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EFFECTS OF ACUPUNCTURE ON THE PAIN AND FUNCTION OF THE HANDS OF SELECTED PATIENTS WITH RHEUMATOID ARTHRITIS

Julho de 2020

Doutoramento em Ciências da Saúde

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ON THE PAIN AND FUNCTION OF THE HANDS OF
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ARTHRITIS

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Tese no âmbito do doutoramento em Ciências da Saúde, no ramo Enfermagem, orientada pelos Professores Doutores Henry Johannes Greten e António Silvério Cabrita, apresentada à Faculdade de Medicina da Universidade de Coimbra.

Julho de 2020

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SERENDIPITY

Publications

The present study was mostly based on work that has been published or submitted for publication in international peer-reviewed journals, posters and oral-communications presented at national and international meetings, with relevance or relation to the published abstracts, as follows:

PUBLICATIONS IN INTERNATIONAL PEER-REVIEWED JOURNALS:

- Seca S, Kirch S, Cabrita AS, Greten HJ. **Evaluation of the effect of acupuncture on hand pain, functional deficits and health-related quality of life in patients with rheumatoid arthritis--A study protocol for a multicenter, double-blind, randomized clinical trial.** Journal of Integrative Medicine. 2016. 14(3):219-27. Doi:10.1016/S2095-4964(16)60254-6. PMID: 27181129

- Seca S, Miranda D, Cardoso D, Greten HJ, Cabrita A, Rodrigues MA. **The effectiveness of acupuncture on pain, physical function and health-related quality of life in patients with Rheumatoid Arthritis: a systematic review protocol.** JBI Database of Systematic Reviews and Implementation Reports. 2016. 14(5):18-26. Doi:10.11124/JBISRIR-2016-002543

- Seca S, Miranda D, Cardoso D, Nogueira B, Greten HJ, Cabrita A, Rodrigues MA. **The effectiveness of acupuncture on pain, physical function and health-related quality of life in patients with Rheumatoid Arthritis: a systematic review of quantitative evidence.** Chinese Journal of Integrative Medicine. 2019. 25 (9): 704-709. Doi:https://doi.org/10.1007/s11655-018-2914-x

- Seca S, Miranda D, Patrício M, et al. **New Pressure Algometry Device for the Quantification of Acupuncture Induced Pain Relief.** Journal of Alternative and Complementar Integrative Medicine. 2017. 3: 019. Doi: 10.24966/ACIM-7562/100019

- Seca S, Franconi G. **Understanding Chinese Medicine patterns of Rheumatoid Arthritis and related biomarkers.** Medicines. 2018. 5 (17). Doi: 10.3390/medicines5010017

- Seca S. Seca S, Patricio M, Kirch S, Franconi G, Cabrita AS, Greten HJ. **Chinese Medicine functional diagnosis: an integrative insight to understand Rheumatoid Arthritis of the hand.** European Journal of Integrative Medicine. 2018. 2:10-15. Doi:org/10.1016/j.eujim.2018.07.005

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ORAL-COMMUNICATIONS:

- Seca, S. **Homogenization of patient samples by Chinese diagnosis as an inclusion criterion.** DCFG-TCM Congress - 8th International Workshop on Traditional Chinese Medicine. "TCM in Science – Science in TCM". 03-05 October 2014 Porto, Portugal

- Seca S. et al. **Effects of Acupuncture on Rheumatoid Arthritis of the Hand - A double-blind controlled, prospective, randomized controlled trial.** Society for Acupuncture Research 2017 Conference. Advancing the Precision Medicine Initiative through Acupuncture Research. 27-29 April 2017. San Francisco, CA, USA

- Seca S. et al. **Specific effects of acupuncture on rheumatoid arthritis of the hand-double-blind, randomized clinical trial.** 2nd International Conference on Autoimmunity. 6-7 November 2017, Frankfurt Germany. Doi:10.4172/2155-9899-C1-043

- Seca S. et al. **Effects of Acupuncture on Rheumatoid Arthritis of the Hand.** DGF-TCM Congress - 10th International Workshop on TCM. "TCM in Science – Science in TCM". 20–22 April 2018, Porto, Portugal

POSTERS

- Seca et al. **Efficacy of Acupuncture on Rheumatoid Arthritis of the Hand - prospective double-blind RCT.** XXV Jornadas Internacionais do Instituto Português de Reumatologia. 23-24 November, 2017, Lisboa, Portugal

