%), osteoporosis (22%) and diabetes (19%) were the most prevalent comorbidities. The most prevalent types of drug treatments are – MET is used by 79% participants with T2D; ST is used by 65% participants with dyslipidemia; ACEi is used by 33% participants with hypertension, and 22% used ACEi plus another first-line antihypertensive. Moreover, within groups there were no significant differences in drug treatments and doses maintained throughout the intervention period.

In T2D, all participants of MET and MEX+MET used metformin (850 mg twice daily). In the hypertensive participants, in the isolated ACEi group: 37% used Perindopril – 2mg (5%), 4mg (90%), 10mg (5%); 23% used Lisinopril – 10mg (13%), 20mg (87%); 20% used Enalapril – 5mg (9%), 20 mg (91%); and 20% used Ramipril – 2,5mg (90%), 5mg (10%). In the MEX+ACEi, 34% used Perindopril – 2mg (2%), 4mg (91%), 10mg (7%); 26% consumed Lisinopril – 10 mg (15%), 20 mg (85%); 12% used Enalapril – 5mg (10%), 20mg (90%); 19% used Ramipril – 2,5mg (92%), 5mg (8%); and 9% used Captopril 25mg. In the dyslipidemic participants, 62% used Simvastatin (20 mg), 15% used Atorvastatin (10 mg), 11% used Pravastatin (20 mg), 4% consumed Rosuvastatin (20 mg) and 3% used Pitavastatin (2 mg). In the MEX+ST, 68% of participants consumed Simvastatin (20 mg), 15% used Atorvastatin (10mg), 13% used Pravastatin (20 mg), 9% used Pitavastatin (2 mg) and 6% used Rosusvatatin (20 mg).

At baseline, groups were quite homogeneous, except in blood pressure variables, the number of medicines used and the HRQoL self-perception. Comparatively to the CO group, MEX participants had higher SBP and DBP ($p<0.001$), consumed more medicines but had better HRQoL perception. In terms of sub-group analysis, T2D participants were also quite similar across all groups, except for TC, LDL-C, medication number and annual cost, which revealed higher results by the MEX participants, but had lower medication used (2.5± 2.1) and annual medication cost than the other 2 groups. In the hypertensive sub-group, MEX group exhibited higher SBP and DBP, but participants in the ACEi group had more comorbidities (2.8± 1.6), used more medicines (3.1± 1.2), had higher annual

medication cost and revealed worst HRQoL than the other 2 groups. The MEX participants in the dyslipidemic sub-group, also presented higher SBP and DBP (p<0.001) and worst LDL-C. The participants in the ST group presented worst glycaemia (112±81), had more comorbidities (2.5±1.6), and worst HRQoL. The combined group showed worst TG (130±61) profile, higher used of medication (3.2±1.3), and consequently had also more annual medication costs. Relatively to the comparison between those with more and less comorbidities, differences were very pronounced in almost all outcomes analyzed. Those that had more comorbidities (≥ 3 morbidities), had worst anthropometric and hemodynamic profile, used more medicines and had higher annual medication expenditure, presented worst CRF and lower HRQoL than those with less than 1 morbidity.

4.8.4.2. Differences between groups after the 24-month intervention

After the 24-months intervention, differences between groups and sub-groups occurred in SBP, DBP, CRF and HRQoL (p<0.001) (Table 4.8.3). These results maintained even after adjusting to sex, age, comorbidity number and baseline value scores. Moreover, for the T2D participants differences between groups also occurred in medication number (p<0.001), TC (p=0.046) and LDL-C (p=0.023); in the hypertensive sub-group differences presented also in medication number (p<0.001), glycaemia (p=0.017) and HDL-C (p=0.004); and the dyslipidemic participants also had differences in glycaemia (p=0.027), TC (p= 0.024), LDL-C (p=0.020) and HDL-C (p=0.021). However, after adjusting to sex, age, comorbidity number and baseline value scores, these differences disappeared (p> 0.05). Relatively to the comorbidity sub-group, the differences that existed at baseline continue to manifest in all the outcomes, except for the DBP and TC (p>0.05). Nevertheless, these differences disappeared after adjusting to the covariates previously mentioned.

Table 4.8.1- Descriptive demographic and medical characteristics of the sample in baseline (N = 1473)

Variables	N	Percentage (%)
SEX		
Male	367	24,9
Female	1106	75,1
AGE (Years)		
< 64 Y-old	559	37,9
65- 74 Y-old	666	45,2
>75 Y-old	240	16,3
EDUCATION		
High school or less	1436	97,5
College or more	37	2,5
LIVING SITUATION		
Living with other	1064	72,2
Living Alone	409	27,8
COMORBIDITY		
None	226	15,3
One or Two	687	46,7
Three or more	560	38,0
BODY MASS INDEX		
20-24,9	214	18,7
25-29,9	540	47,2
30- 34,9	305	26,7
≥35	84	7,3
THROMBOSIS		
Yes	54	3,7
No	1419	96,3
CHEST ANGINA		
Yes	37	2,5
No	1436	97,5
HYPERTENSION		
Yes	930	63,1
No	543	36,9
TYPE 2 DIABETES		
Yes	284	19,3
No	1189	80,7
RESPIRATORY DISEASES		
Yes	179	12,1
No	1294	87,9
OSTEOPOROSIS		
Yes	331	22,4
No	1142	77,6
OSTEOARTHROSIS		
Yes	384	26,0
No	1089	74,0
DYSLIPIDEMIA		
Yes	1049	71,2
No	424	28,8
COMORBIDITY		
≤1 Comorbidities	561	38.1
2 Comorbidities	325	22.1
≥3 Comorbidities	587	39.9
ANTIHYPERTENSIVE		
Diuretics	40	4.3
Angiotensin converting enzyme inhibitors	302	32.5
Angiotensin receptor blocker	152	16.3
Calcium Channel Blockers	28	3.0
B- Blockers	47	5.1
Combined (≥ 2 sub-groups)	245	26.3
No medication	116	12.5
ANTIHYPERGLICEMIC		
Metformin	225	79.2
Insulin (Type 1 Diabetes)	7	2.5
No medication	59	20.8
ANTIDYSLIPIDEMIC		
Statins	683	65.1
Other	68	6.5
No medication	298	28.4

Table 4.8.2- Differences in anthropometric, hemodynamic, CRF, HRQoL and medication use between groups at baseline using T- Student test and one-way ANOVA (*N*=1473)

DISEASE	GROUPS	BMI (kg/m^2)	SBP (mmHg)	DBP (mmHg)	Glycaemia (mg/dL)	TC (mg/dL)	HDL (mg/dL)	LDL (mg/dL)	TG (mg/dL)	Comorbidity (n)	Medicines (n)	Annual Cost (€)	HRQoL TSF-36	6-min walk test (m)
TOTAL SAMPLE (N=1473)	**CO (n=252)**	28.3 (4.0)	131 (17)	76 (9)	110 (76)	199 (39)	52 (13)	120 (33)	123 (68)	2.3 (1.5)	1.8 (1.6)	277.2 (267.4)	70 (18)	448 (66)
	EX (n= 1221)	28.7 (4.3)	141 (17)	80 (11)	104 (25)	199 (39)	54 (15)	121 (34)	119 (54)	2.1 (1.6)	2.2 (1.6)	287.5 (288.8)	74 (16)	450 (120)
	***P* Values**	0.155	**<0.001****	**<0.001****	0.057	0.913	0.070	0.772	0.426	0.162	**0.001***	0.649	**<0.001****	0.746
T2D (n=284)	**EX (n=59)**	30.1 (4.3)	140 (20)	79 (13)	128 (27)	199 (37)	48 (9)	127 (33)	126 (56)	1.9 (1.3)	2.5 (2.1)	323.7 (227.2)	73 (17)	429 (127)
	M (n=30)	30.4 (4.2)	139 (15)	77 (10)	134 (47)	169 (25)	45 (10)	97 (26)	131 (70)	2.2 (1.4)	3.8 (1.5)	378.4 (373.9)	66 (19)	427 (76)
	M+EX (n=195)	29.9 (4.7)	141 (18)	79 (11)	128 (33)	180 (34)	50 (19)	106 (31)	130 (58)	1.7 (1.3)	4.2 (1.5)	492.2 (396.4)	73 (16)	447 (113)
	***P* Values**	0.805	0.911	0.673	0.547	**0.001***	0.334	**<0.001****	0.941	0.070	**<0.001****	**0.019***	0.096	0.430
HYPERTENSION (n=418)	**EX (n=116)**	28.1 (4.4)	147 (10)	85 (10)	100 (25)	205 (32)	57 (14)	123 (30)	121 (65)	1.8 (1.5)	1.5 (1.1)	226.0 (278.99	74 (15)	470 (121)
	ACEi (n=70)	29.0 (3.5)	133 (17)	77 (9)	106 (28)	203 (45)	50 (14)	124 (35)	139 (82)	2.8 (1.6)	3.1 (1.2)	343.0 (313.0)	68 (20)	440 (77)
	ACEi+EX (n=232)	29.4 (4.1)	139 (14)	78 (11)	104 (24)	198 (38)	53 (13)	119 (33)	124 (57)	2.4 (1.6)	2.7 (1.2)	312.4 (293.2)	72 (16)	444 (116)
	***P* Values**	**0.034***	**<0.001****	**<0.001****	0.347	0.299	**0.014***	0.440	0.199	**<0.001****	**<0.001****	**0.012***	**<0.044***	0.086
DYSLIPIDEMIA (n= 981)	**EX (n=298)**	28.5 (4.0)	140 (17)	80 (11)	99 (21)	205 (35)	52 (12)	132 (28)	113 (47)	2.1 (1.5)	1.6 (1.4)	231.6 (242.0)	73 (15)	455 (117)
	ST (n=178)	28.5 (3.2)	131 (17)	76 (9)	112 (81)	201 (39)	52 (13)	123 (33)	129 (71)	2.5 (1.6)	2.2 (1.5)	285.3 (277.3)	70 (18)	450 (65)
	ST+EX (n=505)	29.2 (4.2)	141 (17)	79 (11)	107 (28)	201 (42)	53 (16)	120 (36)	130 (61)	2.4 (1.7)	3.2 (1.3)	339.0 (297.3)	74 (16)	436 (116)
	***P* Values**	0.060	**<0.001****	**0.002***	**0.008***	0.374	0.061	**<0.001****	**0.001***	**0.041***	**<0.001****	**<0.001****	**0.015***	0.079
COMORBIDITY (n=1473)	**≤1 DISEASE (*n*=561)**	27.8 (4.1)	137 (17)	79 (11)	96 (17)	202 (39)	56 (13)	126 (32)	105 (46)	-	0.4 (0.5)	154.8 (194.5)	76 (15)	471 (105)
	2 DISEASES (*n*= 325)	28.8 (3.9)	138 (17)	79 (11)	101 (23)	200 (36)	54 (12)	122 (32)	118 (57)	-	2.0 (0.1)	207.3 (198.3)	73 (16)	448 (109)
	≥3 DISEASE (*n*= 587)	29.3 (4.4)	142 (18)	79 (11)	110 (49)	196 (40)	53 (16)	118 (35)	128 (60)	-	3.7 (0.9)	395.4 (320.8)	71 (16)	430 (113)
	***P* Value**	**<0.001****	**<0.001****	0.949	**<0.001****	0.148	**0.017***	**0.004***	**<0.001****	-	**<0.001****	**<0.001****	**<0.001****	**<0.001****

Data are expressed as mean (SD). BMI- Body mass index. SBP- Systolic blood pressure. DBP- Diastolic blood pressure. TC- Total cholesterol. HDL- High density lipoprotein cholesterol. LDL- Low density lipoprotein cholesterol. TG- Triglycerides. HRQoL- Health-related quality of life. TSF-36- Total SF-36. T2D- Type 2 diabetes. CO-Control group. EX- Multicomponent exercise training. M- Metformin group. ACEi- Angiotensin converting enzyme inhibitor group. ST- Statins. * Differences between evaluations ($p \leq 0.05$). ** Differences between evaluations ($p \leq 0.001$).

Table 4.8.3- Differences in anthropometric, hemodynamic and medication use between groups at 24-month intervention using ANOVA and ANCOVA adjusted to sex, age, comorbidity number and baseline values scores

DISEASE	GROUPS	BMI (kg/m^2)	SBP (mmHg)	DBP (mmHg)	Glycaemia (mg/dL)	TC (mg/dL)	HDL (mg/dL)	LDL (mg/dL)	TG (mg/dL)	Medicines (n)	Annual Cost (€)	HRQoL TSF-36	6-min walk test (m)
TOTAL SAMPLE (n=1226)	**CO (n=240)**	28.6 (4.1)	137 (17)	78 (9)	111 (39)	186 (44)	51 (11)	115 (25)	125 (67)	1.6 (1.5)	313.3 (303.3)	65 (17)	427 (60)
	MEX (n= 986)	28.3 (4.0)	127 (15)	74 (10)	107 (30)	193 (41)	54 (14)	117 (33)	120 (71)	2.0 (1.6)	313.9 (312.6)	77 (14)	570 (102)
	Unadjusted *P* Value	0.439	**<0.001****	**<0.001****	0.237	0.122	0.054	0.578	0.597	**<0.001****	0.981	**<0.001****	**<0.001****
	Adjusted *P* Value	**<0.001****	**<0.001****	**<0.001****	0.797	0.180	0.209	0.861	0.927	**0.021***	0.444	**<0.001****	**<0.001****
T2D (n=284)	**MEX (n= 59)**	29.3 (4.7)	126 (15)	71 (7)	115 (26)	188 (41)	49 (10)	120 (32)	115 (55)	2.5 (2.2)	436.4 (373.1)	79 (14)	521 (83)
	MET (n= 30)	30.9 (4.3)	147 (14)	79 (11)	142 (54)	158 (49)	44 (7)	103 (23)	128 (95)	3.5 (1.9)	446.6 (322.0)	64 (16)	426 (62)
	MEX+MET (n= 195)	29.6 (4.3)	129 (14)	73 (10)	135 (39)	177 (38)	49 (11)	103 (31)	133 (73)	3.9 (1.7)	520.9 (384.2)	76 (14)	545 (110)
	Unadjusted *P* Value	0.332	**<0.001****	**0.003***	**0.014***	**0.046***	0.226	**0.023***	0.483	**<0.001****	0.311	**<0.001****	**<0.001****
	Adjusted *P* Value	**0.015***	**<0.001****	**0.011***	**0.009***	0.675	0.871	0.411	0.098	0.716	0.509	**<0.001****	**<0.001****
HYPERTENSION (n=342)	**MEX (n=90)**	27.7 (3.8)	131 (12)	76 (9)	100 (20)	193 (49)	60 (27)	119 (35)	117 (59)	1.7 (1.3)	286.9 (371.8)	79 (15)	577 (92)
	ACEi (n=66)	29.0 (3.5)	141 (17)	79 (10)	120 (50)	187 (45)	49 (10)	111 (24)	142 (70)	2.6 (1.4)	386.1 (306.3)	63 (17)	425 (60)
	MEX+ACEi (n=186)	29.0 (4.0)	128 (15)	75 (10)	108 (29)	193 (34)	53 (12)	113 (33)	130 (61)	2.4 (1.3)	322.0 (291.2)	77 (14)	564 (101)
	Unadjusted *P* Value	**0.015***	**<0.001****	**0.009***	**0.017***	0.658	**0.004***	0.536	0.192	**<0.001****	0.131	**<0.001****	**<0.001****
	Adjusted *P* Value	**0.001***	**<0.001****	**<0.001****	0.605	0.393	0.220	0.609	0.338	0.615	0.221	**<0.001****	**<0.001****
DYSLIPIDEMIA (n=912)	**MEX (n=251)**	28.4 (4.1)	127 (17)	74 (10)	103 (23)	197 (34)	51 (12)	122 (29)	118 (50)	1.7 (1.4)	261.8 (263.2)	76 (14)	571 (102)
	ST (n=161)	28.8 (3.8)	137 (17)	77 (9)	114 (41)	181 (47)	50 (11)	112 (24)	125 (63)	1.9 (1.5)	323.3 (316.8)	65 (17)	430 (51)
	MEX+ST (n=415)	28.7 (3.7)	128 (15)	73 (9)	110 (33)	191 (45)	54 (12)	114 (35)	130 (85)	2.8 (1.5)	359.8 (318.3)	78 (14)	561 (103)
	Unadjusted *P* Value	0.489	**<0.001****	**<0.001****	**0.027***	**0.024***	**0.020***	**0.021***	0.266	**<0.001****	**<0.001****	**<0.001****	**<0.001****
	Adjusted *P* Value	**<0.001****	**<0.001****	**<0.001****	0.425	0.076	0.626	0.160	0.969	**0.026***	0.873	**<0.001****	**<0.001****
COMORBIDITY (n=1168)	**≤1 DISEASE (n=445)**	27.7 (4.0)	129 (15)	75 (9)	99 (23)	197 (42)	56 (18)	124 (29)	107 (50)	0.6 (0.9)	197.9 (265.8)	76 (15)	551 (116)
	2 DISEASES (n= 269)	28.5 (3.9)	128 (17)	74 (9)	106 (27)	193 (37)	54 (12)	116 (28)	122 (102)	1.9 (0.9)	249.0 (244.3)	76 (15)	550 (116)
	≥3 DISEASE (n= 454)	29.0 (4.1)	131 (16)	74 (10)	113 (36)	190 (42)	52 (12)	113 (35)	128 (63)	3.2 (1.4)	408.7 (335.0)	73 (16)	524 (107)
	Unadjusted *P* Value	**<0.001****	**0.027***	0.333	**<0.001****	0.160	**0.005***	**0.001***	**0.004***	**<0.001****	**<0.001****	**0.002***	**<0.001****
	Adjusted *P* Value	0.833	0.724	0.504	0.112	0.867	0.793	0.052	0.243	0.978	0.108	0.544	0.192

