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THYROID STATUS OF FIBROMYALGIA PATIENTS AND ITS RELATIONSHIP WITH FEATURES OF THE DISEASE

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Thyroid status of fibromyalgia patients and its relationship with features of the disease.

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Summary

RESUMO

Introdução: A Fibromialgia é uma patologia caracterizada pela existência de dor musculo-esquelética crónica e generalizada. Encontra-se muitas vezes associada a outras queixas, tais como fadiga, alterações do sono e distúrbios do humor, nomeadamente depressão. Esta doença representa um grande impacto na vida dos doentes, causando morbilidade e incapacidade graves e a sua prevalência é de cerca de 3,6% na população em geral.

As hormonas tiroideias desempenham um papel importante no crescimento e na regulação do metabolismo basal e estudos prévios investigaram a sua possível relação com a fibromialgia e com alguns dos seus aspectos clínicos.

Objectivos: O objectivo do nosso estudo foi a avaliação da função tiroideia em pacientes com fibromialgia e sua comparação com controlos saudáveis. Visámos também investigar as potenciais relações entre os níveis destas hormonas e alguns dos domínios característicos da fibromialgia, nomeadamente impacto da doença, dor e sintomas depressivos.

Métodos: Num estudo transversal foram medidos os níveis de hormonas tiroideias em 21 pacientes com fibromialgia e nas suas irmãs saudáveis, que constituíram o grupo controlo. Foram medidos os níveis de TSH, T3 livre e T4 livre em amostras sanguíneas colhidas ao mesmo tempo para cada par: doente com fibromialgia/irmã saudável. Todas as participantes foram sujeitas a exame físico que incluiu medições antropométricas e avaliação do limiar de dor através de dolorimetria. As participantes responderam ainda a um curto inquérito demográfico, bem como à versão portuguesa dos inquéritos Fibromylagia Impact Questionnaire e Hospital Anxiety and Depression Scale.

Resultados: Relativamente à população estudada, a informação obtida indicou que ambos os grupos eram equivalentes para idade, medidas antropométricas e outros parâmetros sociodemográficos. A comparação da função tiroideia entre os grupos não revelou diferenças significativas no que diz respeito às médias dos valores de hormonas tiroideias. Além disto, a análise de uma possível correlação entre os níveis destas hormonas com o limiar de dor, resultados do FIQ e índices de depressão não revelou relações significativas entre estas variáveis.

Conclusões: A nossa investigação não mostrou quaisquer alterações significativas relativamente à função tiroideia das pacientes com fibromialgia quando comparadas com controlos saudáveis. Também não verificámos que os níveis de hormonas tiroideias influenciassem ou modelassem os indicadores dos aspectos clínicos de fibromialgia estudados.

Palavras-chave: fibromialgia, hormonas tiroideias, limiar de dor, depressão

ABSTRACT

Background: Fibromyalgia is a condition characterized by chronic generalized musculo-skeletal pain. It is often associated with other complaints, such as fatigue, sleep disturbances or mood disorders, namely depression. The disease has a great impact upon patients' lives, causing severe morbidity and impairment, and its prevalence is about 3,6% in the general population.

Thyroid hormones play an important role in human growth and in the regulation of basal metabolism and previous works have investigated their possible relationship with fibromyalgia and some of its clinical features.

Objectives: The aim of our study was to assess the thyroid function of fibromyalgia patients when compared to healthy controls. We also investigated possible correlations between the values of thyroid hormones and some of the typical domains of fibromyalgia, namely impact of disease, pain and depressive symptoms.

Methods: In a transversal study we measured the serum thyroid hormone levels of 21 patients with fibromyalgia and their healthy sisters who constituted the control group. Serum levels of TSH, free T3 and free T4 were measured from a fasting blood sample taken at the same time for each pair: fibromyalgia patient/healthy sister. All subjects underwent physical examination, which included anthropometric measurements and pain threshold evaluation by dolorimetry. The participants also answered a brief demographic questionnaire, as well as the Portuguese versions of the Fibromyalgia Impact Questionnaire and Hospital Anxiety and Depression Scale.

Results: Regarding the studied population, the data collected indicated both groups to be matched for age, anthropometric measures and sociodemographic parameters. The comparison of thyroid status between groups revealed no significant differences in the mean values of thyroid hormones. Furthermore the analysis of possible correlations of thyroid hormones levels with pain threshold, FIQ scores and depression scores demonstrated no significant associations between these variables.

Conclusions: Our investigation did not reveal any significant differences regarding thyroid function in fibromyalgia patients when compared to matched healthy controls. We also did not find any significant correlation between thyroid hormones levels and the fibromyalgia clinical features studied.

Keywords: fibromyalgia, thyroid hormones, pain threshold, depression

Introduction

Fibromyalgia (FM) is a common condition characterized by chronic generalized musculo-skeletal pain. It is defined, according to the 1990 American College of Rheumatology criteria, by the presence of widespread pain for at least 3 months as well as pain in 11 of 18 anatomically defined tender point sites on digital palpation [1]. FM patients often refer several other complaints, such as fatigue, sleep disturbances, cognitive dysfunction or mood disorders, namely depressive episodes [2-4]. Other disorders commonly associated with FM include irritable bowel syndrome and irritable bladder syndrome [2, 3, 5]. The condition has a great impact upon several domains of patients' lives leading to great suffering, morbidity and impairment of quality of life.

The estimated prevalence of FM in the general population in Portugal is about 3,6%, women being 6 to 8 times more frequently affected than men [6].

The pathophysiology of FM remains unclear. However, a number of potential mechanisms and factors have been described which could be involved in the development of the disease, ranging from genetic predisposition, neuroendocrine dysfunction, abnormal central processing of nociceptive pain (central sensitization) or psycho-social factors [2, 7-11].

In this paper we will focus on the neuroendocrine dimension of FM, namely in the possible role of thyroid hormones and its relationship with the disease.