- Seca et al. **Efficacy of Acupuncture on Rheumatoid Arthritis of the Hand - results of the first prospective double-blind RCT.** DGF-TCM Congress - 10th International Workshop on TCM. "TCM in Science – Science in TCM". 20–22 April 2018, Porto, Portugal

- Seca et al. **New Pressure Algometry Device for the Quantification of Acupuncture Induced Pain Relief.** DGF-TCM Congress - 10th International Workshop on TCM. "TCM in Science – Science in TCM". 20–22 April 2018, Porto, Portugal

- Seca et al. **The effectiveness of acupuncture on pain, physical function and health-related quality of life in patients with Rheumatoid Arthritis: a systematic review of quantitative evidence.** DGF-TCM Congress - 10th International Workshop on TCM. "TCM in Science – Science in TCM". 20–22 April 2018, Porto, Portugal

- Seca S, Franconi G. **Understanding Chinese Medicine patterns of Rheumatoid Arthritis and related biomarkers – review.** DGF-TCM Congress - 10th International Workshop on TCM. "TCM in Science – Science in TCM". 20–22 April 2018, Porto, Portugal

Acknowledgements

Abstract

Rheumatoid arthritis (RA) is the most common chronic inflammatory autoimmune arthritis characterized by persistent synovitis and destructive and symmetrical polyarthritis of the small and large joints. The development of the disease is associated with an increased risk of organ failure, persistent pain, progressive disability and reduced quality of life (QoL) as well as high social-economic impact on the individuals and on the health care system.

Although the course of RA has greatly improved in the last years, there is no cure and the drugs used to reduce inflammation and to slow down the progression of joint damage carry some notable side effects, ranging from an irritated stomach, to liver damage or an increased susceptibility to serious infections. Women who wish to become pregnant and/or breastfeed often need to modify their medications to optimise the health of their baby.

Given the fact of the expanding awareness of unwanted side effects of pharmaceutical treatment, there has been an increased utilization of acupuncture which has been reported as a kind of safe management. Evidence suggests that acupuncture interventions may have a positive effect on pain relief, physical function and QoL in RA patients. However, due to the heterogeneity and methodologic limitations of the randomized clinical trials, ineffective allocation of acupoints, lack of double blinding and quantification of its effects, evidence is not strong enough to produce a good practice guideline.

Acupuncture has its roots in the most significant component of complementary and alternative medicine, Chinese Medicine (CM).

RA patients may be divided into different CM syndromes wich different biomarkers, molecular signatures and, as such, with different reactions to certain treatments. That is why acupuncture treatments should be designed with acupoints corresponding to the CM syndrome differentiation.

We aimed to assess acupuncture effects in the pain and function of the hands of selected patients with RA based on clear allocation criteria of acupoints, objective and valid assessment of effects and, for the first time, with randomized, double-blinded controls.

Several methodologies, applying the CONSORT guidelines, were used to strengthen the evidence base on acupuncture treatment and to understand its specific effects.

First, in order to clearly quantify the effects of acupuncture for relieving pain and reducing inflammatory effects associated to RA, we tested a newly pressure algometry device designed to assess the pressure tolerated by RA patients with hand pain and the effects on this of acupuncture. The pressure algometry device proved to be suitable to quantify the differences between the hand pressure tolerate before and after the acupuncture treatments.

After that, 190 RA patients with stable symptoms and stable conventional treatment, diagnosed by an independent rheumatologist that had not been involved in the study and according the criteria of the American College of Rheumatology, were stratified into two groups: "hand pain worsened by handgrip" or "hand pain worsened by thumb resistance". After analysing these patients we found different features

between RA patients with handgrip pain, and these differences were compatible with different CM syndromes.

79.5% of the 190 participants showed worsening hand pain by handgrip. The CM diagnosis of these patients' group was obtained through inspection, auscultation, interrogation and palpation. CM diagnosis of RA patients with "hand pain worsened by handgrip" showed that they all had concomitant presence of imbalances and intermingled symptoms and clinical findings of the invasion of the pathogen agent algor/"cold", namely: cold hands (62.9%), tearing and localized pain with gradual onset (82.9%), worse pain upon cold exposure (82.9%), pain relief by applying warmth to the affected area (62.9%), tongue exhibiting a hyaline (85.7%) and white coating (52.4%).