Data are expressed as mean (SD). BMI- Body mass index. SBP- Systolic blood pressure. DBP- Diastolic blood pressure. TC- Total cholesterol. HDL- High density lipoprotein cholesterol. LDL- Low density lipoprotein cholesterol. TG- Triglycerides. HRQoL- Health-related quality of life. TSF-36- Total SF-36. T2D- Type 2 diabetes. CO-Control group. MEX- Multicomponent exercise training. MET- Metformin. ACEi- Angiotensin converting enzyme inhibitor. ST- Statins. * Differences between evaluations ($p \leq 0.05$). ** Differences between evaluations ($p \leq 0.001$).

4.8.4.3. Differences within groups from baseline to 24-month intervention

The MEX and combined therapy groups decreased important CVR factors and also the number of medicines used, despite the worst hemodynamic profile at baseline. Nevertheless, the decreases in the number of medicines presented some differences according to the disease sub-group, being in some sub-groups accompanied by an increase in the annual medication cost (Table 4.8.4). Contrarily, participants only with pharmacological treatments (standard care) deteriorated their anthropometric and hemodynamic profile, CRF and HRQoL, but in some disease sub-groups also reduced the number of medicines. In summary, after the 24-months intervention, MEX participants decreased 10% SBP, 8% DBP, 4% TC, 5% LDL-C, 8% the number of medicines used to treat other morbidities, and augmented 20% CRF and 4% HRQoL. Contrarily, participants under standard care (pharmacological therapy) increased 1% BMI, 4% SBP and 2% DBP, but also decreased 12% the number of medicines, 5% CRF and 9% HRQoL.

Likewise in the sub-group analysis, participants under MEX or under combined therapy improved their anthropometric and hemodynamic profile and also improved CRF and HRQoL perception, reversely to all isolated pharmacological sub-groups that deteriorated all these outcomes. In fact, in the T2D sub-group, MEX participants reduced 2% BMI, 14% SBP, 13% DBP, 11% glycaemia, 19% TG and improved 20% CRF. However, this group also augmented 28% the annual medication expenditure. Similarly, but in a smaller proportion, the MEX+MET participants also reduced 1% BMI, 10% SBP, 8% DBP, decrease 9% the number of medicines consumed and increased 20% CRF and 5% HRQoL, whereas the MET group augmented 1% BMI and 5% SBP.

In the hypertensive sub-group, MEX participants reduced 13% SBP, 12% DBP, 7% TC and augmented 18% CRF and 6% HRQoL. Also, the combined group (MEX+ACEi) decreased 1% BMI, 9% SBP, 5% DBP, 6% LDL-C, reduced 11% the number of medicines used, and increased 21% CRF and 4% HRQoL perception. Contrarily, participants under exclusively ACEi treatment augmented 1% BMI, 6% SBP and reduced 4% CRF, 8% HRQoL but also decreased 11% TC and 17% the consumption of medicines.

Relatively to the dyslipidemic sub-group, MEX participants once again displayed an improved profile after the intervention, reducing SBP (10%), DBP (8%), TC (3%), LDL-C (5%), and increasing CRF (19%), HRQoL (4%) and annual medication expenditure (12%). Similarly, the combined group (MEX+ST) also decreased their BMI

(1%), SBP (10%), DBP (8%), TC (5%), LDL-C (5%), and the number of medicines consumed (14%), and increased CRF (21%) and HRQoL (4%). Contrarily, the ST participants augmented BMI (1%), SBP (5%) and DBP (2%), and decreased CRF (4%), HRQoL (4%), TC (10%) and the number of medicines used (16%).

4.8.4.3. Comparative effectiveness of exercise and first-line pharmacological therapies

After the 24-months intervention, the odds ratio for exercise training or combined therapy effectiveness to reduce the medication consumption were higher (OR > 1) in total sample and in the sub-group analysis, comparing with the isolated pharmacological treatment (Table 4.8.5). In fact, participants exposed to the MEX comparing with those under pharmacological therapy (CO group- standard care) had higher odds ratio to reduce the number of medicines, that gradually increased from 30% [OR (95%CI); 1.3 (0.9: 2.0)] for those in 2-3 medications to approximately 88% [(OR-1)x100; (1.883-1)x100] in the smaller medication category (0-1 medication). Likewise in the T2D sub-group, MEX effectiveness comparing with MET treatment was also higher with the decrease in the number of medicines.

Comparing T2D older adults taking 4 or more medications with those in the middle category (2-3 medications), MEX participants had higher odds ratio [2.2 (1.0: 5.0)] than MET therapy, and this effectiveness significantly increased to 610% [7.1 (3.3: 15.3)] with the reduction of medicines (0-1) comparing with those in the higher class (≥ 4 medications). Similarly, in the hypertensive and dyslipidemic sub-groups, MEX was more effective to decrease the number of medicines than isolated ACEi and ST therapy, respectively. The MEX odds ratio augmented from 74% [1.7 (0.73: 4.2)] in the 2-3 medication category to 580% [6.8 (2.6: 17.8)] in the lowest medication use (0-1) in the hypertensive sub-group. In the dyslipidemic sub-group, MEX group also improve his efficacy from 90% [1.9 (1.2: 2.9)] in the middle medication class (2-3 medicines comparing with ≥ 4 medications) to 510% [6.1 (4.0:9.5)] in those in the opposite pols (0-1 with ≥ 4 medications).

An interesting result was the intermediated effectiveness of the combined groups between MEX and the isolated pharmacological treatments, once all combined groups presented higher odds ratio (OR > 1) than pharmacological standard care. However, the odds ratios for these groups were smaller than EX treatment groups.

Table 4.8.4- Differences in anthropometric, hemodynamic and medication use within groups from baseline to 24-month intervention using ANOVA for repeated measures, Δ percentage difference and Cohen *d* effect size

DISEASE	GROUPS	BMI	SBP	DBP	Glycaemia	TC	HDL	LDL	TG	Medicines	Annual Cost	HRQoL TSF-36	6-min walk test
TOTAL SAMPLE (n=1226)	**Δ % CO (n=240)**	1.0	3.7	1.7	-4.4	-9.0	-2.1	-5.1	-4.3	-12.0	8.7	-8.7	-5.0
	P Value	**<0.001****	**<0.001****	**0.004**	0.659	**0.002***	0.205	0.231	0.380	**0.005***	**0.048***	**<0.001****	**<0.001****
	Effect Size	0.071	**0.340**	0.141	0.065	**0.389**	0.091	0.201	0.077	0.122	0.100	**0.324**	**0.342**
	Δ % MEX (n= 986)	**-0.9**	-10.2	-7.8	1.7	-4.0	-0.0	-4.8	-0.9	-8.0	6.9	**3.9**	**20.1**
	P Value	**<0.001**	**<0.001****	**<0.001****	0.058	**<0.001****	0.948	**0.001****	0.720	**<0.001****	**0.004***	**<0.001****	**<0.001****
	Effect Size	0.063	**0.798**	**0.561**	0.063	0.193	0.002	0.165	0.016	0.101	0.073	0.210	**1.036**
T2D (n=284)	**Δ % MEX (n= 59)**	-1.8	-14.3	-12.7	-11.3	-5.5	3.7	-6.6	-18.8	2.0	27.6	5.9	20.0
	P Value	**0.007***	**<0.001****	**<0.001****	**0.003***	0.196	0.212	0.338	**0.019***	0.759	**0.010***	0.065	**<0.001****
	Effect Size	0.112	**1.009**	**1.435**	**0.471**	0.256	0.190	0.223	**0.372**	0.023	**0.400**	0.300	**1.051**
	Δ % MET (n= 30)	0.7	4.8	1.7	2.0	-6.2	2.2	2.6	2.1	-9.4	12.1	-2.4	-0.8
	P Value	**0.048***	**0.001***	0.416	0.769	0.489	0.492	0.579	0.763	0.265	0.186	0.371	0.716
	Effect Size	0.052	**0.512**	0.128	**0.054**	0.248	0.115	0.121	0.032	0.194	0.152	0.087	0.050
	Δ % MEX+MET (n= 195)	**-0.8**	**-10.1**	**-7.9**	5.2	-1.1	2.0	-2.4	2.3	-8.7	3.0	**4.5**	20.4
	P Value	**0.016***	**<0.001****	**<0.001****	**0.017***	0.537	0.214	0.328	0.547	**<0.001****	0.465	**0.006***	**<0.001****
	Effect Size	0.055	**0.828**	**0.582**	0.199	0.054	0.095	0.079	0.047	**0.215**	0.040	**0.231**	**1.007**
HYPERTENSION (n=342)	**Δ % MEX (n=90)**	-0.6	-12.7	-11.5	0.1	-7.7	1.1	-2.9	-9.0	8.3	19.8	5.9	17.6
	P Value	0.175	**<0.001****	**<0.001****	0.964	**0.041***	0.721	0.578	0.211	0.207	0.076	**<0.001****	**<0.001****
	Effect Size	0.046	**1.515**	**0.908**	0.006	**0.359**	0.043	0.107	0.154	0.114	0.172	**0.332**	**0.954**
	Δ % ACEi (n=66)	1.0	5.7	2.0	4.6	-10.6	-3.1	-7.3	-11.3	-17.1	8.0	-8.0	-4.0
	P Value	**<0.001****	**<0.001****	0.051	0.205	**0.024***	0.245	0.192	0.194	**0.001***	0.225	**0.012***	**0.001***
	Effect Size	0.081	**0.470**	0.166	0.126	**0.437**	0.139	0.280	0.227	**0.336**	0.099	0.273	0.250
	Δ % MEX+ACEi (n=186)	-1.1	-9.0	-5.4	1.0	-2.8	0.8	-5.7	0.7	-10.5	0.4	4.1	21.0
	***P* Value**	**<0.001****	**<0.001****	**<0.001****	0.497	0.069	0.478	**0.043***	0.845	**<0.001****	0.914	**0.001***	**<0.001****
	Effect Size	**0.089**	**0.773**	**0.399**	0.037	0.146	0.035	0.191	0.014	**0.211**	0.004	**0.213**	**1093**
DYSLIPIDEMIA (n=912)	**Δ % MEX (n= 257)**	-0.0	-10.2	-7.5	1.5	-3.2	1.2	-5.3	-0.2	4.8	11.5	4.2	19.2
	P Value	**0.004***	**<0.001****	**<0.001****	0.163	**0.009***	0.259	**0.006***	0.938	0.135	**0.012***	**<0.001****	**<0.001****
	Effect Size	0.063	**0.771**	**0.502**	0.068	**0.195**	0.052	**0.233**	0.006	0.057	0.122	**0.223**	**1.020**
	Δ % ST (n= 177)	1.0	4.6	1.5	-5.6	-9.9	-1.6	-6.4	-4.9	-16.1	8.5	-6.6	-4.4
	P Value	**<0.001****	**<0.001****	**0.034***	0.611	**0.002***	0.364	0.169	0.331	**0.001***	0.080	**<0.001****	**<0.001****
	Effect Size	0.074	**0.382**	**0.129**	0.080	**0.414**	0.070	0.246	0.091	**0.207**	0.095	**0.237**	**0.310**
	Δ % MEX+ST (n= 478)	-1.0	-10.1	-8.4	0.9	-5.2	-0.9	-5.2	-2.4	-13.7	3.5	4.3	20.7
	***P* Value**	**<0.001****	**<0.001****	**<0.001****	0.499	**<0.001****	0.444	**0.010***	0.515	**<0.001****	0.235	**<0.001****	**<0.001****
	Effect Size	0.071	**0.798**	**0.615**	0.031	**0.221**	0.036	**0.163**	0.040	**0.274**	0.038	**0.230**	**1074**

Δ data are expressed as percentage. BMI- Body mass index. SBP- Systolic blood pressure. DBP- Diastolic blood pressure. TC- Total cholesterol. HDL- High density lipoprotein cholesterol. LDL- Low density lipoprotein cholesterol. TG- Triglycerides. HRQoL- Health-related quality of life. TSF-36- Total SF-36. T2D- Type 2 diabetes. CO-Control group. MEX- Multicomponent exercise training. MET- Metformin group. ACEi- Angiotensin converting enzyme inhibitor group. ST- Statins. * Differences between evaluations ($p \leq 0.05$). ** Differences between evaluations ($p \leq 0.001$). Effects sizes were classified as small (<0.20), moderate (0.20-0.79) and large (>0.80).

Table 4.8.5- Multinominal logistic regression model for the association of medication use with treatment type, according to the disease after 24 month follow-up

Disease	Variables	0-1 Medications		2-3 Medications	
		OR (95% CI)	***P* Value**	**OR (95% CI)**	***P* Value**
	Group:				
	Control group	ref		ref	
TOTAL SAMPLE	Exercise Group	1.883 (1.230: 2.883)	0.004*	1.321 (0.854: 2.044)	0.211
	Therapy				
T2D	MET	ref.		ref.	
	MEX	7.148 (3.331: 15.339)	<0.001**	2.214 (0.974: 5.035)	0.050*
	MEX+MET	1.398 (0.367: 5.326)	0.623	1.703 (0.815: 3.561)	0.157
	Therapy				
HYPERTENSION	ACEi	ref.		ref.	
	MEX	6.844 (2.634: 17.781)	<0.001**	1.744 (0.729: 4.172)	<0.001**
	MEX+ACEi	1.420 (0.650: 3.100)	0.379	1.120 (0.592: 2.119)	0.728
	Therapy				
DYSLIPIDEMIA	ST	ref.		ref.	
	MEX	6.141 (3.985:9.464)	<0.001**	1.887 (1.247: 2.858)	0.003*
	MEX+ST	4.035 (2.436: 6.683)	<0.001**	1.775 (1.104: 2.854)	0.018*

Ref. -reference category: ≥4 Medication. OR- Odds ratio. * $p \leq 0.05$. ** $p \leq 0.001$. Interpretation of the results- when the OR > 1 the odds for exercise training or combined therapy effectiveness are higher, whereas when OR < 1 the effectiveness of isolated pharmacological treatment is more probable.