The thyroid gland produces and secretes two major hormones: thyroxine and triiodothyronine, commonly designated as T4 and T3 respectively. They play an essential role in tissue differentiation, growth and greatly contribute to increase the metabolic rate of the body. Thyroid hormones (TH) synthesis and secretion are tightly regulated by a negative-

feedback system which involves the hypothalamus, pituitary and thyroid gland. The main regulator of TH release and secretion is TSH (from the anterior pituitary gland), which in turn is regulated by TRH from the hypothalamus. Both TRH and TSH secretion are also negatively regulated by TH levels. Furthermore, TH production is also directly connected to the levels of available iodine, an element needed for the synthesis of these molecules, since TH are iodothyronines, and the only iodine-containing hormones in vertebrates.

Circulating TH are almost entirely combined with several plasma proteins, mainly with thyroxin binding globulin, which transport them to the target tissues. Once in the target cells, the general action of TH is to activate nuclear transcription of a large number of genes, with effects in virtually all tissues. These range from stimulation of carbohydrate and fat metabolism, inotropic and chronotropic effects on cardiac function, sleep regulation, and muscle activity [12-15].

Some of the clinical findings in FM such as muscle pain and tenderness, fatigue and exhaustion, reduced exercise capacity or cold intolerance show remarkable similarities with the symptoms of thyroid dysfunction, particularly hypothyroidism [3, 15, 16].

Previous studies have reported disturbances in the production or utilization of TH and discussed the possible role of TH resistance in the development of FM [17-19]. Dynamic studies have shown a blunted response of TH following the administration of TRH in FM patients, while reporting no differences in baseline serum levels of TH [20, 21].

More recently other studies have shown an association between thyroid autoimmunity and the presence of FM, reporting higher prevalence of thyroid auto-antibodies in patients than in controls [22, 23].

The relationship of thyroid dysfunction and the presence of overt depression and depressive symptoms has also been long discussed, with various studies reporting lowered TH

levels in patients with depression. The use of TH as adjuvant treatment of patients with depressive symptoms has been shown to modulate the expression of these symptoms [24-26].

Thus, the aim of this paper is to characterize the thyroid function in FM patients when compared to their healthy sisters and to investigate a possible correlation between thyroid status and some aspects of FM, namely the impact of the disease in patients' lives, pain symptoms and the presence of depression.

Materials and Methods

Study population

In order to address the hypothesis described above we decided to study female patients with fibromyalgia paired with an unaffected sister.

Participants were drawn from a list of 712 patients with an established diagnosis of FM from a single site (all diagnosed and followed by Prof. J.A.P. da Silva). The following screening criteria were used for selection: Female gender, age between 18 and 55 years, absence of any other chronic pain condition, residence within a radius of 100 Km from the study centre. Selected patients were contacted by phone and invited to participate if 1. they had at least one unaffected sister, 2 the mother of both was the same person, still alive and capable of participating and providing reliable information, and 3. all the family members were willing to travel to the research site and participate in the study, which involved signing an informed consent, responding to questionnaires, providing a blood sample and undergoing physical examination. Participants were reimbursed for transportation costs but no other compensations were offered.

The study was approved by Ethical Committee of the Faculty of Medicine of the Universidade de Coimbra.

Interview and questionnaires

All research proceedings were performed in the morning. After receiving an explanation of the study procedures and having an opportunity to present any questions and discuss all issues, participants signed an informed consent form. This was followed by a fasting blood sample collection. Breakfast was offered to participants before the other procedures were started.

Serum was extracted by centrifugation at 5000 rpm for 10 minutes and stored frozen at -20ºC until analysis, which was performed less than a month after sample collection.

A brief custom demographic questionnaire was given to all participants, which recorded several features, such as age, marital status, country of birth, years of education, medication use and co-morbidities, amongst others.

To estimate the impact of FM and the overall effect of the disease's symptomatology, the validated Portuguese version of the "Fibromyalgia Impact Questionnaire" was used [27]. The FIQ is a self-administered instrument, taking approximately 3-5 minutes to complete, composed of 20 questions distributed by 10 items, the first one including 11 questions, which are answered either as Likert-type or visual analogical scales. The FIQ is scored in such a way that a higher score indicates a higher impact of the disease on the person. Each item has a maximum score of 10, so the total scores range from 0 (no impact) to 100 (maximum impact). The average fibromyalgia patient scores about 50, and severely afflicted patients are usually at 70 plus [28].

As for the screening of depression we made use of the validated Portuguese version of the "Hospital Anxiety and Depression Scale" [29]. The HADS is an instrument used to identify the presence of depression and anxiety disorders in nonpsychiatric patients within a

hospital setting. This instrument consists of 2 independent subscales which are scored separately, one measuring depression and the other measuring anxiety, each consisting of 7 items. Each item is answered by the patient on a 4-point (0 – 3) response category so the possible scores range from 0 to 21 for anxiety and 0 to 21 for depression. The authors recommended that a score of 8 or above in an independent scale would be regarded as a possible case and a score above 10 a probable case. Further works enabled a division of each mood state into 4 ranges: a score between 0 and 7 is "normal", between 8 and 10 "mild", between 11 and 14 "moderate" and between 15 and 21 "severe" and this is the form the HADS is now issued. [30-32].

Physical examination

Physical examination included the evaluation of subjects' weight and height and the correspondent body mass index calculation, as well as the characterization of pain sensitivity. Pressure pain threshold was evaluated in each participant using a pressure dolorimeter. With this instrument, pressure was applied gradually and the subject was instructed to say when the procedure became painful and not just tender. Pain threshold, established as the pressure at that point, in Kg/cm2, was determined in the following sites: midpoint of the sternal manubrium, and, bilaterally, at midtibia and nail bed of the forefinger. The pain threshold was calculated as the mean of 2 measurements.