In the last phase, 105 RA patients with the CM functional diagnosis of a "pivotal syndrome" or Turning point syndrome (TPS) were randomly assigned to a verum acupuncture, a control acupuncture or a waiting list group (each group n = 35). In the verum and control group the exact same number, depth and stimulation of needles was used as described previously in a double-blind assay.

The double-blind experiment showed that RA patients with a TPS, that were treated with verum acupuncture significantly improved in: self-reported pain (Z = -5.099, p < 0.001), pressure algometry (Z = -5.086, p < 0.001); hand grip strength (Z = -5.086, p < 0.001) and arm strength (Z = -5.086, p < 0.001), health assessement questionnaire (p < 0.001, Z = -4.895) and 7/8 QoL survey domains. The number of swollen joints (Z = -2.862, p = 0.004) and tender joints (Z = -3.986, p < 0.001) significantly decreased in the verum acupuncture group. Patients treated with false acupuncture showed no significant changes. The waiting list group showed an overall worsening. The erythrocyte sedimentation rate and the c-reactive-protein rate remained unchanged.

This first double-blind controlled study on acupuncture in RA objectively assessed specific effects supporting its integration in rheumatology and in the health care systems.

The combination of disease diagnosis in biomedicine and integrative approaches such as CM diagnosis, identification of joint non-related symptoms and pathogenic external factors such as algor/"cold" can help to identify different functional diagnoses of RA and improve treatment strategies.

By integrating the CM diagnosis as an inclusion criterion, there is homogenization of biomedical parameters and classification of CM diagnosis. Furthermore, it provides clear evidence about the importance of synergy that must exist between the diagnosis in CM and the respective selection of acupoints and it is essential for clinical practice because it might allocate interventions more adequately to the patient complaints.

KEY WORDS: Rheumatology, acupuncture, hand pain, Heidelberg model, double-blind, quality of life

Resumo

A artrite reumatóide (AR) é a forma mais comum de artrite crónica inflamatória e auto-imune caracterizada por persistente sinovite, destruição e poliartrite simétrica das pequenas e grandes articulações.

O desenvolvimento da doença está associado ao aumento do risco de falência orgânica, à dor persistente, incapacidade progressiva, redução da qualidade de vida (QV), e um alto impacto socioeconómico nos indivíduos e nos sistemas de saúde.

Embora o curso da AR tenha melhorado muito nos últimos anos, não existe cura e os tratamentos farmacêuticos utilizados para reduzir a inflamação e retardar a progressão da doença provocam efeitos secundários notáveis, desde lesões ao nível do tracto gastrointestinal até danos hepáticos ou o aumento da susceptibilidade a infecções graves. As mulheres que desejam engravidar e/ ou amamentar muitas vezes necessitam de modificar a terapêutica utilizada para optimizar a saúde do recém-nascido.

Dado o facto da crescente consciencialização dos efeitos colaterais indesejados da medicação utilizada, tem havido um aumento na procura dos tratamentos de acupunctura, que tem sido classificada como uma técnica segura.

Evidências sugerem que as intervenções de acupunctura podem ter um efeito positivo no alívio da dor, função física e QV em pacientes com AR. No entanto, devido à heterogeneidade e limitações metodológicas dos ensaios clínicos randomizados, nomeadamente a alocação eficaz dos pontos de acupunctura, a falta de dupla ocultação e a quantificação dos seus efeitos, as evidências não são fortes o suficiente para produzir uma directriz de boas práticas.

A acupunctura tem origem na componente mais significativa da medicina complementar e alternativa, a medicina chinesa (MC).

Os doentes com AR podem ser divididos em diferentes síndromes segundo a MC, correspondentes a diferentes biomarcadores e mecanismos moleculares e, como tal, com diferentes reacções a determinado tratamento. Portanto, os tratamentos de acupunctura devem ser planeados com acupontos unânimes de acordo com as diferentes síndromes.

O nosso objectivo foi avaliar os efeitos da acupunctura na dor e função das mãos de pacientes selecionados com AR com base em critérios claros de alocação dos pontos de acupunctura, avaliações objectivas e válidas dos efeitos e seguindo, pela primeira vez, um ensaio clinico randomizado e duplo-cego.