4.8.5. Discussion

This longitudinal cohort study, to our knowledge, is the first to compare MEX and first-line pharmacological drugs and to demonstrate that chronic multicomponent MEX *per se* is more effective to reduce multifactorial CVR factors, medication consumption and increase CRF and HRQoL than pharmacological therapies (MET, ACEi and ST) in comorbid older adults, independently of the disease. Furthermore, our results highlight the effectiveness of the combined therapy with pharmacological treatment and MEX to improve these outcomes for those that really need to use an oral medication, supporting and adding new information to previous suggestions (Buford, 2016)(Bamman et al., 2014)(Anton et al., 2015)(Gui et al., 2017). Contrarily, isolated oral medication treatment may have longitudinal negative effects on the hemodynamic profile and HRQoL.

Despite the several studies addressing to the benefits of MEX on CVR factors, CRF and HRQoL in several pathologies (Pedersen & Saltin, 2015; Sharman et al., 2015), the effectiveness of MEX comparing with first-line pharmacological drugs is under investigated in older adults with comorbidities due to the exclusion of these population group from clinical trials (Cruz-Jentoft et al., 2013) and to the clear lack of exercise and drug comparisons trials, evaluating the effectiveness of pharmacotherapy with exercise as an arm-comparator (Naci & Ioannidis, 2013).

Previous evidence demonstrated that lifestyle intervention (ie, moderate-intensity PA combined with a reduced- calorie diet) outperformed MET in a large population of obese individuals at risk for T2D, and the benefits of PA plus diet versus MET were actually underestimated due to intent-to-treat analysis (Knowler et al., 2002). Furthermore, in a posterior analysis, these lifestyle interventions promoted fewer hospitalizations, fewer medications, and lower health-care costs over a 10-year period than standard care (Espeland et al., 2014). Reversely, in the single meta-analysis that compared the effectiveness of exercise and drug interventions in the mortality risk (Naci & Ioannidis, 2013), authors concluded that both therapies had potentially similar effects in terms of their mortality benefits in the secondary prevention of coronary heart disease, rehabilitation after stroke, treatment of heart failure, and prevention of diabetes. However, our results addressed to CVR factors, medication consumption, CRF and HRQoL, does not support

the similarities of effects between drugs and MEX, but rather highlight the effectiveness of MEX and even the combination of both therapies, over isolated drug treatment.

Exercise activates a multi-complex array of coordinated cellular and molecular processes involving a wide signaling networks and transcriptional regulators that differentially affect virtually every human tissue and organ system (Bamman et al., 2014)(Sharman et al., 2015). Unfortunately, MEX is regularly prescribed/ performed as an "adjunctive therapy" to drug therapy across a wide range of diseases despite the known-documented improvements in cardiac function, muscle oxidative capacity, metabolic health, glucose and lipid homeostasis, adiposity, inflammatory burden, muscle mass and strength, joint pain, mobility function, depression, anxiety and cognition (Bamman et al., 2014). Moreover, due to the tendency of expert bodies and physicians to prioritize the roles of diet and medication over exercise in their treatment plans (O'Hagan et al., 2013), but also to the participants own intrinsic barriers to an "active" treatment plan (Ambrose & Golightly, 2015), elderly exercise engagement is suboptimal (World Health Organization, 2014). Thus, these interventions often result in impressive rates of initial behavior changes, but frequently are not translated into long-term behavioral maintenance (Artinian et al., 2010). So the adoption and long-term maintenance of "active" interventions pose challenges for many individuals but, as demonstrated by the results of our MEX, are the most empowering therapies, improving multifactorial CVR factors, CRF, medication consumption and yield impressive benefits and largest improvements of symptoms and overall quality of life (Ambrose & Golightly, 2015). Furthermore, our results, confirm that higher exercise patterns and CRF levels are associated with better health outcomes (J. Myers et al., 2015), independently of the baseline age, chronic disease, severity and associated CVR factors once that our participants in all the isolated MEX and combined therapies groups (MEX+MET; MEX+ACEi; MEX+ST) were older, had worst hemodynamic profile, consumed more medicines and had a higher number of comorbidities. However, at the end of the study they were able to reverse these outcomes to normal ranges, with little to no adverse effects (Bamman et al., 2014), contrarily to the isolated pharmacological groups that not only aggravated their hemodynamic profile but decreased their CRF and HRQoL. Moreover, associated with this negative effects, pharmacologic therapies are frequently associated with an elevate risk of adverse drug reactions, that grows with the increase in the number of medications, particularly in

multimorbid older adults (Fabbri et al., 2015). If treating one disease in older adults is usually complex and multidimensional, in the presence of multiple chronic diseases, like in our sample, these process is even harder, due to difficulties with therapeutic compliance, to the higher vulnerability to suffer adverse events, psychological distress and depression, higher admissions to hospital and longer hospital stays that ultimately may lead to mortality (Fabbri et al., 2015).

Medicines normally act in one specific component – MET acts into mitochondrial respiratory-chain complex resulting in a decrease in hepatic energy status, activating the AMP-activated protein kinase, a cellular metabolic sensor; ACEi acts on the renin–angiotensin–aldosterone system (Sever & Messerli, 2011), blocking Angiotensin I to Angiotensin II conversion by inhibiting ACE activity, preventing the constriction of blood vessels, and lowering blood pressure (Simon et al., 2015); ST reduces the synthesis of cholesterol in the liver by competitively inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A reductase activity (Catapano et al., 2016), increasing expression of LDL-C receptor on the surface of the hepatocytes, which results in increased uptake of LDL-C from the blood and a decreased plasma concentration of LDL-C and TG (Catapano et al., 2016). However, the management of multimorbid older adults does not necessarily correspond to the optimal treatment of each of their individual chronic disease, but rather to the management of these multifactorial disease systems. Thus, a "holistic" approach addressed to target multifactorial risk factors should be promoted. In fact, our results confirm the rationale that a moderate reduction in various risk factors may be more effective than a major reduction in only one of them (Véronique A. Cornelissen & Fagard, 2005; Sharman et al., 2015).

Single-target drugs cannot mimic the complex, multisystem effects of MEX (Bamman et al., 2014), involving inhibition of pro-inflammatory and stimulation of anti-inflammatory paths (Balducci et al., 2010), whilst, as proven by our study, the isolated pharmacological drugs just moderately improve one risk factor, diminishing all the others, contrarily to MEX groups, that improved several CVR factors, CRF and HRQoL. Thus, the potential benefit of a medication must be out-weighted against possible risks arising from its use (Singh & Bajorek, 2015) because although our participants in the isolated pharmacological therapies did not presented adverse effects associated with medication use, which may be related with the drugs initiation time (participants had at least one year of each medication) and to the low dose consumed (Catapano et al., 2016)(Colagiuri et al.,

2014)(Mancia et al., 2013), the chronic negative pressure in the other CVR factors will impose at long-term a vicious circle that will aggravate morbidity and the own diseases. Thus, non-pharmacological therapies should be considered by clinicians as an effective first-line therapeutic plan for those in the initial stage of these diseases and not as a "adjunctive therapy" (Bamman et al., 2014).

For people that clearly need a pharmacological therapy, exercise can serve as a positive behavioral and physiologic modifier of the disease process (Bamman et al., 2014), once exercise can positively influence drug pharmacokinetics (T. L. Lenz, 2011). This rationale is supported by the results obtained in our combined groups, where MEX seems to have counterbalanced the negative effects that pharmacological treatment had in CVR factors, CRF, medication consumption and HRQoL, once these groups (MEX+MET; MEX+ACEi; MEX+ST) presented intermediated improvements- smaller than isolated MEX groups but higher than isolated pharmacological treatments. These findings are consistent with previous studies (Buford et al., 2012)(Cadeddu et al., 2014)(Gui et al., 2017).

One surprising result was the augment in the annual medication expenditure after the 24-months intervention in all groups, despite the reduction in the number of medicines used in some sub-groups. The explanation may be related with the higher retail prices of medicines, to the decrease in the reimbursement percentage of National Health System but also to the increase of users co-payment, overloading the small budgets that older adults monthly live. This effect is also a concerning factor once the majority of our participants live with a retirement pension below the national minimum wage (557 €) and the minimum old-age pension of 264 euros (PORDATA, 2017), reflecting the economic "burden" that medication has in these individuals. In a retrospective cohort study, exercise training participants had similar total healthcare costs during the first year, but during the second year, adjusted total costs were lower than for non-exercise training users, highlighting the important role of the long-term exercise commitment in physical health but also in the health costs (Ackermann et al., 2008). So, it is important to find cost-effective solutions to minimize morbidity, decrease CVR factors, medication consumption and enhance HRQoL once the aggravation of multimorbidity will probably imply an increase of medicines, that in turn may lead to other important issues regarding drug–drug interactions, drug–disease interactions, therapeutic competition, poor adherence to treatment, adverse drug events,

hospitalization and mortality, related not only with the number of medications, but also with the regimen complexity, impairing the efficacy of treatment but also the users quality of life (Bell & Saraf, 2016; Charlesworth et al., 2015a; Colagiuri et al., 2014; Singh & Bajorek, 2015). This vicious cycle may lead to the exacerbation of morbidity, decrease of functionality and health status but also to the increase of extra health costs, pressuring once again the economic individual situation.

This study has several strengths including its longitudinal design, the large sample group composed by older adults with comorbidities, long-term supervised MEX intervention. Moreover, the use of well-validated instruments and the wide range of outcomes objectively measuring key outcomes that are particularly important to older adults, such as HRQoL, CRF, CVR factors and therapeutic treatments (Rich et al., 2016) were important methodological issues in the present scientific field.

In contrast, the non- randomized methodological design and the relative heterogeneous sample represent some drawbacks that may have limited some results. Nevertheless, the penalizing variables were worst to the combined groups (MEX+MET; MEX+ACEi; MEX+ST) and MEX participants, that as demonstrated by our results, achieved the largest improvements in all the outcomes after the intervention, which limits in part this drawback. Nevertheless, the causality relationship should be carefully interpreted once the different sample sizes within each study sub-groups and the non-randomized methodological design might have caused some bias in our results.

We tried to mitigate these limitations adopting specific statistical procedures to counteract these effects, particularly controlling for several covariates that were available and evaluated as potential confounders and also measuring the magnitude of the results out-weighting to the different samples sizes with the Cohen *d* effect size. Unfortunately, residual confounding factors due to unknown or incompletely measured factors cannot be excluded. Thus, future studies on this topic should use a randomized controlled trial design with a similar sample size, testing for other comorbidities.

Regardless of the limitations, these results have important clinical implications once our results showed that MEX is an effective management plan in all the chronic diseases analyzed and even though this conclusion cannot be generalized to all older adults, it was proven that in older patients in early stage of T2D (HbA1c < 7,5%), in hypertensive older adults in grade 1, and in dyslipidemic older adults, chronic isolated

MEX obtained more pronounced effects than pharmacological drugs alone. Furthermore, cost-effectiveness cannot be simply limited to the medication costs alone once as shown by our results, the value of regular exercise far exceeds the monetized benefits alone. Indeed, as our results proved, exercise positively affected multifactorial CVR factors, physical and mental functioning, HRQoL and other dimensions of health and wellbeing that cannot be calculated as they occur in health-related dimensions or factors but that contribute to a general well-being that exceeds the economic cost alone. Moreover, for those that need pharmacological treatment to manage their diseases, physicians should prescribe an exercise training to counterbalance the negative effects that ageing and drugs do. So it is necessary to rethink the understanding of health by shifting the focus of investment priorities and health policies, develop new health strategies along with political action plans at various levels, focusing in more "holistic", "active" approaches like exercise training that despite the initial and immediate cost, will lead to long-term health savings.

4.8.6. Conclusion

The main findings of the present study suggest that chronic MEX is more effective than first-line pharmacological drugs (MET, ACEi and ST) to manage overall CVR factors, to improve CRF and HRQoL, and to reduce medication consumption in older adults with comorbidities. Furthermore, current results proved that isolated pharmacological therapy decrease hemodynamic profile along with HRQoL and may be significantly attenuated/ counterbalanced by the inclusion of MEX regimen. In fact, the combined therapy (pharmacological treatment + exercise) is more effective than isolated pharmacologic therapy.

These results provide further support and may guide health care professionals and health organizations in the counseling and prescription process, according with two conditions: *i*) in older adults with comorbidities, in the initial stage of T2D, hypertension and dyslipidemia, multicomponent exercise programs should be prescribed, as the first-line treatment; and *ii*) for those that are in advance stage of these diseases and need pharmacologic treatment, long-term multicomponent exercise training should be added to the management plan to mitigate/counterbalance the negative effects of drugs use.

5. GENERAL DISCUSSION

This thesis explored the longitudinal and causal relationships between exercise and/or medication relatively to the cardiovascular risk factors, physical fitness, medication consumption and HRQoL in older adults with comorbidities, which has been considered a gap in the literature (Fabbri et al., 2015).

Understanding these interacting processes and their causal contributions to age-related multisystem decline may help scientists, political and health professionals to develop cost- effective interventions aimed to prevent or delay the onset of age-related chronic diseases, reduce the burdens of comorbidity and disability and expand healthy human life span (Fabbri et al., 2015).

Extensive discussions of each of the studies main findings were included in the respective sections. The rationale of this chapter was to gather and integrate the global contributions of the 8 studies by summarizing the main results and reflecting them with the existent literature.

5.1- The effect of exercise and/or medication on cardiovascular risk factors

An increased understanding of the biological and behavioral mechanisms that contribute to the decline in chronic diseases like diabetes, hypertension and dyslipidaemia can aid in the development of future interventions, particularly those designed to improve cardiovascular risk factors and to reduce the decline in physical function and HRQoL in older adults (Anton et al., 2015).