Laboratory tests

Thyroid function was assessed by serum TSH, free T3 and free T4 levels. TSH and fT3 levels were measured by chemiluminescence immunoassay, Siemens reagent kit (ADVIA Centaur® XP). TSH levels are expressed in µIU/mL and fT3 levels in pg/mL. Free T4 levels were measured by enzyme-labeled chemiluminescente competitive immunoassay, Siemens reagent kit (IMMULITE® 2000 Systems Analyzers). Its levels are expressed in ng/dL. All laboratory tests were conducted in the Hormonology Laboratory of Hospitais da Universidade de Coimbra. The normal range values used as reference in this institution are as follows: TSH: 0,4 – 4,0 µIU/mL; free T3: 1,8 – 4,2 pg/mL; free T4: 0,8 – 1,9 ng/dL.

Statistical analysis

All the data was stored in a database created in Microsoft® Office Excel® 2010, and statistical analysis was carried out using PASW Statistics® 18.0.

The normality of the distribution was tested using Kolmogorov-Smirnov and Shapiro-Wilk tests, depending on whether we were analyzing the whole sample (N>30), or analyzing independent groups (N<30 in each group). Comparisons of means between groups were performed with Student's t-test and Mann-Whitney U test, when considering independent samples and paired t-tests or Wilcoxon signed ranks test for paired samples (depending on the normality of the distribution of each variable). Nominal variables were compared using χ^2 test or Fisher's exact test, depending on whether the number of subjects of each category was greater or lesser than 5. Correlations between variables were assessed using Spearman's rank correlation coefficient or Pearson product-moment correlation coefficient, depending on the

normality of the distribution of selected variables. The minimum significance level to reject null hypothesis, in all used statistic tests, was set to 0,05.

Paired samples were used when comparing FM features and mean TH levels between groups. For these, the pair FM patient/healthy sister was considered.

Results

Population

The screening criteria described above reduced the potential population to 317 individuals, which were contacted by phone. Of these, 278 were excluded for the following reasons: 121 did not have an unaffected sister, 27 their sister lived too far away to attend, 73 were already orphans or their mother was not capable of participating, 57 were not reachable through the phone. Of the remaining 38 families, satisfying inclusion criteria, 11 refused to participate and 6 never made themselves available to attend the research centre. This study was performed as a part of a larger project designated as ScanFM, involving other investigators.

Altogether, 22 families, composed of a FM patient, one unaffected sister and the mother of both were involved in the study. However, one of these families was excluded, since the sister presented a positive screening for FM, thus not fulfilling the criteria described above. Mothers were not involved in this specific study. So, our sample was composed of 42 participants: 21 FM patients and their unaffected sisters.

Their demographic characteristics are presented in table I.

Table I - Demographic data and clinical characteristics of the studied population.

		FM Group (n = 21)	Control Group (n = 21)	*p* value
Sex	Female	21 (100,0%)	21 (100,0%)	
Age (years)		40,86 ± 10,30	40,10 ± 10,27	0,821 *
Years of education (years)		12,62 ± 4,18	12,05 ± 5,36	0,702
Marital Status	Single	4 (19,0%)	7 (33,3%)	0,159 **
	Married	17 (81,0%)	12 (57,1%)	
	Divorced	0 (0%)	2 (9,5%)	
Weight (kg)		64,89 ± 7,41	66,86 ± 10,88	0,495
Height (m)		1,60 ± 0,06	1,60 ± 0,05	0,814
BMI (kg/m^2)		25,54 ± 2,98	26,25 ± 4,88	0,572
Previous thyroid disease	Not present	16 (76,2%)	18 (85,7%)	0,697 ***
	Present	5 (23,8%)	3 (14,3%)	
Medication with levothyroxine	Not present	16 (76,2%)	18 (85,7%)	0,697 ***
	Present	5 (23,8%)	3 (14,3%)	
Previous thyroid surgery	Not present	19 (90,5%)	19 (90,5%)	
	Present	2 (9,5%)	2 (9,5%)	

Results are expressed as mean ± SD or as number of individuals (percentage). Statistical analysis by Student's t-test, Mann-Whitney U test (*), Qui square test (**) or Fisher's exact test (***). BMI, Body Mass Index.

All the participants in this study were female. Mean age in the FM group was 40,86 ± 10,30 years old and in the control group was 40,10 ± 10,27. No statistically significant differences were found between the demographic features presented in table I.

FM Dimensions – Pain, impact of the disease and depressive symptoms

Table II – Comparison of pain threshold measurements, FIQ scores and HADS depression subscale scores in both groups.

	FM Group (n = 21)	Control Group (n = 21)	*p* value
Right tibia PT (kg/cm^2)	3,08 ± 1,94	4,82 ± 1,86	0,023
Left tibia PT (kg/cm^2)	2,94 ± 1,41	4,54 ± 1,62	0,005
Sternal manubrium PT (kg/cm^2)	1,91 ± 1,46	3,16 ± 1,21	0,011
Right nail bed PT (kg/cm^2)	3,16 ± 1,61	4,91 ± 2,03	0,015
Left nail bed PT (kg/cm^2)	3,09 ± 2,07	4,87 ± 1,91	0,017
FIQ	49,62 ± 13,23	18,56 ± 14,75	0,000
HADS - D	7,90 ± 4,27	4,10 ± 2,90	0,006 *

Results are shown as mean ± SD. Statistical analysis performed with Wilcoxon signed ranks test for paired samples and Student's t test for paired samples (*). PT, pain threshold; FIQ, fibromyalgia impact questionnaire score; HADS-D, HADS depression subscale score. Report to the methods section for information on the questionnaires.

Accordingly to our expectations, subjects with FM described pain with lower pressure levels than their matched controls in every site evaluated. The differences are shown to be statistically significant for all sites, according to the Wilcoxon signed ranks test. FM patients also show statistically significant higher values of the FIQ score and depression subscale score.

Figure 1 - Comparison of PT measurements in both groups.