Diversas metodologias, aplicando as recomendações CONSORT, foram utilizadas para fortalecer a evidência dos tratamentos de acupunctura e para entender os seus efeitos específicos. Primeiro, a fim de quantificar os efeitos da acupunctura no alívio da dor e inflamcção associadas à AR, testamos um novo algómetro projectado para avaliar a pressão tolerada pela dor na mão em pacientes com AR e os efeitos dos tratamentos de acupunctura. O algómetro de pressão demonstrou-se adequado

para quantificar as diferenças entre a pressão da mão tolerada antes e após os tratamentos de acupunctura.

Depois disso, 190 pacientes com AR, com sintomas e tratamento farmacológico convencional estáveis, diagnosticados por um médico reumatologista independente que não estava envolvido no estudo e de acordo com os critérios do Colégio Americano de Reumatologia, foram estratificados em dois grupos: "pior dor ao apertar a mão" ou "pior dor provocada pela resistência do polegar". Ao analisar estes pacientes encontrámos diferentes características entre os pacientes com AR com "pior dor ao apertar a mão" ou "pior dor provocada pela resistência do polegar", e essas diferenças foram compatíveis com diferentes síndromes da MC.

79,5% dos 190 participantes apresentaram "pior dor ao apertar a mão". Foi realizado o diagnóstico médico chinês deste grupo de pacientes por meio da inspeção, auscultação, interrogatório e palpação. O diagnóstico chinês dos pacientes com "pior dor ao apertar a mão" revelou que todos eles apresentavam presença concomitante e intercalada de desequilíbrios diferenciados, sintomas e sinais clínicos da invasão do agente patogénico algor/"frio", nomeadamente: mãos frias (62,9%), dor localizada, gradual e acompanhada da sensação de rasgar (82,9%), dor pior ao frio (82,9%), alívio da dor pela aplicação de calor na área afetada (62,9%), língua com hialina (85,7%) e cobertura branca (52,4%).

Na última fase, 105 pacientes, com AR e com o diagnóstico funcional segundo a MC de uma "síndrome pivot" ou "ponto de viragem", foram aleatoriamente destribuídos nos grupos acupunctura verdadeira, acupunctura falsa e lista de espera (cada grupo n = 35), aplicando exactamente o mesmo número, profundidade e estimulação de agulhas de acordo com a metodologia de dupla ocultação já descrita em trabalhos anteriores realizados pelos elementos deste grupo de investigação.

O ensaio duplo-cego demostrou que os pacientes com AR com uma "síndrome pivot" e tratados com acupunctura verdadeira melhoraram significativamente: a dor auto-relatada ($Z = -5,099$, $p < 0,001$), a algometria de pressão ($Z = -5,086$, $p < 0,001$), a força de preensão manual ($Z = -5,086$, $p < 0,001$) e a força do braço ($Z = -5,086$, $p < 0,001$), a capacidade funcional ($p = 0,001$, $Z = -4,895$) e 7/8 dos domínios de pesquisa da QV. O número de articulações inchadas ($Z = -2,862$, $p = 0,004$) e dolorosas ($Z = -3,986$, $p = 0,001$) diminuiu significativamente. Os pacientes tratados com acupuntura falsa não apresentaram alterações significativas, e os pacientes do grupo "lista de espera" pioraram de uma forma geral os parâmetros avaliados. A taxa de sedimentação e a dosagem da proteína C reactiva não se alteraram significativamente em qualquer um dos grupos avaliados.

Este é o primeiro ensaio clínico randomizado e duplo-cego que avalia os efeitos da acupuntura na AR e objetivamente avaliou os seus efeitos específicos, apoiando a sua integração na reumatologia e nos serviços de saúde.

A combinação do diagnóstico biomédico com uma abordagem integrativa como o diagnóstico da MC, a identificação dos sinais e sintomas relevantes e não relacionados com as articulações e a avaliação dos factores externos patogénicos como é o caso do algor/"frio" podem ajudar a identificar diferentes diagnósticos funcionais da AR e a melhorar as estratégias de tratamento.

A integração do diagnóstico da MC como um critério de inclusão, permitiu homogeneizar os parâmetros biomédicos e a respectiva relação com os parâmetros de classificação e diagnóstico segundo a MC, enfatizando a evidência clara e a importância da sinergia que deve existir entre o diagnóstico em MC e a respectiva seleção de acupontos como aspecto essencial para a investigação e para a prática clínica, pois permite alocar as intervenções de uma forma mais adequada às queixas individuais.