Previous randomized control trials with lifestyle interventions (Diabetes Prevention Program Research Group, 2009; Griffin et al., 2011; Lindstrom et al., 2003; The Look AHEAD Research Group, 2010) in middle-aged high risk adults and with T2D, showed long-term benefits on anthropometric profile, CRF, CVD risk factors, diabetes management and ultimately, morbidity and mortality. However, the relative/single effect of exercise training was difficult to determinate, because in these interventions, exercise was

combined with caloric restrictions (Thompson et al., 2014) or with pharmacological treatment (Stevens et al., 2015) or with another form of intervention (Thomas et al., 2006). Furthermore, the generalization of these results was limited in older adults with comorbidities due to the fact that clinical trials frequently excluded this population group based on the safety and counfounding effects criteria (Cruz-Jentoft et al., 2013). Nevertheless, our research tried to fulfill these gaps and our results highlighted the effectivity of chronic multicomponent exercise training in the reduction of cardiovascular risk factors reinforcing his importance, as a multifactorial cardiovascular risk intervention on the enhancement of anthropometric and hemodynamic profile, blood glucose and CRF in all the chronic diseases analysed. Indeed, after the 24-month intervention, the participants in the isolated MEX therapy presented a reduction in BM, WC, WHR and improvement in CRF in all chronic diseases (T2D, hypertension and dyslipidemia) (**Studies I, II, IV, VII and VIII**), with important anti-inflammatory clinical benefits. Actually, it is well established the relathionship between the increase of obesity, specially central obesity, with the augments of several pro-inflammatory metabolic markers, particularly, insulin resistance and some biomarkers like interleukin-6, C-reactive protein and tumor necrosis factor α, which in turn, seem to be related to the genesis or aggravation of these chronic diseases (Anton et al., 2015; Buford, 2016). Moreover, as we previously explained in Chapter 2, chronic elevations in inflammatory mediators during late life contribute to a deleterious chronic overproduction of reactive oxygen species, that coupled with aged-related declines in nitric oxide production and bioavailability, contributes to an imbalance between the production and breakdown of reactive oxygen species, augmenting oxidative stress (Buford, 2016). The increase of inflammation and oxidative stress also contribute to endothelium dysfunction, which in turn, increase systemic vascular resistance and therefore increase blood pressure (Buford, 2016). These imbalance between vasodilatory and vasocontrictory substances promotes to further exacerbating inflammation and oxidative stress, creating an even larger vicious cycle (Buford, 2016) and this way worsening participants hypertension, T2D and dyslipidaemia. However, our experimental groups of older adults that engaged in the 24-month multicomponent exercise training programme, despite the presence of hypertension, or T2D, or dyslipidemia, were able to decrease their SBP and DBP (**Studies I, II, IV and VII**) due to this improved anti-inflammatory cycle (Buford, 2016), implying a more favorable vascular profile,

particularly important to the management of these diseases. Furthermore, higher exercise patterns and CRF levels are associated with better health outcomes (J. Myers et al., 2015). The results of our MEX participants confirm this evidence once by improving their CRF, important clinical benefits were promoted in terms of improvement of the anti-inflammatory cascade pathway (Buford, 2016)(Balducci et al., 2010), allowed them to enhance metabolic and physiological mechanisms (anthropometric and hemodynamic profile) that ultimately, led to a better disease condition, independently of the chronic disease these participants possessed **(Studies I, II, IV, V, VI, VII and VIII)**.

Relatively to the lipid profile, the results were not so uniform, with some differences according to the disease. In fact, in **Study I** (that compared the effects of long-term multicomponent exercise with a control group in T2D older adults) participants of the long-term MEX improved HDL cholesterol and maintained the other cholesterol components (TC, LDL, TG and glycaemia) comparatively to the control group. In **Study II** which compared the effect of exercise training with MET in older adults in an early stage (HgA1c < 7,5%) of T2D, participants decreased 21% TG and 12% glycaemia but unchanged the other cholesterol components, while in **Study IV** (that compared the effect of exercise with ACEi in hypertensive older adults), participants of the MEX group improved TC but maintained glycaemia and TG. **In Study VII**, participants of MEX group, decreased 3% TC and 5% LDL cholesterol. Collectively, these results reflect positive anti-inflammatory effects despite the baseline "normal" lipid ranges (Catapano et al., 2016). Furthermore, notwithstanding the negative inflammatory ageing pressure on cholesterol mechanism (Morgan, Mooney, Wilkinson, Pickles, & Mc Auley, 2016), long-term exercise training was able to produce significant changes in all the diseases, through the improvement of different lipid components, that in our opinion, are related to the own aetiologic mechanisms of each disease. So, while in T2D, the management of blood glucose is mandatory due to their repercutions on insulin resistance (American Diabetes Association, 2016), in hypertension and dyslipidemia, controlling the range levels of LDL and HDL cholesterol (that are lipid components of TC) is also important due to their effects on the atherosclerotic plaque formation, which is associated not only with the aggravation of hypertension but also with the increase of dyslipidemia, coronary and cerebrovascular events (Piepoli et al., 2016).

In terms of pharmachological therapy, our results seem to contradict previous research and international guidelines (American Diabetes Association, 2016; Aschner et al., 2014; UK Prospective Diabetes Study (UKPDS) Group, 1998), particularly those highlighting the effectiveness of MET as a "weight neutral" or "weight-loss" medication in the maintaince of the anthropometric components.

In a previous randomized control trial, the UKPDS group (1998), that intented to compare the effect of MET with others anti-hyperglycemic drugs (chlorpropamide, glibenclamide, or insulin) not with exercise training, the results highlighted MET effectiveness to the detriment of the other drugs, but authors did not compare with exercise training and used middle-aged adults with newly T2D diagnose. Nevertheless, in our study which intented to compare the effectiveness of MET with exercise training, the efficacy of MET seems to be somehow questioned because after 24-month of use, our MET group augmented 2% WC and 3% WHR (**Study II**), which did not occur in the other two groups (isolated MEX and the combined therapy group- exercise plus MET). Another interesting result was the 5% increase in SBP in the MET group (**Study II**), contrary to the conclusions obtained by Wulffelé and colleagues (Wulffelé, Kooy, De Zeeuw, Stehouwer, & Gansevoort, 2004), which found that MET had none or rather limited effects on blood pressure and plasma lipid profile. However, in this systematic review, MET significantly reduced plasma TC and LDL cholesterol by a glycaemia-lowering independent mechanism (Wulffelé et al., 2004), contrarily to our MET participants who decreased their TC by reducing the HDL cholesterol and increasing the LDL component (**Study II**). However, there are no large trials of lipid-lowering interventions, specifically in older adults with T2D. The MET benefits have been extrapolated from trials of older adults that includ but were not limited to those with diabetes and trials of people with diabetes including but not limited to older adults (Kirkman et al., 2012). Thus, colletively our results with an exclusive sample of older adults with T2D add new information, suggesting that contrary to previous evidence with short follow-up, the long-term effect of MET may have in fact, a pro-inflammatory anthropometric and hemodynamic evolution that is still necessary to understand.

Relatively to ACEi efficacy to decrease cardiovascular risk factors, our results seem once again, to contradict previous evidence (C S Carter, Onder, Kritchevsky, & Pahor, 2005; Mateo Cesari et al., 2009). Whereas in the review of Carter and colleagues (2005),

the authors reported ACEis potential to improve body composition and physical performance among older adults, Cesari and colleagues (Mateo Cesari et al., 2009) found no significant modification in major biomarkers of inflammation, hemostasis, and endothelial function after 6-months of fosinopril compared to placebo. Reversely, our study showed that after the 24-month intervention, ACEi use, may in fact aggravate hypertension due to the negative evolution of the anthropometric, hemodynamic, lipid profile and CRF (**Study IV**), although we can neither disassociate this result from the ageing effect on the renin- angiotensin system (Buford, 2016; Simon et al., 2015) nor to the ineffectiveness of the ACEi monotherapy (Gu Q Dillon CF, et al., 2012; Mancia et al., 2013).

In terms of ST monotherapy, and its effect on cardiovascular risk factors, this pharmacological therapy followed the same path that the others isolated pharmachological therapies (MET and ACEi). After the 24-month intervention, ST group decreased/ aggravated their anthropometric and hemodynamic profile, with exception of LDL cholesterol improvement (**Study VII**). Thus, even though ST improved one risk factor (LDL cholesterol), the collectively effect on the others cardiovascular risk factors, led to the aggravation of participants dyslipidemia, particularly those related to the augments on the visceral fat (ST increase WC, BM, BMI and WHR) that are associated with several pro-inflammatory metabolic markers, leading to poorest control and to a worst lipid profile. Thus, although MET clinical use is over 50 years and ACEi and ST are among the most prescribed drugs, only in the last decade their molecular mechanisms are starting to be known (Rena et al., 2013). Furthermore, ACEi and ST applicability is nowadays controversial and only now, it is starting to be completely understood (Simon et al., 2015). Thus, more research is needed to clarify the long-term effects of these pharmacological therapies in cardiovascular risk factor in older adults with comorbidities.

According to several authors, despite the potential utility of each of the aforementioned approaches, the most promising interventions to treat the multiple cardiovascular risks factors in these chronic conditions could be those incorporating multiple treatments modalities- pharmacological and non-pharmacological (Anton et al., 2015; Buford, 2016; Buford et al., 2015; Fabbri et al., 2015). This rationale was our starting point and was the main factor to the stablishement of our main hypothesis,

meaning that, in each study, we hypothesized that the combined group that assembled both forms of treatment would reveal higher clinical benefits than each treatment alone.

Surprinsigly, the literature examining the synergetic and/or antagonist relationship of exercise and pharmacological therapies, or how exercise and pharmacological treatment affect each other, or if their combination offers more benefits than each therapy alone, is very scarce. However, the few studies that exist, seem to suggest that the benefits of exercise and pharmacological therapies (MET, ACEi and ST) are not completely additive (Boulé et al., 2011; Cadeddu et al., 2014).

In a study that intented to determine the effect of MET on the acute metabolic response to sub-maximal exercise in participants with T2D, the authors found that MET affected exercise by increasing heart rate, leading to the prescription of lower exercise workloads (Boulé et al., 2011). Additionally, in an interesting investigation (Cadeddu et al., 2014) MET also decreased the peak VO_2 and the ability to work in insulin resistant adults. Similarly, the results of our combined group (MEX+MET) also revealed an improvement in CRF but in a smaller range when compared to the isolated MEX participants. These results confirm these previous findings and add new information regarding the long-term negative consequences of MET use in T2D older adults with comorbidities. One possible explanation may be related to the MET effect in peak VO_2 capacity (Cadeddu et al., 2014) that may have mitigated exercise cardiometabolic benefits (**Study II**).

Interestingly, the combined group of ACEi with exercise training follow the same MET pathway, in terms of smaller improvements in the anthropometric, hemodynamic components and CRF, comparatively to isolated MEX group **(Study IV)**. So although, the combination of exercise training with ACEi medication has been linked to physiologic changes including improved capillary density, increased percentage of type-1 muscle fibers (Guo et al., 2010) and to the activation of a virtuous cycle determined by an improved cardiovascular system (Buford, 2016; Matteo Cesari et al., 2010; Simon et al., 2015), contraditory evidence exists and showed that ACEis may not significantly modify major biomarkers of inflammation, hemostasis and endothelial function (Mateo Cesari et al., 2009). This previous evidence may explain the results in our combined group once even though, exercise potentiated anti-inflammatory pathways that led to an improved cardiovascular system, ACEi use may have blunted this effect in terms of inflammatory

biomarkers. Thus, contradicting previous evidence (Guo et al., 2010), our study suggests that exercise and ACEi therapy may have a non-addictive effect in cardiovascular risk factors.

Surprinsingly, in our dyslipidemic participants, the combined group (MEX+ST) was similarly effective as MEX group, to reduce overall cardiovascular risk factors. This result is consistent with previous evidence (Gui et al., 2017) and demonstrates the synergetic role that both therapies had in this pathologie. Nevertheless, these results raise a new issue: why the combined group was only effective as MEX in the dyslipidemic older adults sample and not in the other two chronic diseases? In our opinion, the logical explanation is related to the participants baseline lipid profile, once participants in the MEX+MET and MEX+ ACEi groups were in a lipid "normal" range, according to the guidelines levels (Catapano et al., 2016). This fact, may have limited the potential benefits of the pharmacological treatments. On the contrary, the participants in the MEX+ST group had a worst lipid profile at baseline, however, due to the synergetic effect of exercise in terms of promotion of anti-inflammatory pathways, hemostasis and endothelium function, combined with ST action mechanism in the LDL cholesterol levels (Gui et al., 2017), may have promoted positive effects in overall cardiovascular risk factors. Furthermore, as previously seen in chapter 2, some drugs may be more effective than others. Previous evidence confirms and supports that both MET (Cadeddu et al., 2014)(Boulé et al., 2011) and ACEi (Guo et al., 2010) may be ineffective to manage overall cardiovascular risk factors.

Collectively, ou results partly support our main hypothesis once only the combined group (MEX+ST) of dyslipidemic older adults presented similar effects to isolated MEX therapy (**Study VIII**). Nonetheless, the other combined groups (MEX+MET; MEX+ACEi) (**Study II, IV**) showed an anthropometric, hemodynamic, lipid and CRF improvement but in a smaller range than the isolated MEX group. Thus, these results highlight three important conclusions: *i*) firstly, it was proven that after 24-month intervention the combined groups revealed an intermediate pattern between the improvements in the isolated MEX and the decreases of the pharmachological treatments alone (MET and ACEi), suggesting that the pharmacological treatments may have, in fact, blunted the beneficial effects of exercise in some groups; *ii*) in some pathologies (dyslipidemia), the combined therapy (MEX+ST) was as effective as MEX treatment, suggesting that both

therapies modes acted synergistically to promote an overall enhancement of cardiometabolic profile; *iii*) long-term negative effects of pharmacological therapy (MET, ACEi and ST) may be detrimental in overall cardiovascular risk factors, suggesting that for those that need pharmacological treatment, adopting a long-term exercise training regimen, will help them to counterbalance the potential negative effects that medicines have in terms of cardiovascular risk factors and CRF in their chronic diseases.

Unfortunately, our data did not provide sufficient evidence in terms of the therapeutic mechanisms that are potentially underlying exercise and pharmacological therapies interaction and the literature evidence is very limited. So, more research is needed to understand the biological and physiological interaction mechanisms of exercise and pharmacological therapies to support our results. Understanding these underlaying interaction mechanisms may point towards the development of effective therapies according to the own characteristic of the patients, particularly those with several comorbidities.

5.2- The effect of exercise and/or medication on functional status

Older adults are a specific high risk group for falls and fractures (Berlowitz et al., 2016), physical disability (Buford, 2016), hospitalization, surgical outcomes and mortality (Dumurgier et al., 2009). Additionally, multimorbidity (Marventano et al., 2014), lifestyle habits (low level of exercise, smoking and excessive alcohol consumption, among others), and polypharmacy use (Charlesworth et al., 2015a; Peron et al., 2011) are also important risk factors for the functional status decline. These increasing prevalence of functionally-limited individuals (Hajjar et al., 2016) highlight the need of intervention to reduce the burden of ageing-disability (Buford, 2016) and to maximize the chances of healthy ageing (*Estratégia Nacional para o envelhecimento activo e saudável 2017-2025*, 2017). Indeed, it is suggested that an efficacious pharmacologic intervention could have significant clinical impact because usually, these regimens typically require "minimal effort" on the part of patient, an important issue that should be acknowledge, given that the initial effort to begin an intervention programme is the first barrier to exercise treatment (Simon et al.,

2015). This rationale was the starting-point of several previous studies addressed to understand the re-applicability of several pharmachological agents that have been suggested as therapeutic strategies for enhancing physical function and mobility in older adults due to their action mechanisms. For example, MET, a first-line anti-hyperglycemic drug, has been suggested as a potentially pharmachological treatment to improve physical function and reduce frailty risk in older adults with T2D (Wang et al., 2014) once his action mechanism is to activate the enzyme AMP- activated protein kinase, a key sensor of cellular energy status (Anton et al., 2015), that will decrease insulin levels by reducing insulin/insulin-like growth factor-1 (IGF-1) signaling, inhibiting mTOR and mitochondrial complex I in the electron transport chain, reducing endogenous production of reactive oxygen species, that in turn, will help in ageing, body composition and function status mechanisms (Christy S. Carter et al., 2012; De Cabo et al., 2014). Unfortunately, to date, only 2 studies (Boulé et al., 2011; Cadeddu et al., 2014) have examined MET effect on exercise performance; one assessed the acute metabolic response to submaximal exercise (Boulé et al., 2011) and the other analyze the maximal aerobic capacity in a short follow-up (12 Weeks) (Cadeddu et al., 2014). These previous results contradict the positive effect of MET in exercise performance suggesting in fact, that MET decreases the peak VO_2 and the ability to work. Similarly, our long-term results support these previous evidence once the isolated MET therapy group, slightly decrease the 6-minute walk distance test, even though, without statistical differences (**Study II**). Our study adds new information of the long-term MET effects on functional status in comorbid T2D older adults. Nevertheless, it is our pretension to do in the future a more robust analysis of the isolated effect of MET with other physical performance measures, namely strength, flexibility and agility/dynamic balance. Additionally, a deeper knowledge of the physiological mechanism of MET in functional performance is also needed.