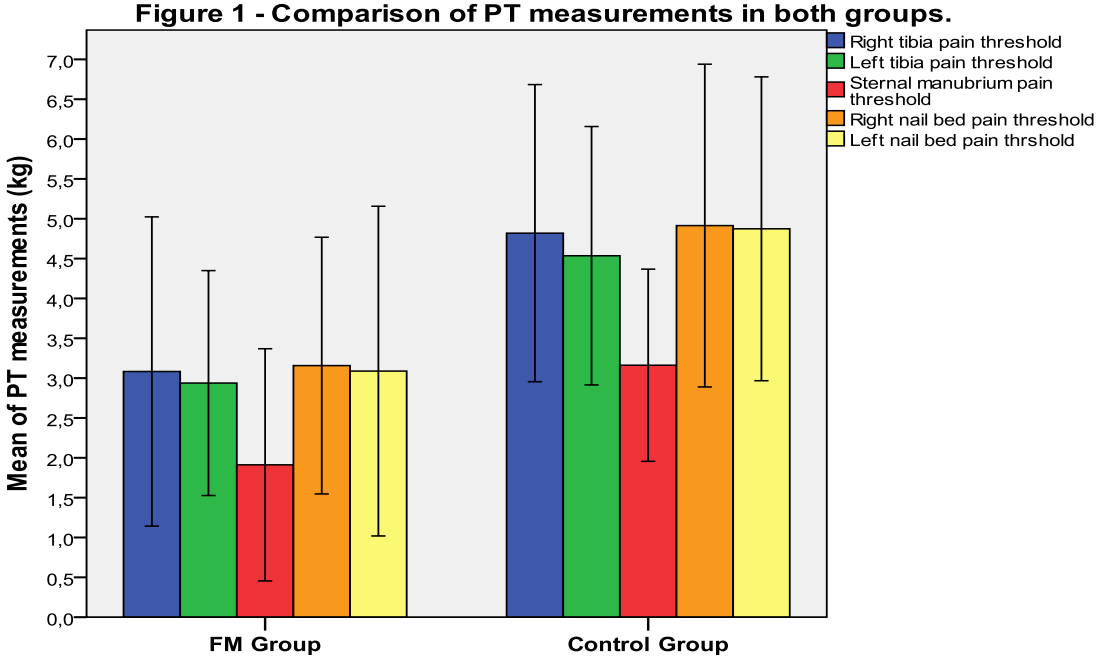


Figure 2 - Comparison of FIQ scores between both groups

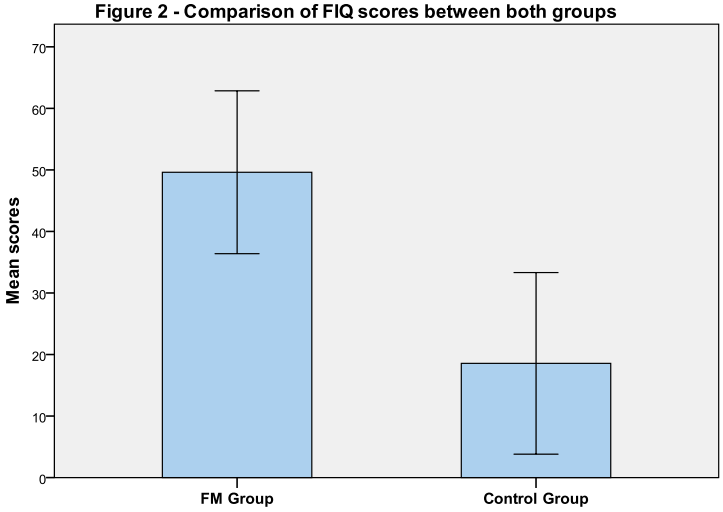
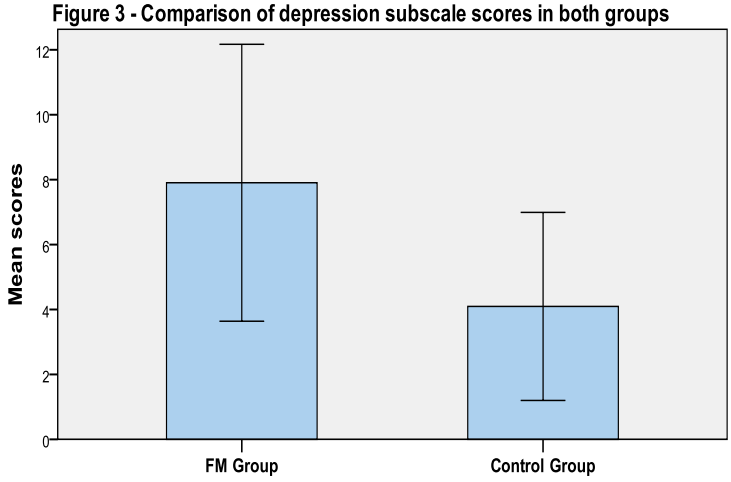


Figure 3 - Comparison of depression subscale scores in both groups



Thyroid status

Table III – Comparison of TH levels between both groups.

	FM Group (n = 21)	Control Group (n = 21)	*p* value
TSH (µIU/mL)	2,05 ± 0,89	1,89 ± 1,42	0,478
Free T3 (pg/mL)	3,27 ± 0,31	3,30 ± 0,46	0,746
Free T4 (ng/dL)	1,11 ± 0,19	1,13 ± 0,36	0,500

Results are expressed as mean ± SD. Statistical analysis with Wilcoxon signed ranks test for paired samples. TH, thyroid hormones.

Concerning the comparison of thyroid function status of FM patients when compared to their healthy family and gender-matched controls, and as shown in table III, no statistically significant differences were found between the groups.

As described above in the demographic characterization of the studied population, some of the participants reported a history of thyroid disease, medication with levothyroxine and/or previous thyroid surgery. As such, and trying to eliminate possible confounding factors of this analysis we proceeded to the same comparison only in participants with an absence of those 3 factors. The results are presented below in table IV. Yet again, no statistically significant differences were found between TH levels of both groups.