PALAVRAS CHAVE: Reumatologia, acupunctura, dor da mão, Modelo de Heidelberg, duplo-cego, qualidade de vida

Thesis Structure

This thesis presents the foundations and the results of five years of work dedicated to prove specific and objective effects of acupuncture in the treatment of Rheumatoid Arthritis. This has been achieved by the use of a systematic strategy to collect scientifically robust evidence regarding the base of acupuncture treatments, as well as optimizing health outcomes through multidisciplinary collaborations among different professionals and researchers of both conventional medical and Chinese Medicine practices.

The thesis is divided into eleven chapters. Six of them (Chapters 3 to 8) correspond to papers that have already been published. They address research questions within the scope of this thesis.

Chapter 1 presents a general description of Rheumatoid Arthritis immunopathology referring to its epidemiological features and socio-economic impact followed by an overview of hand and wrist pain and their resultant impaired function, risk factors, diagnosis and classification criteria. The chapter ends with a brief description of Western medicine treatment strategies.

Chapter 2 introduces a contemporary understanding of Chinese Medicine as a model of system biology with a description of the Chinese Medicine diagnosis as the foundation of acupoint selection, followed by a brief description of neuroimmunology and rheumatology according to Chinese Medicine and its best-known model to interpret the neuro-immune vegetative state, called the Algor Leadens Theory.

An overview is given of Rheumatoid Arthritis and rheumatic pain from a Chinese Medicine perspective as well as a summary of the current scientific research concerning the treatment options of the main complementary and alternative medicines to relieve Rheumatoid Arthritis signs and symptoms, with a special emphasis on acupuncture.

Chapter 3 shows the results of a systematic literature review which suggested that acupuncture interventions might have a positive effect on pain relief, physical function and quality of life of patients with Rheumatoid Arthritis. However, due to the heterogeneity and methodologic limitations of the included studies, the evidence was not strong enough to produce a best practice guideline.

Chapter 4 describes the results of a second systematic literature review which aimed to identify and synthesize the best available evidence regarding the diverse range of biomolecules, proteins and genes from Rheumatoid Arthritis patients that correlate well with cold, heat/hot or deficiency phenotype-based Chinese Medicine patterns.

Chapter 5 includes the original project designed to investigate the effects of an acupuncture treatment on pain, functional deficits and the health-related quality of life of patients with Rheumatoid Arthritis.

Chapter 6 presents the results of a quasi-experimental study developed in order to test the newly developed pressure algometry device, which was designed to assess the tolerance in hand pain in Rheumatoid Arthritis patients and thereby a specific Chinese Medicine vegetative functional state called Turning Point syndrome.

In **Chapter 7** objective assessment strategies are explored, to see if they may help to determine the Chinese Medicine functional diagnosis and if the complicated issues surrounding the symptoms of

Rheumatoid Arthritis of the hand can be easier understood by using the Shang Han Lun (the Treatise on Cold Damage).

Chapter 8 presents the results of the first double-blind randomized controlled trial to assess the specific acupuncture effects on pain and function of the hand and, on the quality of life of selected Rheumatoid Arthritis patients based on clear allocation criteria of acupoints, objective assessment of effects and, for the first time, valid, double-blind controls.

Chapter 9 reports a general idea as to how nurses can use complementary and alternative therapies, especially acupuncture, taking all measures necessary to improve the quality of nursing care that can be supplemented, extended and enriched by knowledge of Chinese medicine.

Chapter 10 is dedicated to the discussion and analysis of critical points that were raised after a preliminary critical assessment of this thesis.

Chapter 11 discusses all the studies by considering the strengths and limitations of the research findings, their potential implications in an integrated perspective and by identifying crucial areas for future work in order to guarantee that all patients with Rheumatoid Arthritis have the chance to take advantage of an integrative care approach including the most appropriate treatments with well-trained professionals.

The work presented in this thesis provides an original and unique opportunity for improvements in the treatment of Rheumatoid Arthritis patients nursing care by showing other valid strategies. It will hopefully contribute significantly to the attainment of invaluable health benefits for our population.