Likewise, recent literature with experimental work in animal and human studies, has suggested that antihypertensive medication may play an important role in hypertension functional decline (Buford et al., 2012; Christy S. Carter et al., 2012; Rosenberg et al., 2008; Shih et al., 2014), but up until now, inconsistent results were reported on the effect of first-line antihypertensive therapies, including not only positive associations between functional status with the use of ACEis (Buford et al., 2012; Christy S. Carter et al., 2012), βBs (Belenkov et al., 2003; Zhubrina et al., 2009), and TDs (Shih et al., 2014), but also

negative associations with the use of ACEis (Sumukadas et al., 2014), CCBs, and TDs (Rosenberg et al., 2008). These contradictory results present specific limitations factors that potentially influenced these conclusions. On one hand, in the Buford and colleagues (2012) research, participants could be using a combined therapy– ACEi and other antihypertensive drug, which may mask the isolated effect of mono-dose ACEi therapy. On the other hand, the lack of response observed by Sumukadas and colleagues (2014) could be related with an exercise programme design flaw to improve the aerobic capacity, but also to lower adherence in the unsupervised home-based exercise regimen. Moreover, due to these inconsistent results, it was suggested that the antihypertensive pharmacological benefits, particularly of ACEis, may only occur if they were combined with exercise training (Buford et al., 2012; Christy S. Carter et al., 2012). Thus, these previous evidence suggests that the efficacy of antihypertensive medication as a therapeutic option for functional status in hypertensive older adults may vary considerably according to certain circumstances (Sica, 2011) such as: practice or not of exercise training, drugs and/or specific populations with different characteristics.

Our data, collected from well characterized hypertensive older adults, with a long-term supervised multicomponent exercise training tried to fulfill these gaps. First, we created a progressive line of research that begun to analyze the effect of ACEi monotherapy comparing with isolated exercise training and the combination of both treatments (**Study IV**). After 24-months of intervention, our study showed that long-term ACEi monotherapy decreased functional status, as occurred in previous studies (Matteo Cesari et al., 2010; George & Verghese, 2016; Gray et al., 2011, 2012; Sumukadas et al., 2014; Zi et al., 2003) but not with others (Buford et al., 2012; Hutcheon et al., 2002; Kurklinsky & Levy, 2013; Onder et al., 2002; Sumukadas et al., 2007). Interestingly, the combination of exercise and ACEi therapy revealed an improvement in functional status but in a smaller range than isolated exercise training, partly supporting previous suggestions (Buford, 2016) and our main hypothesis. Moreover, in this group the additive effect of exercise training and ACEi therapy, targeting different components of skeletal muscle function, preserved functional status (Simon et al., 2015) and improved the physiologic reserve, increasing the lower and upper body strength, the agility and dynamic balance, the upper body flexibility and the cardiorespiratory endurance, counterbalancing the negative effects of isolated ACEi therapy. Possible explanations for the decrease in the

isolated ACEi therapy may include not only the ageing effects, but also the ineffectiveness of the ACEi monotherapy on the renin- angiotensin system (Buford, 2016; Gu Q Dillon CF, et al., 2012; Mancia et al., 2013; Simon et al., 2015) which may have hampered the functional status improvement.

Afterwards, once it was shown the benefic effect of exercise training with ACEi therapy, we tried to understand if there were any differences in terms of functional status using two modes of ACEi therapy (mono-dose or Combined) once monotherapy can only reduce the blood pressure in a limited number of hypertensive individuals, leading that the majority of patients uses the combination of at least two agents to reach hypertensive target levels (Gu Q Dillon CF, et al., 2012; Mancia et al., 2013). Our results in **Study V**- the first to analyze the effect of different modes of therapies (mono-dose ACEi or Combined with other antihypertensive drug), demonstrated once again the positive effect of chronic use of exercise training combined with ACEi in the improvement of functional status in hypertensive older adults with comorbidities, independently of the drug therapy. Curiously, the surprising result of this study was the inexistence of differences between groups after the follow-up. It seemed logical that due to the addictive effect of the Combined treatment that assemble the use of ACEi and other agent, this therapy would provide larger benefits than those offered by a monotherapy, especially due to the synergetic effect of the pharmacological characteristics of the different group classes (Mancia et al., 2013), which did not occur. This result suggests that even though, these agents exert a protective effect in target organs in the treatment of hypertension (Mancia et al., 2013), that lead to a final similar action through different mechanisms (Digne-malcolm et al., 2016), other underlying agent may have a more substantial contribution in this relationship (Buford, 2016). Exercise training, the common element in both groups, might have been the key agent to the inexistence of differences between groups, once it may act as an intermediator in this relationship. Moreover, our results suggest that it is indifferent the type of ACEi therapy when combined with exercise training, highlighting the importance of maintaining/ adopting an exercise training programme for those under ACEi medication. Nevertheless, this rationale could not be totally confirmed by our study, due to the inexistence of a control group without exercise training; therefore future researches should incorporate this previous concern.

Finally, after the stablishement of the positive effect of exercise training in the ACEi therapy, independently of the therapy mode, we analyze the combined effect of exercise with other first-line anti-hypertensive therapies (TDs, CCBs and βBs) to check out if there were any differences among them (**Study VI**). So, after the 24-months of intervention, long-term exercise training plus first-line antihypertensive medications improved functional status in hypertensive older adults, regardless the type of the pharmacological therapy. These results suggest that exercise may mediate the relationship between functional status and pharmachological treatments. The plausible explanation is based on the similar final action exerted by these pharmacological therapies on the target organs of hypertension (heart, renal system, vascular system) (Digne-malcolm et al., 2016), despite the different effects once some agents act as direct vasodilators, whilst others may have indirect effects, which mediated by exercise training promote a benefic anti-inflammatory cascade, improving oxidative stress and endothelium function that lead to the improvement of vascular system and ultimately, physical decline (Buford, 2016), independently of the pharmacological antihypertensive treatment.

Nonetheless, the most important finding and contrary to previous studies (Buford et al., 2012), that suggested that exercise training alone would be insufficient to prevent physical disability in hypertensive older adults, was that after the 24-month intervention, our isolated chronic multicomponent exercise training *per se* revealed as the most effective treatment to reach functional status goals, regardless the antihypertensive or mode of therapy (**Studies IV, V and VI**). Moreover, it was also shown that exercise training may counterbalance the negative effects that isolated pharmacological therapies may have on functional status decline.

Relatively to ST effect on functional status, similarly with other pharmacologic therapies (MET and ACEi), our isolated ST treatment decreased functional status which is consistent with previous studies with short-follow and using mixed aged population (Loenneke & Loprinzi, 2016). Reversely, MEX improved all the functional status outcomes. Interestingly, the combined group (MEX+ST) revealed similar gains as MEX group. This fact, highligths the effectiveness of the combined group (MEX+ST) in the improvement of functional status and confirms our main hypothesis, similarly as previous evidence (Gui et al., 2017). The explanation to this result is related with the synergetic effect that both forms of therapy have in the cardiovascular system. So, while ST improve

the lipid profile that will lead to reduced inflammation and improved exercise performance (Gui et al., 2017), exercise also potentiate these outcomes leading to an additive effect that will further enhance functional status (J. Myers et al., 2015).

Colectively, our findings add new information regarding: *i*) the effectiveness of long-term multicomponent exercise training regardless the disease, antihypertensive class and mode of therapy, or combined with pharmachological therapies in functional status improvement; *ii*) the potencial role of exercise training as mediator in the benefic effect of pharmacological anti-diabetic, antihypertensive or anti-dyslipidemic treatment in the management/ improvement of functional status; *iii*) the ineffectiveness of isolated pharmacological therapies (MET, ACEi and ST) in the management of functional status in older adults with comorbidities. These results have important public health implications once an improved functional status, increases the ability to perform functional movements and daily activities (including personal care, shopping, or housework (Jones, J., Rikli, 2002)), promoting functional independence and preventing physical disability (Buford, 2016).

Unfortunately, there is a scarce number of clinical trials' specifically exploring this topic, highlighting the need for more research, particularly those oriented to the underlying interaction mechanisms of exercise and pharmacological therapies on functional status outcomes.

5.3- The effect of exercise and/or medication on HRQoL

HRQoL as a multidimensional construct and a global indicator of health resulting from the individual's perception of the impact that diseases exert on different spheres of life (physical, mental, social and functional health)(Balboa-Castillo et al., 2011) is thought to be one of the most important factors for assessing the health status and an important outcome measure that is being increasingly used to evaluate the "burden" of chronic diseases in clinical studies with elderly patients (Kim et al., 2012).

Several studies were conducted to evaluate the effects of exercise on HRQoL, but there is still a gap to assess HRQoL as part of large-scale and long-term studies, incorporating standard care as a control group and examine the changes of HRQoL

components over time in different types of treatments in older adults with comorbidities once that the amount, pattern and some treatment types have been associated with impaired HRQoL (Fabbri et al., 2015; Kim et al., 2012). Moreover, most of these studies used cross-sectional and observational designs, and the evidence from randomized controlled trials is both limited and inconsistent, particularly in the mental component (Awick et al., 2015; Cadeddu et al., 2014; Florez et al., 2012; Kelley et al., 2009; Marrero et al., 2014; V. Myers & McVay, 2013). Furthermore, studies that have examined exercise training effects on HRQoL in a pre-post treatment design have used different patient groups and different time lengths (between 3 to 12 months)(Awick et al., 2015; Imayama, Alfano, et al., 2011; Kelley et al., 2009), different exercise types and volumes (Awick et al., 2015; Imayama, Alfano, et al., 2011; V. Myers & McVay, 2013; Nicolucci et al., 2012) and only few studies have concentrated in comparing different types of treatment (Cadeddu et al., 2014; Florez et al., 2012). So, we tried to fulfill these gaps and to understand how these different treatments were perceived by our participants. We seeked a more global vision, including not only the biological perspective but also understanding the longitudinal impact that these treatments have in our participants lives.

Although T2D is a high-impact complex multi-factorial disease that imposes a life-long physical and psychological burden (Aschner et al., 2014) causing frequently disruptive negative effects such as restlessness, distress, anxiety, depression (Abdelhafiz & Sinclair, 2015; Chew, Mohd-Sidik, & Shariff-Ghazali, 2015; Gadsby, 2014) and dementia (Cardoso et al., 2013; Chin et al., 2016; Gudala et al., 2013; Rawlings et al., 2014; Sheen & Sheu, 2016; Sinclair et al., 2014) that may reduce the efficacy of T2D management and HRQoL (American Diabetes Association, 2016), particularly, the mental component of HRQoL, our results showed that after the 24-months intervention the MEX participants decreased their negative mood states like depression, anger and TMD, whereas augmented the vigor state. Furthermore, at the end of the study our participants also perceived better physical and mental HRQoL, contrarily to the MET group that increased tension state and unchanged their HRQoL (**Study I and III**). These results are in line with previous studies (Cadeddu et al., 2014; Florez et al., 2012)(V. Myers & McVay, 2013) but add new information regarding the long-term positive effect of exercise training, in the mental HRQoL improvement, although contradictory evidence also exists (Marrero et al., 2014; Wadden, 2014). Plausible explanations to these inconsistent evidence may be related with

the time of diagnose, and time-length, type and mode of exercise intervention once previous studies (Marrero et al., 2014), reported greater declines immediately post-diagnosis and after 6-months post-diagnosis; others have suggested that the physical component is affected not only by obesity (Florez et al., 2012), but also by the type (Reid et al., 2010), volume (Nicolucci et al., 2012), and time-length of exercise training intervention (Imayama, Plotnikoff, et al., 2011; Marrero et al., 2014; V. Myers & McVay, 2013; Nicolucci et al., 2012; Wadden, 2014). Our long-term multicomponent exercise training, combining both aerobic and resistance training during 24-months, successfully improve all physical and mental HRQoL scores, with important clinical implications once people with higher HRQoL have greater motivation to increase their knowledge about diabetes and consequently enhancing their diabetes behaviors, leading to positive attitudes and promoting self-management activities to maintain their health status or limit the negative physical impact of diabetes (Kueh et al., 2015). Reversely, our study (**Study III**) also showed the MET long-term negative effect on mood states and HRQoL, which associated with diabetes-related distress, may lead to poor self-care activity, diminished disease control, increased risk of both hypoglycemia and hyperglycemia, worst HRQoL, that can progress to depression and increase the risk of cognitive impairment and dementia (Cardoso et al., 2013; Chin et al., 2016; Gudala et al., 2013; Rawlings et al., 2014; Sheen & Sheu, 2016; Sinclair et al., 2014; Van Der Heijden et al., 2013).

Likewise, our sample of hypertensive older adults follow the same path that the T2D older adults group. Our results, support once again the positive effect that isolated chronic exercise training has in the physical HRQoL on hypertensive older adults with comorbities, similarly as previous studies (Kurklinsky & Levy, 2013).

In terms of long-term pharmacological antihypertensive treatment, some authors suggested that it does not seem to negatively impact HRQoL (Aronow et al., 2011) and the benefits on HRQoL seem to be similar among hypertensive patients treated with TDs, βBs, CCBs, and ACEis, with exception for βBs that seem to be associated to increased depressive symptoms (Aronow et al., 2011). Nevertheless, after 24-month intervention our results contradicted this rationale (**Study IV**) once our group on ACEi pharmacological treatment decreased the physical HRQoL (PF, GH and PCS). On the other hand, the results obtained by the combination of exercise with TDs, βBs and CCBs does not support the similarity of effects among these first-line drug classes on HRQoL, since CCBs revealed

higher scores in PF, bodily pain and PCS than the other two antihypertensive group classes- TDs and βBs (**Study VI**). Nevertheless, the small sample size within each group may have reduced the statistical robustness and may be the cause to the lack of statistical significance within TDs and βBs groups because even though, TDs and βBs results did not reach statistical significance, both groups improved their physical HRQoL outcomes.

Similarly, the combined group of ACEi with exercise training (**Study IV**) also lead to physical and mental HRQoL enhancements, suggesting that the improvements in the combined groups of MEX+ACEi and MEX+CCBs, may be related to some specific drug classes (Aronow et al., 2011) and/ or to the presence of the exercise training programme, that seems to mediate the negative effects that ageing and pharmacological treatments may have on HRQoL (Kim et al., 2012).

One surprising result in all the studies on HRQoL, was the higher mean values in the Bodily Pain outcome in the isolated MEX and the combined groups (MEX+MET; MEX+ACEi; MEX+CCBs; MEX+ST), particularly in the case of ST treatment once it is associated with adverse muscle effects (Auer et al., 2016). Nonetheless, we associated the augment of bodily pain to the muscle soreness caused by the "normal" adaptation to the exercise training (Bosomworth, 2016) as explained in studies **I, III, IV, VI and VII**. Indeed, the introduction of a more "active" therapy requiring that individuals participate actively for an extended period of time, with significant behavioral changes (Ambrose & Golightly, 2015), may be interpreted for some individuals as more difficult to accomplish and requiring more effort, traducing in a more fatigue state. So, although people with these chronic diseases may experience adverse effects on HRQoL related to the burden of the disease itself/disease complication, the treatment (pharmacological and/or non-pharmacological) and the so called labeling effect following diagnosis (Tsai et al., 2004), one commom denominator arises from all studies; long-term multicomponent exercise training was the most effective treatment to promote positive HRQoL improvements. Despite being a more "active" treatment and requiring more "effort" than pharmacological therapy, as we confirmed with our results, it is the most empowering and yield the largest improvements in symptoms and overall quality of life (Ambrose & Golightly, 2015).