Table IV - TH levels comparison between both groups excluding subjects with previous thyroid disease, medication with levothyroxine and/or previous thyroid surgery

	FM Group (n = 16)	Control Group (n = 17)	*p* value
TSH (µIU/mL)	2,09 ± 0,93	1,65 ± 0,93	0,149
Free T3 (pg/mL)	3,33 ± 0,33	3,29 ± 0,33	0,537
Free T4 (ng/dL)	1,11 ± 0,19	1,06 ± 0,13	0,348

Results are expressed as mean ± SD. Statistical analysis made with Mann-Whitney U test. TH, thyroid hormones.

Thyroid hormone levels and FM clinical features

Table V - Correlation between TH levels and selected variables in the studied population (n = 42)

		TSH	Free T3	Free T4
Right tibia PT	***rho***	- 0,03	- 0,09	0,12
	***p* value**	0,83	0,58	0,45
Left tibia PT	***rho***	- 0,12	0,04	0,11
	***p* value**	0,47	0,79	0,49
Sternal manubrium PT	***r(*)/rho***	0,03*	- 0,19	0,07
	***p* value**	0,85	0,21	0,67
Right nail bed PT	***r(*)/rho***	0,04*	- 0,12	0,13
	***p* value**	0,79	0,43	0,43
Left nail bed PT	***r(*)/rho***	- 0,01*	- 0,29	0,00
	***p* value**	0,94	0,06	0,99
FIQ	***rho***	0,17	0,00	0,00
	***p* value**	0,29	0,98	0,99
HADS - D	***r(*)/rho***	- 0,04*	0,05	0,23
	***p* value**	0,82	0,76	0,14

Spearman's rank correlation coefficient (rho) or Pearson product-moment correlation coefficient (r) between TH and pain threshold, FIQ scores and depression subscale scores. TH, thyroid hormones; PT, pain threshold; FIQ, fibromyalgia impact questionnaire score; HADS – D, depression subscale of the HADS questionnaire. Refer to the methods section for information on the questionnaires.

According to the values shown in the table above, no significant correlation was found between the levels of TH and pain threshold measurements, FIQ scores or depression subscale scores. This correlation was tested considering the whole studied sample, ie, without excluding those with previous thyroid disease.

A similar analysis was made but considering both groups, FM patients and healthy sisters, separately. Again, no statistically significant correlation was evidenced , between the levels of TH and the clinical features considered. The results of the later are shown below in table VI.

Relatively to TH levels and depression we also compared the levels of these hormones but separating individuals considering whether or not they presented a positive screening for depression (HADS – D score of 8 or above). Considering depressed individual vs non depressed, the mean levels of TSH (1,77 ± 1,01 vs 2,06 ± 1,25), free T3 (3,27 ± 0,32 vs 3,29 ± 0,42) and free T4 (1,11 ± 0,15 vs 1,13 ± 0,33) still did not show any statistically significant differences between both groups.

Table VI - Correlation between TH levels and selected variables in both groups.

		FM Group (n = 21)			Control Group (n = 21)		
		TSH	**Free T3**	**Free T4**	**TSH**	**Free T3**	**Free T4**
Right tibia PT	***r(*)/rho***	0,18*	-0,07*	0,28*	- 0,10	- 0,02	0,16
	***p* value**	0,44	0,77	0,22	0,66	0,95	0,48
Left tibia PT	***r(*)/rho***	0,13*	-0,02*	0,27*	- 0,04	0,27	0,26
	***p* value**	0,58	0,95	0,24	0,86	0,24	0,25
Sternal manubrium PT	***r(*)/rho***	0,32*	-0,03*	0,16*	- 0,19	- 0,23	0,13
	***p* value**	0,15	0,89	0,48	0,40	0,31	0,58
Right nail bed PT	***r(*)/rho***	0,15*	0,03*	0,05*	- 0,05	- 0,13	0,41
	***p* value**	0,52	0,89	0,84	0,84	0,59	0,07
Left nail bed PT	***r(*)/rho***	- 0,12	- 0,18	0,04	0,12	- 0,27	0,20
	***p* value**	0,61	0,43	0,86	0,62	0,25	0,38
FIQ	***r(*)/rho***	-0,12*	0,17*	-0,24*	0,23	- 0,38	- 0,19
	***p* value**	0,61	0,45	0,30	0,32	0,09	0,42
HADS - D	***r(*)/rho***	-0,19*	0,26*	0,14*	0,15	- 0,11	0,16
	***p* value**	0,40	0,26	0,56	0,53	0,65	0,49

Spearman's rank correlation coefficient (rho) or Pearson product-moment correlation coefficient (r) between TH and pain threshold, FIQ scores and depression subscale scores in both groups. TH, thyroid hormones; PT, pain threshold; FIQ, fibromyalgia impact questionnaire score; HADS – D, depression subscale of the HADS questionnaire. Refer to the methods section for information on the questionnaires.

Discussion

Is thyroid function impaired in FM patients?

As for the first objective of this paper, the characterization of thyroid status in FM patients as compared to their healthy sisters, we found no significant differences between both groups, as shown in table III. Mean values of TSH, fT3 and fT4 were similar in both groups and within the normal reference values used in Hospitais da Universidade de Coimbra, as described in Methods. Previous studies have reported similar findings, although in slightly different settings [17, 20, 22].

Neeck, G. and W. Riedel in 1992 described normal TH levels in a sample of FM patients when compared to healthy controls, however the study was performed in a smaller sample and the criteria considered to establish a diagnosis of FM were different than the ones accepted today. The authors also reported a diminished TSH response following a systemic injection of TRH in FM patients compared to the control group, as well as lower levels of fT3 and fT4 in the patients group during the same stimulation test [20]. Our study cannot assert about this aspect, as dynamic approaches to investigate thyroid function were not included.

Lowe, J.C., et al., in 2006 conducted a study designed to characterize the resting metabolic rates of FM patients when compared to healthy controls and their relationship with FM measures. That study was based on the assumption that one of the underlying mechanisms in FM pathophysiology was thyroid dysregulation, either hypothyroidism or peripheral resistance to thyroid hormone. The authors postulated that if this was the case, these changes would have repercussions on the metabolic rates of subjects affected, as seen in many cases of hypothyroidism and resistance to thyroid hormones. The study found TH levels

to be similar between groups, and have no correlation with the measured or predicted resting metabolic rates of the participants [17].