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Rheumatoid Arthritis
- Western Medicine overview

1. Rheumatoid Arthritis

1.1   Rheumatoid Arthritis – Definition and Immunopathogeny

Rheumatoid Arthritis (RA) is a chronic inflammatory, multissystemic and autoimmune disease with an unknown etiology.[1]

Clinically it is characterized by destructive polyarthritis that involves the small and large joints and extra-articular organ involvement including the skin, eye, heart, lung, renal, nervous and gastrointestinal systems. Occasionally there are also systemic manifestations present such as vasculitis, visceral nodules, Sjögren's syndrome, anaemia or pulmonary fibrosis.[2,3]

The course of RA may be cyclic or aggressively active and the progression and rate at which joint destruction occurs can be quite variable.[1]

The pathogenesis of RA (Figure 1) is a multistep process that starts with the development of autoimmunity, continues with local inflammation and finally induces bone destruction.[1,3] This stage, identified as pre-articular or lymphoid phase, can precede the clinical manifestation of the disease by as much as 10 years. The adaptive and the innate immune pathways are activated and both contribute to the inflammatory process and the tissue damage.[3]
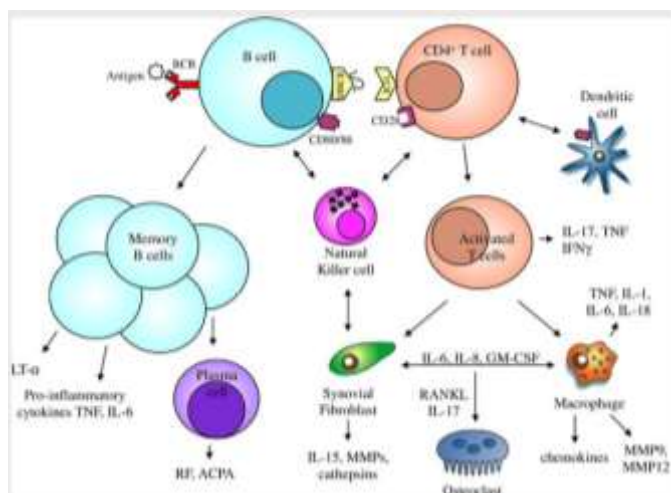
Figure 1. Immune pathways in RA.

The interactions among dendritic cells, T cells and B cells occur primarily in the lymph node and generate both the autoimmune response and the activation of T cells. Upon stimulation by T cells, activated B cells differentiate into memory B cells and plasma cells producing autoantibodies such as rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA). B cells secrete pro-inflammatory cytokines and lymphotoxin-α that enhance inflammation and synovial lymphoneogenesis. In the synovial membrane, cell-contact interactions among T cells, natural killer cells, synovial fibroblasts, macrophages and osteoclasts generate positive feedback loops mediated by cytokines, chemokines, matrix metalloproteases and cathepsins that drive the chronic phase of the disease inducing tissue remodelling and damage. Reproduced from Chimenti et al., The interplay between inflammation and metabolism in Rheumatoid Arthritis, Cell Death and Disease, 2015.[3]

In RA patients, the synovial membrane is characterized by cellular hyperplasia, increased vascularity

and an infiltrate of inflammatory cells that invasively grow and destroy the adjacent cartilage and bone. The term synovial hyperplasia, called 'pannus', describes an increased thickening of the lining layer caused by the combination of cellular proliferation in situ, influx of cells from the circulation and reduced apoptosis with increased oxygen demand and consequent local hypoxia. Inadequate oxygenation drives the inflammatory response and the mechanisms of angiogenesis. This process promotes further infiltration of inflammatory cells, production of inflammatory mediators and matrix degradation.[3]

The development of the inflammatory process in RA involves many different cell types and a complex cytokine network. CD4+T cells, upon activation and expansion, develop into different T- helper cell subsets with different cytokine profiles and distinct effector functions. Activated T- cells that secrete interferon (IFN)-γ, Interleucine (IL)-2, IL-12, IL-18, tumor necrosis factor alpha (TNF-α) and granulocyte-macrophage colony-stimulating factor, typically considered T-helper (Th)1 cytokines, are produced in the synovial fluid and expressed in the synovial membrane. Moreover, IL-17, which is produced by Th17 and mast cells, has been detected in RA synovial fluid. These cytokines activate macrophages to secrete other pro-inflammatory cytokines such as IL-1β, IL-6, TNF-α and IL-12, induce the nuclear factor (NF)-κB ligand expression on T- cells, promote the differentiation of B- cells and stimulate the release of matrix metalloproteases provoking the degradation of the cartilage and the activation of osteoclasts leading to the bone resorption.[3]