However, the effect of isolated pharmacological treatments with TDs, CCBs and βBs, remain elusive. Thus, more research is needed to evaluate the role of exercise training

combined with pharmacological treatments in HRQoL, once our results could not completely explain this relationship on TDs and βBs groups.

5.4- Association between exercise, medication and HRQoL

After the 24-months intervention, despite being older, with the worst hemodynamic profile (higher SBP and DBP), higher baseline medication consumption (2,2 ± 1,6), MEX participants enhanced their hemodynamic profile (to "normal" ranges according to the guidelines levels) (Mancia et al., 2013), decreased the number of medicines, improved their CRF and HRQoL, although with an increased in the annual medication expenditure (**Study VIII**). Reversely, the participants in the CO group increase SBP, decreased CRF and HRQoL, and unchanged medication consumption.

In a more in-depth analysis by disease, at baseline T2D older adults in the MEX group had the worst lipid profile (TC and LDL) but consumed less medication and had lower annual medication expenditures. After the 24-month intervention, T2D MEX participants enhanced their SBP, DBP, glycaemia, TC and LDL cholesterol, maintained the medication number and improved HRQoL and CRF. Contrarily, MET group augmented SBP, glycaemia and decreased HRQoL. One interesting result, was obtained by the combined group (MEX+MET) that had higher medication consumption and annual medication expenditures at baseline but at the end of the intervention was able to decrease the number of medicines used, despite the increase in the annual medication expenditure that grown in all the groups.

Similarly, the hypertensive group followed the same previous path. At baseline, hypertensive MEX participants had worst hemodynamic profile (SBP and DBP) but used less medication and had less annual medication expenditure. The isolated ACEi therapy had more medication consumption with higher annual costs, and less HRQoL. The combined group had an intermediated pattern between the two therapies. Nevertheless, after the 24-month intervention, hypertensive older adults in the MEX group improved their blood pressure profile, HDL cholesterol, CRF and HRQoL, reversely to the pharmacological treatment group that augmented SBP, decreased HDL, CRF, HRQoL and

maintained the number of medicines used. Similarly with the results of the combined group in T2D, our combined group of hypertensive older adults, also enhanced their SBP, CRF and HRQoL, and decreased the medication consumption. However, the annual medication expenditure increased in all groups and did not present any differences between them, despite the decrease in the number of medicines.

In the dyslipidemic sub-groups, at baseline, the MEX participants had the worst hemodynamic and lipid profile (higher SBP, DBP and LDL) but had less morbidity, consumed fewer medicines and had higher HRQoL. The isolated ST group had higher glycaemia and less HRQoL. Similarly with the other combined groups, MEX+ST participants consumed more medicines, had higher annual medication costs and had higher TG. Nevertheless, at the end of the study, our results confirmed that chronic multicomponent exercise training *per se* is more effective to reduce multifactorial cardiovascular risk factors, medication consumption, increase CRF and HRQoL than pharmacological therapies (MET, ACEi and ST) in comorbid older adults, independently of the disease (**Study VIII**). Furthermore, our results also highlight the effectiveness of the combined therapy- pharmacological treatment plus exercise training, for those that need to pharmacological treatments, to improve these outcomes, adding new information to previous suggestions (Anton et al., 2015; Bamman et al., 2014; Buford, 2016; Gui et al., 2017). Contrarily, pharmacological treatment seems to have a long-term negative effect in the hemodynamic profile and HRQoL. Thus, our results confirmed that exercise training is the most effective management plan in all the chronic diseases analysed and even though this conclusion, can not be generalized to all older adults, it was proven that in older patients in early stage of T2D (HbA1c < 7,5%), in hypertensive older adults in grade 1 and in dyslipidemic older adults with comorbidities, chronic multicomponent exercise training promoted more pronounced effects than pharmacological treatment (**Study VIII**).

Exercise activates a multi-complex array of coordinated cellular and molecular processes involving a wide signaling networks and transcriptional regulators that differentially affect virtually every human tissue and organ system (Bamman et al., 2014; Sharman et al., 2015). Unfortunately, exercise training is regularly prescribed/ performed as an “adjunctive therapy” to drug therapy across a wide range of diseases despite the known-documented improvements in cardiac function, muscle oxidative capacity, metabolic health, glucose and lipid homeostasis, adiposity, inflammatory burden, muscle

mass and strength, joint pain, mobility function, depression, anxiety and cognition (Bamman et al., 2014). Moreover, due to the tendency of expert bodies and physicians not only to prioritize the roles of diet and medication over exercise in their treatment plans (O'Hagan et al., 2013) but also to the participants own intrinsic barriers to an "active" treatment plan (Ambrose & Golightly, 2015), elderly exercise engagement is suboptimal (World Health Organization, 2014). Moreover, "active" interventions often result in impressive rates of initial behavior changes, but frequently are not translated into long-term behavioral maintenance (Artinian et al., 2010). So the adoption and the long-term maintenance of "active" interventions pose challenges for many individuals but as demonstrated by the results of our multicomponent exercise training are the most empowering therapies, improving multifactorial cardiovascular risk factors, CRF, medication consumption and yield impressive benefits and largest improvements of symptoms and overall quality of life (Ambrose & Golightly, 2015). Furthermore, our results confirm that higher exercise patterns and CRF levels are associated with better health outcomes (J. Myers et al., 2015), independently of the baseline age, chronic disease, severity and associated cardiovascular risk factors once that our participants in all the MEX and combined therapies groups (MEX+MET; MEX+ACEi; MEX+ST) were older, had the worst hemodynamic profile, consumed more medicines and had a higher number of morbidities. Nevertheless, at the end of the study, these groups were able to reverse these outcomes to "normal" ranges, with few to none adverse effects (Bamman et al., 2014). Thus, multicomponent exercise training promoted important clinical benefits traducing in a decreased multifactorial cardiovascular risk factor profile, improved functional status leading to a more independent daily-life state, with enhanced mood states and with more positive physical and mental HRQoL. This circle, at long-term, will not only traduce in a decrease of the number of medicines and with medication expenditure but also with other health associated costs (costs of hospital, emergency room, urgent care, outpatient services, among others) (Diabetes Prevention Program Reasearch, 2012).

One other important issue regarding pharmacological treatment is that the management of comorbid older adults does not necessarily correspond to the optimal treatment of each of their individual chronic disease, but rather to the management of these multifactorial disease systems (Fabbri et al., 2015). If pharmacological treatment of one disease in older adults is usually complex and multidimensional, in older adults affected by

multiple chronic diseases such as our sample, this process is even harder, due to the difficulties with therapeutic compliance, to the higher vulnerability to suffer adverse events, psychological distress and depression, more admission to hospital and longer hospital stays and may ultimately lead to mortality (Fabbri et al., 2015). Thus, our pharmacological groups by aggravating their hemodynamic profile, decreasing their CRF and HRQoL, augmented the odds of suffering these previous adverse pharmacological effects related with pharmacological treatment and polypharmacy use. Therefore, the potential benefit of a medication must be out-weighted against possible risks arising from its use (Singh & Bajorek, 2015). Although our participants in the pharmacological groups did not presented adverse effects associated with medication use, which may be related with the drug initiation time (participants had at least one year of their medication) and to the low dose consumed (Catapano et al., 2016; Colagiuri et al., 2014; Mancia et al., 2013), the chronic negative pressure in other cardiovascular risk factors will impose at long-term, a deleterious vicious circle that will lead in turn, to the aggravation of each their diseases, of morbidity, functional status, medication consumption and HRQoL. Thus, single-target drugs cannot mimic the complex, multisystem effects of exercise training (Bamman et al., 2014), involving inhibition of pro-inflammatory and stimulation of anti-inflammatory paths (Balducci et al., 2010), as it was proved by the results of our study. Pharmacological treatment (MET, ACEi, ST) moderately improve one risk factor, and worsened all the others. Contrarily, MEX training improved several cardiovascular risk factors, CRF and HRQoL, independently of the disease. Therefore, a more "holistic" approache addressed to target multifactorial cardiovascular risk factors should be promoted, once a moderate reduction in several risk factors may be more effective to reduce cardiovascular risk, functional status, medication consumption and HRQoL than a major reduction in only one of them (Véronique A. Cornelissen & Fagard, 2005; Sharman et al., 2015), as confirmed by our investigation.

One surprising result was the augment in the annual medication expenditure after the 24-month intervention in all groups, despite the decrease in the number of medicines in some sub-groups. This result may be explained by the higher retail prices of medicines and by the decrease in the percentage of NHS reimbursement level but also to the increase of users co-payment, overloading the small budgets that older adults monthly have to survive. The majority of Portuguese older adults live with a retirement pension under the national

minimum wage (557€) and the minimum old-age pension of 264€ (PORDATA, 2017). This concerning increase of annual medication cost, reflects the "burden" that medicines have in the individual economic situation. So it is important to find cost-effective solutions to minimize medication consumption, morbidity, decrease cardiovascular risk factors, physical disability, and enhance HRQoL, once the aggravation of morbidity will probably imply an increase of medicine use, which in turn, may lead to the pressure of the monthly budgets but also to other important issues regarding drug–drug interactions, drug–disease interactions, poor adherence to treatment, adverse drug events, hospitalization and mortality, related not only with the number of medications, but also with the regimen complexity (Bell & Saraf, 2016; Charlesworth et al., 2015a; Colagiuri et al., 2014; Singh & Bajorek, 2015). Moreover, this vicious cycle will probably lead to the exacerbation of morbidity, to the decrease of functionality and health status, to the increase of extra health costs, pressuring once again the economic individual situation and health care systems, impairing the efficacy of treatment but also the users quality of life (Bell & Saraf, 2016; Charlesworth et al., 2015a; Colagiuri et al., 2014; Singh & Bajorek, 2015). Nevertheless, cost-effectiveness cannot be simply limited to the medication expenditure once as shown by our study, the value of regular exercise far exceeds the monetized benefits. Indeed, as proved by our study, exercise positively affected multifactorial cardiovascular risk factors, physical and mental functioning, HRQoL and other dimensions of health and wellbeing that cannot be calculated, as they occur in health-related dimensions or factors but that contribute to a general wellbeing that exceeds the economic cost alone. Thus, non-pharmacological therapies should be considered by clinicians as an effective first-line therapeutic plan for those at the initial stage of these diseases and not merely an "adjunctive therapy" (Bamman et al., 2014). For those, that clearly need pharmacological treatment, exercise can serve as a positive behavioral and physiologic modifier of the pharmacological and disease effects (Bamman et al., 2014). Consistent with previous studies (Buford et al., 2012; Cadeddu et al., 2014; Gui et al., 2017), this rationale seem to be supported by the results obtained in our combined groups (MEX+MET; MEX+ACEi; MEX+ST), where exercise training seems to have counterbalanced the negative effects that pharmacological treatment had in cardiovascular risk factors, CRF, medication consumption and HRQoL in all the groups.

In summary, these results provide further support and may guide health care professionals and health organizations in the prescription process, according with two conditions: *i*) in older adults with comorbidities in the initial stage of T2D, hypertension and dyslipidemia, multicomponent exercise programs should be prescribed, as the first-line treatment; *ii*) for those that are in advance stage of the disease, due to severity or other associated risk factors and need pharmacologic treatment, long-term multicomponent exercise training should be added to the management plan to mitigate/counterbalance the negative effects that drugs use may have. Moreover, our results suggests that it is necessary to rethink the understanding of health by shifting the focus of investment priorities and health policies, develop new health strategies along with political action plans at various levels, integrating new professionals from other areas (exercise specialists, among others), focusing in more "holistics", "active" approaches that despite the initial and immediate cost, will lead to long-term health savings, encouraging the maintenance of an active lifestyle, improving functional capacities and promoting an independent functional life (Direcção Geral de Saúde, 2016; World Health Organisation, 2016).

5.5- Strengths and limitations

The longitudinal design of the present thesis has several strengths, including the large community sample exclusively composed by older adults with comorbidities, the long-term supervised exercise training intervention, the use of well-validated instruments and the range of outcomes measuring different aspects of medication, physical fitness, cardiovascular risk factors and HRQoL. Although, this study had a long-term intervention with different measurement points, the causality relationship should be carefully interpreted once some limitations might have caused some bias in our results, particularly the different sample sizes within each study groups and the non- randomized methodological design. Though, we tried to mitigate these limitations adopting specific statistical procedures to counteract these effects, particularly controlling for several covariates that were available and evaluated as potential confounders and also measuring the magnitude of the results out-weighting to the different samples sizes with the Hedges *g* effect size, reducing in part these limitations. However, residual confounding factors due to unknown or incompletely measured factors cannot be excluded.

6. CONCLUSION

The purpose of the present study was to analyze the effects of chronic multicomponent exercise training and/or pharmacological treatments in medication consumption, functional status, anthropometric, hemodynamic variables, mood states and HRQoL in older adults above 60 years of age. Thus, a group of 1221 older adults, enrolled in a supervised multi-component exercise programme 3 times/ week with 60 minutes duration and were compared with a control group of 252 inactive older adults. It was used a general health history questionnaire, SF-36 and mood states (POMS), it was measured the anthropometric and hemodynamic profile and used the Senior Fitness Test battery (R.E. Rikli & Jones, 1999).

Considering the results presented and discussed previously, it can be affirmed that the purposes established for the present thesis were reached, although in future investigations the limitation factors should be overcome. As it is intended in a study of this nature, we will try to highlight the most important facts that emerged from the data analysis:

- Long-term multicomponent exercise training:

  i) *Per se* was the most effective therapy, reinforcing his importance as multifactorial cardiovascular risk intervention on the enhancement of anthropometric and hemodynamic profile, blood glucose, medication consumption, functional status, CRF, improving mood states, physical and mental HRQoL in T2D, hypertension and dyslipidemia in older adults with comorbidities.

  ii) *Per se* was the most effective treatment to reach functional status goals, regardless the anti-diabetic, antihypertensive (ACEi, TDs, CCBs, βBs) antidyslipidemic or mode of antihypertensive therapy (Mono or Combined therapy).

  iii) May have counterbalanced the negative effects which isolated pharmacological therapies (MET, ACEi, ST) may have on cardiovascular risk factors, functional status, mood states, medication consumption and HRQoL decline, revealing his potencial role as

intermediator in the relationship between pharmacological therapies and the outcomes analyzed.

- Pharmacological therapies:

  iv) Metformin increased anthropometric and SBP profile, augmented tension, unchangead CRF and HRQoL and decreased functional status, suggesting that it´s long-term use may have a pro-inflammatory anthropometric and hemodynamic evolution that may worsen functionality and mood states in T2D older adults. Nevertheless, more research is needed to understand the underlying mechanisms of these changes.

  v) ACEi monotherapy aggravated hypertension due to the negative evolution of the anthropometric and hemodynamic components, lipid profile and CRF, that may have led to the decrease of functional status and HRQoL.

  vi) Statin monotherapy decreased not only functional status and physical HRQoL, but also aggravated anthropometric and hemodynamic profile. However, it improved LDL cholesterol without any associated muscle adverse effect once this group decreased bodily pain.

- The combined treatments:

  vii) MEX+MET and MEX+ACEi showed an anthropometric, hemodynamic, lipid, CRF, functional status, mood states and HRQoL improvement but in a smaller range than the isolated multicomponent exercise training group, presenting an intermediated pattern between the improvements in the multicomponent exercise training and the decreases with pharmachological therapy alone (MET, ACEi), confirming that the long-term benefits of exercise and pharmacological drugs in these pathologies, does not seem to be totally additive. MEX+ST was similarly effective as MEX, in terms of the enhancement of the anthopometric and hemodynamic profile, functional status outcomes and HRQoL demonstrating that in this chronic disease both forms of treatment acted synergistically.