More recently, Bazzichi, L., et al in 2007 also reported on the thyroid status of FM patients when compared to a healthy control group, while studying the association between thyroid autoimmunity and FM. The authors found the mean basal TH values to be within the normal range in both groups considered. However in that study, no results are presented referring to statistical differences between the mean levels of one group versus the other, nor do they specify the normal reference range employed [22].

We believe that, relatively to the characterization of thyroid status in patients with FM, our study primed for the use of an adequate control group. By using patients and controls from the same family we tried to diminish possible differences in sociodemographic aspects such as professional activity, geographic area, education levels, food habits, genetic influences and others in hope that possible differences we found would be more related to FM. In fact, the comparison of the demographic data of both patients and controls showed that the groups were matched in age and anthropometric parameters. Taken together, these facts enabled us to make statistical comparisons of TH levels considering paired samples, which could strengthen the significance of a possible association between variables since the test is less confounded by the within-sample variability. However, as stated above no significant differences were found in thyroid status of the FM group when compared to the healthy controls.

We repeated the comparison of TH values in the FM group and in the control group, but this time including only subjects with no register of previous thyroid disease, medication with levothyroxine or any kind of thyroid surgery. Yet again, no statistically significant differences were found. As for these aspects, and according to the data presented in the demographic table, although the presence of antecedents of thyroid disease and the use of therapeutical

levothyroxine was slightly more frequent in the FM group, the statistical analysis showed that these differences were not significant.

Considering the facts and results outlined above can we securely rule out the existence of any kind of dysfunction in the thyroid axis related to FM? We believe that although the basal values of TH were found to be in the normal range and no difference was highlighted between both groups, the presence of inadequate mechanisms and dysregulations involving thyroid hormones can still be present in patients with FM. Some works have raised the hypothesis that FM could, in some cases, be related to thyroid hormone resistance, more specifically with peripheral thyroid hormone resistance in euthyroid FM patients [18, 19]. Our study cannot rule out such an hypothesis

Furthermore, other studies have reported an association between thyroid autoimmunity and FM [22, 23, 33]. Each of these studies has found a significantly higher prevalence of thyroid antibodies in patients with FM when compared to healthy controls. Soy, M., et al., in 2007, when conducting a study to evaluate the frequency of rheumatic conditions amongst patients with autoimmune thyroid diseases reported that in the sample of patients with thyroid immunity considered, 31% met the ACR criteria for the diagnosis of FM [34].

Are TH levels related to FM severity?

Despite our findings relatively to the thyroid status of the studied population we decided to cross the values of TH with the FIQ scores and with the measurements of pain threshold to investigate whether or not different levels of these hormones could modulate the impact of FM in patients' lives or their pain symptoms.

As expected, FM patients presented significantly higher FIQ scores when compared to the control group (49,62 ± 13,23 vs 18,56 ± 14,75) and expressed pain when exposed to significantly lower levels of pressure in every site tested. This is in agreement with the general profile of FM and corroborates the design of our paper concerning the subjects studied.

The correlation between TSH, fT3 and fT4 levels and the mean measurements of the pain threshold in each site observed did not show any significant associations as shown in table V and VI. This correlation was analyzed both in the whole population studied as well as separately in each group. This is in sharp contrast with Lowe, J.C., et al., in 2006, in the same study outlined above, who reported that TSH levels accounted for 29% of the variability in pain area distribution and fT3 levels accounted for 30% of the variability in pressure-pain threshold in FM patients, both statistically significant ($p < 0.05$). Relatively to these findings, the author of that study suggested that low fT3 concentrations in nociceptive afferent neurons led to impaired inhibition of substance P synthesis and secretion. This would lead to higher concentrations of this neuropeptide and its augmentation of nociceptive signals[17]. To our knowledge there are no other studies comparable to ours, investigating if differences in TH levels are associated with variations in values of pressure necessary to induce pain.

As to impact of FM, the correlation tests we used found no significant association between the levels of TH and the scores of FIQ. Again we investigated a possible correlation either in the whole sample ($n = 42$) as well as in both groups separately.

What about TH and depression?

The association between depression and FM has long been discussed, with the two conditions presenting overlapping aspects and depressive episodes and symptoms being important comorbidities of FM [11, 35].

On the other hand, the relationship between thyroid dysfunction and depression has also been described in previous works [36]. The reported alterations of thyroid status amongst depressed patients, however, are not concordant.

Brouwer, J.P., et al., in 2005, when investigating thyroid and adrenal function in patients with major depressive disorder compared with sex and age matched controls reported findings of elevated TSH levels in depressed patients [37].

Stipcevic, T., et al., in 2008 also compared the thyroid activity of depressed patients when compared to healthy controls, having reported significantly lower T3 and TSH levels in the depressed patients group comparatively with the control group [25].

Furthermore thyroid hormones, particularly T3 but also T4, have been shown to potentiate the therapeutical effects of other anti-depressants [38, 39]. Aronson, R., et al., in a meta-analysis of controlled clinical trials of triiodothyronine augmentation in euthyroid patients with refractory depression reported that patients treated with triiodothyronine augmentation were twice as likely to respond as controls, corresponding to a 23.2% absolute improvement in response rates.

In our study, patients with FM presented significantly higher scores in the depression subscale of the HADS questionnaire when compared to their healthy sisters (7,90 ± 4,27 vs 4,10 ± 2,90; p = 0,006), as was expected.