6.1- Clinical implications and future recommendations

Despite the limitations, our results have important clinical implications, as the first long- term study to evaluate the relationship and impact/ effectiveness of several pharmachological and/or non-pharmacological therapies in older adults with comorbidities.

We demonstrated that multicomponent exercise training is more effective than isolated pharmacological treatments (MET, ACEi and ST) to improve multifactorial cardiovascular risk factors, functional status, mood states, medication consumption and HRQoL, and consequently these results may aid in the management of several CVDs, particularly, T2D, hypertension and dyslipidemia. Reversely, we showed that the long-term use of isolated pharmacological medications may have a pro-inflammatory evolution. This result is particularly important for those that need pharmacological drugs to manage their chronic diseases, highlighting the need to adopt a long-term exercise training regimen to mitigate these negative effects that medicines have in terms of cardiovascular risk factors, functional status, mood states, medication consumption and HRQoL.

On the other hand, the ineffectiveness of the isolated pharmacological therapies (MET, ACEi and ST) may have been counterbalanced by the long-term exercise training in the combined groups, reinforcing his role as an intermediator in the relationship between pharmacological therapies and the outcomes analyzed, confirming also that the long-term benefits of exercise and pharmacological drugs does not seem to be totally additive. Furthermore, as demonstrated, the improvements in a cluster of cardiovascular risk factors, as occurred in the MEX groups may have more pronounced effects than treating one major isolated risk factor, has occurred with the pharmachological therapies, especially in terms of cardiovascular risk factors, functional status, mood states and HRQoL in comorbid older adults, once the underlying mechanisms seem to be most likely the same; those that drive ageing also may conduct multiple age- related chronic diseases (Fabbri et al., 2015).

These facts allow a new research pathway through the use of pharmacological and non-pharmachological approaches aimed at one or more of the ageing mechanisms, with the hope that, by addressing these fundamental determinants, a positive impact could be achieved in combating not one, but multiple chronic diseases in parallel (Hodes et al., 2016). So addressing efforts to reduce these mechanisms may decrease the development of morbidity, produce substantial gains in health status, reduce disability and increase functional independence. Furthermore, our results seem to confirm that the paradigm of "1 patient–1 disease" (Fabbri et al., 2015) no longer fits the medical necessities and needs of

most elderly, due to the increasing numbers of comorbidities (Bell & Saraf, 2016), and that a more "holistic" treatment approach, like exercise training, targeting multifactorial cardiovascular risk factors, should be adopted in standard care and local communities.

To substantiate this rationale, new studies investigating potential interactions of management strategies to improve the long-term care of complex, multimorbid participants are critical to progress, in particular, clinical trials that target the efficacy of treatments with multiple drugs and/or with non-pharmachological treatments. Additionally, there is a need for adjunctive exercise plus medication interventions to determine if exercise training enhances or interferes with drug outcomes or vice versa (Bamman et al., 2014).

Although, exercise benefits are undeniable, to fully potentialize exercise efectivety, key knowledge gaps demands more research, particularly by: i) continuing developing understanding on exercise-drug interaction, synergism, or antagonism; ii) determinants of both exercise/ pharmachological treatments eficaccy (in terms of new research fields advances like genomics, epigenetics, proteomics, metabolomics, stem cell biology to shed light on the complexity of exercise adaptation); iii) understanding the role of exercise stimulus repurposition use for currently available medications.

Given the scarcity of financial resources to fund future trials of exercise interventions, one option would be to require such evidence from pharmaceutical companies that are under increasing pressure to perform active-comparator trials for market entry (Bamman et al., 2014). For example, regulators could consider requiring pharmaceutical sponsors to include exercise interventions as an active arm- comparator in drug trials. In cases where drug options provided only modest benefit, isolated exercise training and/or the combination of both could be out-weighted to understand the relative real impact that exercise might have on specific chronic conditions, as we observed with our study.

Finally, the creation of a national database with these indicators would be a valuable tool to assess the treatments and health evolution. Furthermore, it was interesting and appropriate to implement this research in a national representative sample, in order to be able to analyze the direct health costs and savings, to effectively fulfill the strategies that are preconized in the "*Estratégia Nacional para o envelhecimento activo e saudável 2017-2025*" by our interminsterial group team (*Estratégia Nacional para o envelhecimento activo e saudável 2017-2025*, 2017).

To sum up, research on exercise as a "medicine" (American College of Sports Medicine, 2014) should be embraced as a new opportunity to advance knowledge, in order to combat the global health crises driven largely by common chronic diseases, namely the non-communicable diseases. Independently of the disease, long-term multicomponent exercise training presents as the most effective treatment, improving multifactorial cardiovascular risk factors, increasing functional status, augmenting positive mood states, managing medication consumption and HRQoL in older adults with comorbidities, particularly in those under pharmacological therapies. Furthermore, exercise training assumes as an effective therapy to physical and mental health-enhancing, to manage and to delay the deleterious effects of chronic diseases and age-related declines and assures a multidimensional "holístic" intervention, promoting a healthy and active ageing among older adults with comorbidities.

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APPENDIX-1

1.1. Health Related Quality of Life Questionnaire- SF-36

1.2. Mood States Questionnaire-POMS-SF

1.3. Anthropometric Measurements Sheet

1.4. Health History Questionnaire

QUESTIONÁRIO DE ESTADO DE SAÚDE (SF-36V2)

INSTRUÇÕES: As questões que se seguem pedem-lhe opinião sobre a sua saúde, a forma como se sente e sobre a sua capacidade de desempenhar as actividades habituais.

Pedimos que leia com atenção cada pergunta e responda o mais honestamente possível. se não tiver a certeza sobre a resposta a dar, dê-nos a que achar mais apropriada e, se quiser, escreva um comentário a seguir à pergunta.

Para as perguntas 1 e 2, por favor coloque um círculo no número que melhor descreve a sua saúde.

1. Em geral, diria que a sua saúde é:

Óptima	Muito boa	Boa	Razoável	Fraca
1	2	3	4	5

2. Comparando com o que acontecia há um ano, como descreve o seu estado geral actual:

Muito melhor	Com algumas melhoras	Aproximadamente igual	Um pouco pior	Muito pior
1	2	3	4	5

3. As perguntas que se seguem são sobre actividades que executa no seu dia-a-dia. Será que a sua saúde o/a limita nestas actividades? Se sim, quanto?

(*Por favor assinale com um círculo um número em cada linha)*

	Sim, muito limitado/a	Sim, um pouco limitado/a	Não, nada limitado/a
a. **Actividades violentas**, tais como correr, levantar pesos, participar em desportos extenuantes.....	1	2	3
b. **Actividades moderadas**, tais como deslocar uma mesa ou aspirar a casa.....	1	2	3
c. Levantar ou pegar nas compras da mercearia.....	1	2	3
d. Subir **vários** lanços de escadas.....	1	2	3
e. Subir **um** lanço de escadas.....	1	2	3
f. Inclinar-se, ajoelhar-se ou baixar-se.....	1	2	3
g. Andar **mais de 1 Km**.....	1	2	3
h. Andas **várias** centenas de metros.....	1	2	3
i. Andar **uma** centena de metros.....	1	2	3
j. Tomar banho ou vestir-se sozinho/a.....	1	2	3

4. Durante as últimas 4 semanas teve, no seu trabalho ou actividades diárias, algum dos problemas apresentados a seguir como consequência do seu estado de saúde físico?

Quanto tempo, nas **últimas quatro semanas...**	**Sempre**	**A maior parte do tempo**	**Algum tempo**	**Pouco tempo**	**Nunca**
a. Diminuiu o **tempo gasto** a trabalhar ou outras actividades	1	2	3	4	5
b. Fez **menos** do que queria?.....	1	2	3	4	5
c. Sentiu-se limitado/a no tipo de trabalho ou outras actividades	1	2	3	4	5
d. Teve **dificuldade** em executar o seu trabalho ou outras actividades (por exemplo, foi preciso mais esforço).....	1	2	3	4	5

5. Durante as últimas 4 semanas, teve com o seu trabalho ou com as suas actividades diárias, algum dos problemas apresentados a seguir devido a quaisquer problemas emocionais (tal como sentir-se deprimido/a ou ansioso/a)?

Quanto tempo, nas **últimas quatro semanas...**	**Sempre**	**A maior parte do tempo**	**Algum tempo**	**Pouco tempo**	**Nunca**
a. Diminuiu o **tempo gasto** a trabalhar ou outras actividades	1	2	3	4	5
b. Fez **menos** do que queria?.....	1	2	3	4	5
c. Executou o seu trabalho ou outras actividades **menos** cuidadosamente do que era costume.....	1	2	3	4	5

Para cada uma das perguntas 6, 7 e 8, por favor ponha um círculo no número que melhor descreve a sua saúde.

6. Durante as últimas 4 semanas, em que medida é que a sua saúde física ou problemas emocionais interferiram no seu relacionamento social normal com a família, amigos, vizinhos ou outras pessoas?

Absolutamente nada	**Pouco**	**Moderadamente**	**Bastante**	**Imenso**
1	2	3	4	5

7. Durante as últimas 4 semanas teve dores?

Nenhumas	Muito fracas	Ligeiras	Moderadas	Fortes	Muito fortes
1	2	3	4	5	6

8. Durante as últimas 4 semanas, de que forma é que a dor interferiu com o seu trabalho normal (tanto o trabalho fora de casa como o trabalho doméstico)?

Absolutamente nada	Pouco	Moderadamente	Bastante	Imenso
1	2	3	4	5

9. As perguntas que se seguem pretendem avaliar a forma como se sentiu e como lhe correram as coisas nas últimas quatro semanas.
Para cada pergunta, coloque por favor um círculo à volta do número que melhor descreve a forma como se sentiu.
Certifique-se que coloca um círculo em cada linha.

Quanto tempo, nas **últimas quatro semanas...**	**Sempre**	**A maior parte do tempo**	**Algum tempo**	**Pouco tempo**	**Nunca**
a. Se sentiu cheio/a de vitalidade?.....	1	2	3	4	5
b. Se sentiu muito nervoso/a?.....	1	2	3	4	5
c. Se sentiu tão deprimido/a que nada o/a animava?.....	1	2	3	4	5
d. Se sentiu calmo/a e tranquilo/a?.....	1	2	3	4	5
e. Se sentiu com muita energia?.....	1	2	3	4	5
f. Se sentiu deprimido/a?.....	1	2	3	4	5
g. Se sentiu estafado/a?.....	1	2	3	4	5
h. Se sentiu feliz?.....	1	2	3	4	5
i. Se sentiu cansado/a?.....	1	2	3	4	5

10. Durante as últimas quatro semanas, até que ponto é que a sua saúde física ou problemas emocionais limitaram a sua actividade social (tal como visitar amigos ou familiares próximos)?

Sempre	A maior parte do tempo	Algum tempo	Pouco tempo	Nunca
1	2	3	4	5

11. Por favor, diga em que medida são verdadeiras ou falsas as seguintes afirmações. Ponha um círculo para cada linha.

	Absolutamente verdade	Verdade	Não sei	Falso	Absolutamente falso
a. Parece que adoeço mais facilmente do que os outros.....	1	2	3	4	5
b. Sou tão saudável como qualquer outra pessoa.....	1	2	3	4	5
c. Estou convencido/a que a minha saúde vai piorar.....	1	2	3	4	5
d. A minha saúde é óptima.....	1	2	3	4	5

MUITO OBRIGADO

APTIDÃO FÍSICA FUNCIONAL

LOCAL…….

NOME……

PA repouso 1.º medição ……./……. mmHg 2.º medição……./……..mmHg

FC repouso 1.º medição……bat/min 2.º medição……bat/min

Massa Corporal	kg
Estatura	cm
Circunferência Anca Plano horizontal que passa pela sínfise púbica	cm
Circunferência Cintura No menor perímetro do ronco, entre o umbigo e apêndice xifóide	cm
Circunferência abdominal Na maior extensão abdominal anterior, geralmente ao nível do umbigo)	cm

TESTES

	1.º Tentativa	2.º Tentativa
Levantar e sentar na cadeira (em 30 segundos)		
Flexão do antebraço (em 30 segundos)		
Sentado e alcançar		
Sentado, caminhar 2,44m e voltar a sentar		
Alcançar atrás das costas		

Caminhar 6 minutos (perímetro de 50m- ex 15m+10+15+10)

Volta	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Tempo																				

POMS-SF

Local _____ Data ____/____/____ Hora ___:___

Nome _____

Instruções: A seguir encontrará uma lista de palavras que descrevem sentimentos que as pessoas têm. Por favor leia cada uma com cuidado. À frente de cada palavra coloque um círculo (O) no algarismo que melhor descreve **como se tem sentido durante a última semana, incluindo hoje**.

	De maneira nenhuma	Um pouco	Moderadamente	Muito	Muitíssimo
1. Tenso	0	1	2	3	4
2. Esgotado	0	1	2	3	4
3. Animado	0	1	2	3	4
4. Confuso	0	1	2	3	4
5. Triste	0	1	2	3	4
6. Activo	0	1	2	3	4
7. Mal-humorado	0	1	2	3	4
8. Enérgico	0	1	2	3	4
9. Indigno	0	1	2	3	4
10. Inquieto	0	1	2	3	4
11. Fatigado	0	1	2	3	4
12. Desencorajado	0	1	2	3	4
13. Nervoso	0	1	2	3	4
14. Só	0	1	2	3	4
15. Baralhado	0	1	2	3	4
16. Exausto	0	1	2	3	4
17. Ansioso	0	1	2	3	4
18. Desanimado	0	1	2	3	4
19. Cansado	0	1	2	3	4
20. Furioso	0	1	2	3	4
21. Cheio de vida	0	1	2	3	4
22. Com mau feitio	0	1	2	3	4

Obrigado pela colaboração.

QUESTIONÁRIO GERAL DE SAÚDE E ACTIVIDADE FÍSICA[1]

Local _____ Data ____/____/____ Hora_____:____

Nome _____

Morada _____

Data de nascimento_____/_____/_____ Estatura_____(m) Peso__(kg)

Peso aproximado aos 20 anos_____kg; Peso médio entre os 40 e os 50 anos_____kg

Historial de actividade física

Alguma vez foi atleta? Não ☐ Sim ☐

Se sim, em que idade iniciou?_____(anos); Em que idade terminou?_____(anos) Qual a modalidade que praticou? _____

Ainda pratica alguma modalidade (ex.: caminhadas)? Não ☐ Sim ☐

Quantas vezes/semana?_____ Durante quanto tempo?_____(min)

Historial da função reprodutiva (sexo feminino)

Idade da menarca_____(anos). Menopausa_____(anos) Espontânea ☐ Cirúrgica ☐ Usou hormonas após a menopausa? Não ☐ Sim ☐ Quantos anos? ____

Alguma vez o médico o informou que tem ou teve:

	Sim	Com que idade (aprox.)	
Ataque cardíaco	☐		
Angina de peito	☐		
Trombose	☐		
Pressão arterial elevada	☐		
Outras doenças cardiovasculares	☐	_____	
Diabetes	☐	_____	
Doenças respiratórias Doença de	☐	_____	
Parkinson Osteoporose	☐	_____	
Osteoartrose	☐	_____	
Cancro	☐	_____	Onde _____
	☐	_____	Tipo _____

[1] Questionário adaptado de:
Sardinha LB (1999). Programa de Actividade Física para a Pessoa Idosa do Concelho de Oeiras – Concepção, actividades e avaliação da aptidão física funcional. Edição: Câmara Municipal de Oeiras e Faculdade de Motricidade Humana, pp.16-22.