However, when we tested for a correlation between the levels of thyroid hormones and the scores of the depression subscale of the HADS questionnaire, we found no evidence of significant associations neither considering the whole sample (n = 42) nor both groups separately, as shown in table V and VI. We also analyzed the mean values of TH but this time separating the subjects based on whether the HADS-depression scores presented a positive screening for depression or not. However no statistically significant differences were found between the group of patients with depression and the ones without the condition. In order to conduct this analysis we considered a cutoff value of 8 or higher in the depression subscale of the HADS questionnaire as positive for the screening of depression. According to the authors of this scale a score above 8 indicates the presence of some degree of depression, either mild, moderate or severe [31, 32].

The fact that our results showed no significant correlations or differences between subjects may be related to the fact that we did not control for other variables which could confound the analysis of the relationship between TH and depression, namely the use of medication or antecedents of psychiatric disease, for example.

Limitations and conclusions

Our study was not without limitations. First and foremost, the rigorous screening criteria applied in the design of our work resulted in a rather small sample of subjects which may have had repercussions in the strength of the statistical tests run during the analysis of our results.

Relatively to the specific objectives of this paper, another limitation was the fact that we did not establish records of previous thyroid disease as an exclusion criteria for the selection of the subjects, which could prove to be an important confounding factor in some of the

analysis. This was mainly due to the fact that, the already extremely difficult recruitment of families meeting the criteria mentioned above (in order to get the data needed for all the researchers of this project), would otherwise prove to be unattainable if this factor was included. The same could be said about the use of medication and the control for substances which could affect thyroid function. On the other hand, as a positive factor, regardless of a positive history of thyroid disease or use of exogenous levothyroxine, the serum analysis we conducted (TSH, free T4 and free T3 levels) provide, to our knowledge, reliable information on the thyroid function at the time of the collection. As such the correlation tests between TH levels and FM features should not have suffered the confounding effects of these factors.

Another of the limitations of our investigation was the fact that the data gathered during our study was collected by different people, which may have led to increased measurement variability inherent to the heterogeneity of observers, namely when reporting to physical examination. In order to try to counter this issue a strict protocol was established and followed in every interview.

In conclusion, as to thyroid status of FM patients when compared to healthy controls, no significant differences were highlighted during our work. Relatively to the correlation between thyroid hormones and the clinical features of FM, no significant association was found between the levels of these hormones and the measurements of pain threshold, FIQ scores or depression scores.

Despite this fact, various thyroid abnormalities have already been described and raised as possibilities in patients with FM. Considering this and the overlapping symptoms of FM and thyroid dysfunction, and in face of the still obscure patophysiology mechanisms of the disease, we believe that further studies are necessary in order to clarify the association between the thyroid axis and FM, such as prospective studies focused on the outcomes on FM clinical features following the modulation of the thyroid axis function.

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Appendix

Appendix 1 – Sociodemographic questionnaire

INQUÉRITO DEMOGRÁFICO

Data: ____/____/_____

Nº: 00 A

Iniciais do nome (1,2 e última): _____

Data de nascimento: _____/___/___

Nacionalidade: _____

Residiu no estrangeiro até aos 18 anos? _____

Desde que idade: _____ anos. Regressou aos: _____ anos.

Número de irmãos: _____

Posição na fratria: _____ (do mais velho para o mais novo)

Sexo dos irmãos (F-feminino, M-masculino): ___; ___; ___; ___; ___; ___; ___; ___

(do mais velho para o mais novo)

Tem filhos? Sim ☐ Não ☐

Nº total de filhos vivos: ____ Abortos espontâneos: _____ Abortos Provocados: ____

Filhos falecidos: ____

1.: idade à data da morte: ____ Ano da morte: _____

2.: idade à data da morte: ____ Ano da morte: _____

3.: idade à data da morte: ____ Ano da morte: _____

Pai: vivo ☐ separado ☐ Ano: _____ Falecido ☐ Ano: _____

Estado civil: _____

Profissão:

Por conta própria ☐ Por conta de outrem ☐

Desempregada ☐ Reformada ☐ Com que idade? _____ anos

Anos de educação formal: _____ Concluídos em: ____ anos

Critérios de Fibromialgia: Sim ☐ Não ☐

Data de início dos sintomas (mês e ano): ____/_____

Data em que primeiro procurou cuidados médicos por esses sintomas (mês e ano): ____/_____

Data do diagnostico (mês e ano): ____/_____

Que tratamentos faz actualmente para a Fibromialgia? (fármacos e outros)

_____
_____
_____
_____
_____
_____

Se tem outras doenças, indique quais:

_____
_____
_____
_____

Que tratamentos faz para estas doenças?

_____
_____
_____
_____

Se já fez cirurgias, indique quais, e o ano da cirurgia:

_____
_____
_____
_____

Quem foi, para si, a principal figura maternal durante a sua infância, até aos sete anos?

_____

Appendix 2 – Physical Examination

EXAME FÍSICO

Peso: _____ kg Altura: _____ m IMC: _____ kg/m^2

Nº de pontos dolorosos: ____

Limiar de dor:		**A**	**B**	**Média**
a. Ponto médio da tíbia:	Dta:	_____Kg	_____Kg	_____Kg
	Esq:	_____Kg	_____Kg	_____Kg
b. Ponto médio do manúbrio esternal:		_____Kg	_____Kg	_____Kg
c. Leito ungueal do indicador:	Dta:	_____Kg	_____Kg	_____Kg
	Esq:	_____Kg	_____Kg	_____Kg

Massa gorda:

a. Perímetro abdominal:

(na linha que passa nas cristas ilíacas, numa expiração normal)

A	**B**	**C**	**Média**
_____cm	_____cm	_____ cm	_____ cm

b. Perímetro do braço:

A	**B**	**C**	**Média**
_____cm	_____cm	_____ cm	_____ cm

c. Perímetro da coxa:

A	**B**	**C**	**Média**
_____cm	_____cm	_____ cm	_____ cm

d. Prega bicipital:

(medida três vezes no braço não dominante)

A	**B**	**C**	**Média**
_____mm	_____mm	_____ mm	_____ mm

e. Prega tricipital:

(medida três vezes no braço não dominante)

A	**B**	**C**	**Média**
_____mm	_____mm	_____ mm	_____ mm

f. Prega subescapular:

(medida três vezes no braço não dominante)

A	**B**	**C**	**Média**
_____mm	_____mm	_____ mm	_____ mm

g. Prega da coxa:

A	**B**	**C**	**Média**
_____mm	_____mm	_____ mm	_____ mm

h. Bio-impedância

Appendix 3 – Fibromyalgia Impact Questionnaire (Versão Portuguesa) – FIQ-P

FIBROMYALGIA IMPACT QUESTIONNAIRE
(VERSÃO PORTUGUESA) – FIQ-P

INSTRUÇÕES: Nas perguntas 1 a 11 por favor faça um círculo no número que, em relação à **última semana**, melhor descreve a maneira como, **em geral**, foi capaz de executar as tarefas indicadas. Se habitualmente não faz uma dessas tarefas risque essa pergunta.