Alterações mentais ☐ _____ Tipo _____

Problemas visuais ☐ Tipo_____

_____ Descrição _____

Outros problemas de saúde ☐ _____

Razões médicas limitam frequentemente a sua actividade física? Não ☐ Sim ☐ Se sim, quais? _____

Tomou ou vai tomar a vacina da gripe? Já tomei ☐ Vou tomar ☐

Quantas gripes/constipações tem por ano? 0 ☐ 2 ☐ 4 ☐ Š5 ☐

Lista dos medicamentos que toma actualmente

Tipo de medicação	Dose/dia
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____

Fuma cigarros actualmente? Não ☐ Sim ☐ Nº cigarros/dia _____ Se não, alguma vez fumou? Não ☐ Sim ☐ Nº cigarros/dia _____

Durante quantos anos?_____ Há quanto tempo parou? _____

Consome bebidas alcoólicas? Não ☐ Sim ☐ Tipo_____ Se sim, quantas por semana? < 7 ☐ 7-14 ☐ > 14 ☐

Que acha da sua saúde?

Excelente ☐ Muito boa ☐ Boa ☐ Razoável ☐ Má ☐ Em geral, como avalia a sua qualidade de vida?

Péssima ☐ Má ☐ Satisfatória ☐ Boa ☐ Muito boa ☐ Quantas vezes se sentiu deprimido no último ano?

Nenhuma ☐ 1 a 2 vezes ☐ 3 a 6 vezes ☐ 7 ou mais vezes ☐ Está preocupado com os seus momentos “em baixo”?

Não ☐ Pouco ☐ Moderadamente ☐ Muito ☐ Muitíssimo ☐

Indique a sua capacidade para realizar algumas tarefas. A sua resposta deve indicar se normalmente consegue realizar as actividades, embora não o consiga neste momento. Que consegue realizar?

	Consigo	Consigo com dificuldade ou com ajuda	Não consigo	
Cuidar-me a mim próprio (ex.: vestir-me	☐	☐		☐
sozinho) Tomar banho (imersão ou	☐	☐		☐
duche)		☐	☐	☐
Subir e descer um lanço de escadas (até ao 1º andar)		☐	☐	☐
Caminhar (1 ou 2 quarteirões)		☐	☐	☐
Tarefas domésticas leves (cozinhar, limpar o pó, lavar a loiça, varrer)		☐	☐	☐
Tarefas domésticas pesadas (esfregar o chão, aspirar, varrer o jardim)		☐	☐	☐
Actividades fatigantes (longas caminhadas, cavar,		☐	☐	☐
andar de bicicleta)		☐	☐	☐
Fazer compras (alimentos ou vestuário)				
Segurar e transportar cerca de 4,5kg (saco cheio de mercearia)				

Usa uma ajuda mecânica para andar? Não ☐ Sim ☐ Às vezes ☐ Tipo_____ A actividade física que faz normalmente é suficiente? Não ☐ Sim ☐ Não sei

Da lista seguinte, indique as duas razões mais importantes para praticar actividade física (faça um círculo à volta da letra):

a. Melhorar a saúde **b.** Manter/melhorar a mobilidade **c.** Manter/melhorar a aparência
d. Controlar o peso **e.** Aumentar a força/c.física geral **f.** Sentir-se bem mentalmente
g. Gostar de actividade **h.** Reduzir o stress/ansiedade **i.** Competição/desafio pessoal
j. Reabilitação **k.** Razões sociais/divertimento **l.** Recomendações médicas
m. Sentido de obrigação (ser bom para si) **n.** Outras _____
o. Desempenhar tarefas (domésticas, jardinagem)

Quais são para si os maiores impedimentos para poder praticar actividade física?

a. Falta de tempo **b.** Não ser prioritário **c.** Preguiça/falta de auto-disciplina
d. Doença/lesão **e.** Má imagem do corpo **f.** Falta de aulas estruturadas
g. Clima (quente/frio) **h.** Não gostar de praticar **i.** Envolvim. inseguro/perigoso
j. Medo de lesão **k.** Falta de transporte **l.** Falta de habilidade/conhecim.

m. Falta de confiança **n.** Falta de oportunidade **o.** Falta de apoio dos amigos/s.s.

p. Desconforto/dor **q.** Falta de força de vontade **r.** Outras _____

Qual a sua actividade física favorita (se alguma)?----------

Em geral, qual a situação que prefere para a prática de actividade?

a. Exercício/actividade estruturada (em grupo ou classe) ☐
b. Actividade não estruturada (à sua vontade) ☐
c. Exercício com um ou mais parceiros ☐
d. Sem preferência. De acordo com o tipo de actividade ☐

Nível de escolaridade (faça um círculo no ano em que terminou os estudos).

a. Primário	1	2	3	4			
b. Ensino secundário	1	2	3	4	5	6	7
c. Curso técnico	1	2	3	4	5	. . .	
d. Ensino superior	1	2	3	4	5	. . .	

Estado civil: Casado ☐ Solteiro ☐ Divorciado ☐ Viúvo ☐

APPENDIX-2

2.1. Instructions prior to test administration

2.2. Participants informed consent

2.3. Data Protection Authority-CNPD and Health Administration from North Ethics Committee-ARS/Norte authorizations

2.1. Instruções

O presente trabalho insere-se uma investigação desenvolvida pela Faculdade de Ciências do Desporto e Educação Física, da Universidade de Coimbra, e tem como objectivo estudar os efeitos do exercício físico em vários aspetos relacionados com a qualidade de vida, aptidão física, consumo com medicamentos e autonomia funcional.

Na investigação que irá decorrer estão incluídos:

- Testes físicos (envolvem atividades como andar).
- Medições antropométricas.
- Medições hemodinâmicas (pressão arterial e frequência cardíaca).
- Preenchimento de questionários.

Embora os riscos associados com os testes sejam mínimos é importante ter em consideração alguns aspetos, de modo a garantir a sua segurança e a ajudá-lo a obter o melhor resultado. Assim:

- Evite esforços muito intensos um ou dois dias antes da avaliação;
- Evite o consumo excessivo de álcool nas 23 horas anteriores aos testes;
- Coma uma refeição ligeira uma hora antes da avaliação;
- Vista roupas e calçado adequado para a prática de atividade física (ex: T-shirt, calças ou calções e sapatilhas);
- Informe o responsável pelos testes de alguma situação médica ou de medicamentos que possam afetar o seu desempenho nos testes.
- Deverá entregar os questionários totalmente preenchidos na **aula seguinte**, caso tenha dúvidas, ou não saiba ler e escrever deverá informar o responsável pela investigação.

Participe, conheça as suas capacidades e **Divirta-se**

2.2. CONSENTIMENTO INFORMADO, LIVRE E ESCLARECIDO PARA PARTICIPAÇÃO EM INVESTIGAÇÃO

de acordo com a Declaração de Helsínquia[1] e a Convenção de Oviedo[2]

Título do estudo: Consumo com medicamentos, exercício físico e qualidade de vida na terceira idade

Enquadramento: O presente trabalho insere-se uma investigação desenvolvida pela Faculdade de Ciências do Desporto e Educação Física, da Universidade de Coimbra, e tem como objectivo estudar os efeitos do exercício físico em vários aspetos relacionados com a qualidade de vida, aptidão física, consumo com medicamentos e autonomia funcional.

Explicação do estudo: Na investigação que irá decorrer estão incluídos:

- Testes físicos (envolvem atividades como andar).
- Medições antropométricas (peso, altura, perímetros da cintura, abdominal e anca).
- Medições hemodinâmicas (pressão arterial e frequência cardíaca).
- Preenchimento de questionários (Questionário geral de saúde, estados de Humor e qualidade de vida).

Será instruído para avisar o responsável pela administração dos testes e pelas aulas caso sinta algum desconforto ou sintomas não usuais, como dores no peito, tonturas, batimentos cardíacos irregulares, perdas de equilíbrio ou náuseas. Os dados serão recolhidos presencialmente durante o decorrer das aulas durante 24 meses estando previstos dois momentos de recolha, um num momento inicial e após 24 meses.

Condições e financiamento: A sua participação é inteiramente voluntária e poderá ser interrompida quando o desejar, não existindo prejuízos assistenciais ou outros, caso não queira participar. Não existirá pagamento de deslocações ou contrapartidas. O estudo é financiado pela Fundação de Ciência e Tecnologia e mereceu Parecer favorável da Comissão de Ética para a Saúde da ARSNORTE. A ARS Norte, I.P. não assume a responsabilidade por qualquer consequência resultante da participação no presente projeto de investigação

Confidencialidade e anonimato: Os dados recolhidos, serão mantidos confidenciais, sendo utilizados unicamente para fins de investigação. Será garantido o anonimato, tendo sido pedida e obtida autorização da Comissão Nacional de Proteção de Dados, garantindo, em qualquer caso, que a identificação dos participantes nunca será tornada pública. Todos os contactos serão feitos em ambiente de privacidade. A informação sobre a existência e as condições do direito de acesso e de retificação por parte do respetivo titular serão obtidas junto da responsável da investigação.

Obrigado pela sua participação.

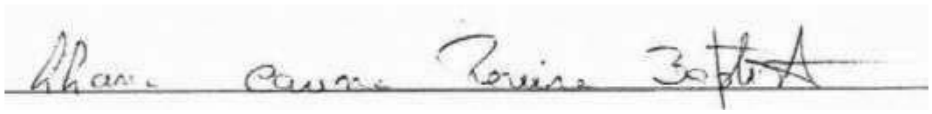
Liliana Carina Pereira Baptista, Doutoranda em Ciências do Desporto.

Contacto telefónico-919650114; endereço electrónico: libaptista10@hotmail.com

[1] http://portal.arsnorte.min-saude.pt/portal/page/portal/ARSNorte/Comiss%C3%A3o%20de%20%C3%89tica/Ficheiros/Declaracao_Helsinquia_2008.pdf

[2] http://dre.pt/pdf1sdip/2001/01/002A00/00140036.pdf

Assinatura:

(Liliana Pereira  Carina Baptista)

Declaro ter lido e compreendido este documento, bem como as informações verbais que me foram fornecidas pela pessoa que acima assina. Foi-me garantida a possibilidade de, em qualquer altura, recusar participar neste estudo sem qualquer tipo de consequências. Desta forma, aceito participar neste estudo e permito a utilização dos dados que de forma voluntária forneço, confiando em que apenas serão utilizados para esta investigação e nas garantias de confidencialidade e anonimato que me são dadas pelo/a investigador/a.

Nome: … … … … … … … …... … … … …... … … … … … … … … … … … …
Assinatura: … … … … … … … …... … … … … ... … … … … … … … … … … … … Data: …… /…… /………..

SE NÃO FOR O PRÓPRIO A ASSINAR POR IDADE OU INCAPACIDADE (se o menor tiver discernimento deve <u>também</u> assinar em cima, se consentir)
NOME: …
BI/CD Nº: .... DATA OU VALIDADE ….. /..… /…....
GRAU DE PARENTESCO OU TIPO DE REPRESENTAÇÃO: ....
ASSINATURA …

ESTE DOCUMENTO É COMPOSTO DE 2 PÁGINAS E FEITO EM DUPLICADO:
UMA VIA PARA A INVESTIGADORA, OUTRA PARA A PESSOA QUE CONSENTE

COMISSÃO NACIONAL
DE PROTECÇÃO DE DADOS

Para:
Liliana Carina Pereira Baptista
Rua luís de Camões, 986
4525 – 404 Santa Maria de Lamas

N/Ref.
02.02
Proc. n.º 11407/2014
Of. n.º 964 2015-01-13

Assunto: Legalização de tratamento de dados pessoais.

No âmbito do processo em epígrafe, fica notificada V. Exª notificada para, nos termos e para os efeitos do disposto no art.º 100º do CPA se pronunciar, querendo, no prazo de dez dias, quanto ao Projeto de Autorização n.º 01/2015 apresentado na Sessão da CNPD de 13.01.2015, cuja cópia se anexa.

Com os melhores cumprimentos

A Secretária da CNPD

(Isabel Cristina Cruz)

MM

Rua de São Bento, 148-3º • 1200-821 LISBOA
Tel: 213 928 400 Fax: 213 976 832
www.cnpd.pt

21 393 00 39
LINHA PRIVACIDADE
Dias úteis das 10 às 13 h
duvidas@cnpd.pt

III. Conclusão

Em face do exposto, a CNPD propõe-se autorizar o tratamento de dados pessoais *supra* apreciado, nos termos do n.º 2 do artigo 7.º, da alínea a) do n.º 1 do artigo 28.º e do n.º 1 do artigo 30.º da LPD, com as condições e limites fixados na referida Deliberação n.º 227/2007, que se dão aqui por reproduzidos e que fundamentam esta decisão, consignando-se o seguinte:

Responsável pelo tratamento: Liliana Carina Pereira Baptista;
Finalidade: estudo "Consumo com Medicamentos, Exercício Físico e Qualidade de Vida em Idosos";
Categoria de Dados pessoais tratados: código do doente; idade; sexo; habilitações literárias; estados de humor; parâmetros antropométricos; parâmetros hemodinâmicos; consumo de medicamentos; aptidão física funcional; qualidade de vida.
Entidades a quem podem ser comunicados: Não há.
Formas de exercício do direito de acesso e retificação: Junto da responsável.
Interconexões de tratamentos: Não há.
Transferência de dados para países terceiros: Não há;
Prazo de conservação: o código do titular deve ser destruído um mês após o fim do estudo.

Notifique-se a requerente, nos termos do disposto no artigo 100.º do Código de Procedimento Administrativo, para, querendo, se pronunciar por escrito, no prazo de dez dias úteis.

Lisboa, 13 de janeiro de 2015

Luís Barroso (Relator)

Rua de São Bento, 148-3º • 1200-821 LISBOA
Tel: 213 928 400 Fax: 213 976 832
www.cnpd.pt

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agrupamento centros de saúde entre douro e vouga I Feira | Arouca

GOVERNO DE PORTUGAL | MINISTÉRIO DA SAÚDE

ARS NORTE Administração Regional de Saúde do Norte, I.P.

Projeto / Estudo n.º 2/2013

Data de Receção: 5 /11/13

PROJECTO DE INVESTIGAÇÃO

Identificação do(s) investigador(es) do estudo

Nome Completo: Liliana Carina Pereira Baptista

Contacto telefónico: 919650114

E.Mail: libaptista10@hotmail.com

Qualificação Académica: Mestrado

Funções que desempenha: Doutoranda
Instituição : Universidade de Coimbra

Designação do Estudo: Consumo com medicamentos, exercício físico e qualidade de vida na terceira idade

Área científica em que se enquadra o estudo: Saúde do Idoso?

Vigência do Estudo (Data de princípio e de fim): 1 de Junho de 2014 e 30 de Junho de 2016

Tipo de análise (quantitativa, qualitativa) Quantitativa.

Palavras – chave: Consumo com medicamentos; exercício físico; qualidade de vida na terceira idade.

Co-Investigador(es) (quando aplicável)

Nome(s) Completo(s):

OUTROS PROFISSIONAIS ENVOLVIDOS

(Exemplo: Orientador)

Nome(s) Completo(s):

Declaro assumir a liderança científica do projeto / estudo e as responsabilidades decorrentes da sua boa execução, bem como a dar feedback do estudo em causa e suas conclusões ao ACeS Grande Porto IV.

Data:

Assinatura:

Projeto / Estudo n.º ____/____

Data de Receção: ___/___/___

PARECER CONSELHO CLÍNICO E DE SAÚDE

Favorável ☒ **Não Favorável** ☐

Data:

Assinaturas:

Presidente do Conselho Clínico do Aces Feira/Arouca

DIRETOR EXECUTIVO

ACeS Entre Douro e Vouga I –

Nada a opor á sua realização.

ACES de Entre Douro e Vouga I - Feira/Arouca
A Directora Executiva

(Dra. Ana Prata)

Nota: Falta o compromisso do investigador no retorno do impacto do estudo