	Sempre	Quase Sempre	Quase nunca	Nunca
Foi capaz de:				
1. Ir às compras?	0	1	2	3
2. Tratar da roupa na máquina de lavar / secar?	0	1	2	3
3. Cozinhar?	0	1	2	3
4. Lavar louça à mão?	0	1	2	3
5. Aspirar a casa?	0	1	2	3
6. Fazer as camas?	0	1	2	3
7. Andar vários quarteirões (200 a 500 metros)?	0	1	2	3
8. Visitar a família ou os amigos?	0	1	2	3
9. Tratar das plantas ou praticar o seu passatempo?	0	1	2	3
10. Se deslocar, no seu próprio carro ou em transportes públicos?	0	1	2	3
11. Subir as escadas?	0	1	2	3

12. Na última semana, em quantos dias se sentiu bem?

0	1	2	3	4	5	6	7

13. Na última semana, quantos dias faltou ao trabalho e/ou não realizou as tarefas domésticas, devido à fibromialgia?

0	1	2	3	4	5	6	7

INSTRUÇÕES: Nas perguntas que se seguem, assinale um ponto na linha que melhor indica o modo como, **em geral**, se sentiu na **última semana**.

14. Nos dias que trabalhou, quanto é que a sua doença – Fibromialgia - interferiu no seu trabalho?

Trabalhei sem problemas •___|___|___|___|___|___|___|___|___|___• Tive grande dificuldade no trabalho

15. Que intensidade teve a sua dor?

Não tive dor •___|___|___|___|___|___|___|___|___|___• Tive dor muito intensa

16. Que cansaço sentiu?

Não senti cansaço •___|___|___|___|___|___|___|___|___|___• Senti um cansaço enorme

17. Como se sentiu quando se levantava de manhã?

Acordei bem repousada •___|___|___|___|___|___|___|___|___|___• Acordei muito cansada

18. Que rigidez sentiu?

Não tive rigidez •___|___|___|___|___|___|___|___|___|___• Senti muita rigidez

19. Sentiu-se nervosa ou ansiosa?

Não tive ansiedade •___|___|___|___|___|___|___|___|___|___• Senti-me muito ansiosa

20. Sentiu-se triste ou deprimida?

Não me senti deprimida •___|___|___|___|___|___|___|___|___|___• Senti-me muito deprimida

Appendix 4 – Hospital Anxiety and Depression Scale (versão portuguesa)

Este questionário foi concebido para ajudar a saber como se sente. Pedimos-lhe que leia cada uma das perguntas e faça uma cruz (X) no espaço anterior à resposta que melhor descreve a forma como se tem sentido na última semana.

Não demore muito tempo a pensar nas respostas. A sua reacção imediata a cada questão será provavelmente mais correcta do que uma resposta muito ponderada.
Por favor, faça apenas uma cruz em cada pergunta.

1. Sinto-me tenso/a ou nervoso/a: ___ Quase sempre ___ Muitas vezes ___ Por vezes ___ Nunca	**8. Sinto-me mais lento/a, como se fizesse as coisas mais devagar:** ___ Quase sempre ___ Muitas vezes ___ Por vezes ___ Nunca
2. Ainda sinto prazer nas coisas de que costumava gostar: ___ Tanto como antes ___ Não tanto agora ___ Só um pouco ___ Quase nada	**9. Fico de tal forma apreensivo/a (com medo), que até sinto um aperto no estômago:** ___ Nunca ___ Por vezes ___ Muitas vezes ___ Quase sempre
3. Tenho uma sensação de medo, como se algo terrível estivesse para acontecer: ___ Sim e muito forte ___ Sim, mas não muito forte ___ Um pouco, mas não me aflige ___ De modo algum	**10. Perdi o interesse em cuidar do meu aspecto físico** ___ Completamente ___ Não tenho o cuidado que devia ___ Talvez cuide menos do que antes ___ Tenho o mesmo interesse de sempre
4. Sou capaz de rir e de ver o lado divertido das coisas: ___ Tanto como antes ___ Não tanto como antes ___ Muitos menos agora ___ Nunca	**11. Sinto-me de tal forma inquieto/a que não consigo estar parado/a** ___ Muito ___ Bastante ___ Não muito ___ Nada
5. Tenho a cabeça cheia de preocupações ___ A maior parte do tempo ___ Muitas vezes ___ Por vezes ___ Quase nunca	**12. Penso com prazer nas coisas que podem acontecer no futuro:** ___ Tanto como antes ___ Não tanto como antes ___ Bastante menos agora ___ Quase nunca
6. Sinto-me animado/a ___ Nunca ___ Poucas vezes ___ De vez em quando ___ Quase sempre	**13. De repente tenho sensações de pânico** ___ Muitas vezes ___ Bastantes vezes ___ Por vezes ___ Nunca
7. Sou capaz de estar descontraidamente sentado/a e sentir-me relaxado/a: ___ Quase sempre ___ Muitas vezes ___ Por vezes ___ Nunca	**14. Sou capaz de apreciar um bom livro ou um bom programa de rádio ou televisão:** ___ Muitas vezes ___ De vez em quando ___ Poucas vezes ___ Quase nunca