Macrophages are the most important source of those cytokines. However, many studies demonstrate that cell contact interactions between synovial T lymphocytes and adjacent macrophages or fibroblasts represent an alternative route to generate cytokines.[3]

1.2 Epidemiology: Incidence and socio-economic impact

Approximately 1% of the world's population suffer from RA and its prevalence is about 0.8% to 1.5% in the Portuguese population.[4,5] RA typically affects people in active age and is known to have a female to male prevalence ratio of 3:1.[6] The extra-articular manifestations of RA can occur at any age after onset, are more common in males and in patients with severe, active disease.[2] The occurrence of systemic manifestations is a major predictor of mortality in patients with RA.[2]

RA annual costs have been estimated at over $56 billion in the United States in 2016,[7] around €3.5 billions in Italy[8] and, if we consider 35,000 patients with RA in Portugal, the annual cost would be €119,525,000 per year.[9] Thus, the social-economic impact is high on the individuals, on work-related problems like absenteeism or on inability to work as well as additional impacts on the health care system.[7,10]

Treatment and management of RA consume time because daily life tasks take longer as a result of pain, stiffness and functional disability. RA patients take 1.15 extra hours to do the same daily activities mostly spent on the need for more rest time. The time spent for medical appointments, exams and the need for physical therapy is 1.9 hours in some studies while the global reduction of work time is 11.6%. Co-morbidities as well as disease activity and disability are also involved in extra time spent, worse

radiological status, poor functional performance, erythrocyte sedimentation rate (ESR) and c-reactiv protein (CRP) but also cumulative damage which all contribute to the loss of occupational and recreational time.[9]

In RA, early diagnosis is crucial because at the end of the first 3 years of the disease the percentage of patients already in retirement is nearly one third. In addition to retirement, RA causes a reduction in income that is usually 27% and 48% less for men and women with RA respectively in comparison to healthy workers and 40% less than before becoming ill.[9]

RA is an increasing cause of disability and is responsible for more than two thirds of patients with disability (37.6%), with an expectable increase of 21.4 million to 41.4 million patients by 2030.[9]

1.3 Pain in the Wrist and Hand

More than 90% of patients with RA have involvement of the hands and impairments seem to lead to activity limitations in 30% of the patients.[11] In RA patients, the condition of the hand is associated with pain, reduced grip strength, loss of range of motion and joint stiffness leading to impaired hand function and difficulty with daily activities.[12]

Prominent swelling of the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints is one of the hallmark signs of RA and one that distinguishes RA from osteoarthritis even in its inflammatory form.[1]

Flexion deformities associated with muscle atrophy and consequently loss of mobility of the PIP joints include radial deviation of the wrist and the beginning of the ulnar deviation of the digits.[1] With disease progression the patients will experience tenosynovitis, hyperextension deformity of the thumb and grasp and pinch are severely compromised.[1]

The very late stages of this type of hand results in a 'paddle' which provides very little in the way of hand function. It is not known how this deformity arises. It appears that the navicular bone at the wrist rotates, causing the wrist to deviate towards the ulnar side. Biomechanical forces then come into play during normal hand function and subsequently cause a compensatory movement of the fingers toward the radial side, producing the zigzag deformity.[1]

Classic late-stage manifestations of RA, including hyperextension of the PIP joint of the thumb, subluxation at the MCP joints, and swan-neck deformities, including the typical 'Z' or zigzag deformity of the hand (so commonly seen in the 1960s and 1970s),[1] has significantly declined with the early institution of combinations of aggressive therapy.[11]

According to the EULAR, the optimal management of the hand in RA patients allows them to maintain or regain maximum self-sufficiency, joint strength and function, range of motion and reduction in stiffness, when considering pain relief, their needs and wishes, since a functioning hand prolongs the ability to take food and drink, to wash and dress themselves, to use the toilet, to do personal hygiene, to walk until to manage a wheelchair.[1,12]

The non-pharmacological and non-surgical treatments, including acupuncture, heat therapy and massage, are recommended for relieving pain and improving hand function, although the level of evidence supporting this recommendation should be identified.[8]

1.4 Risk Factors

Several environmental factors have been studied in RA and the interaction between genetic and environmental factors have been demonstrated (Figure 2).[13]
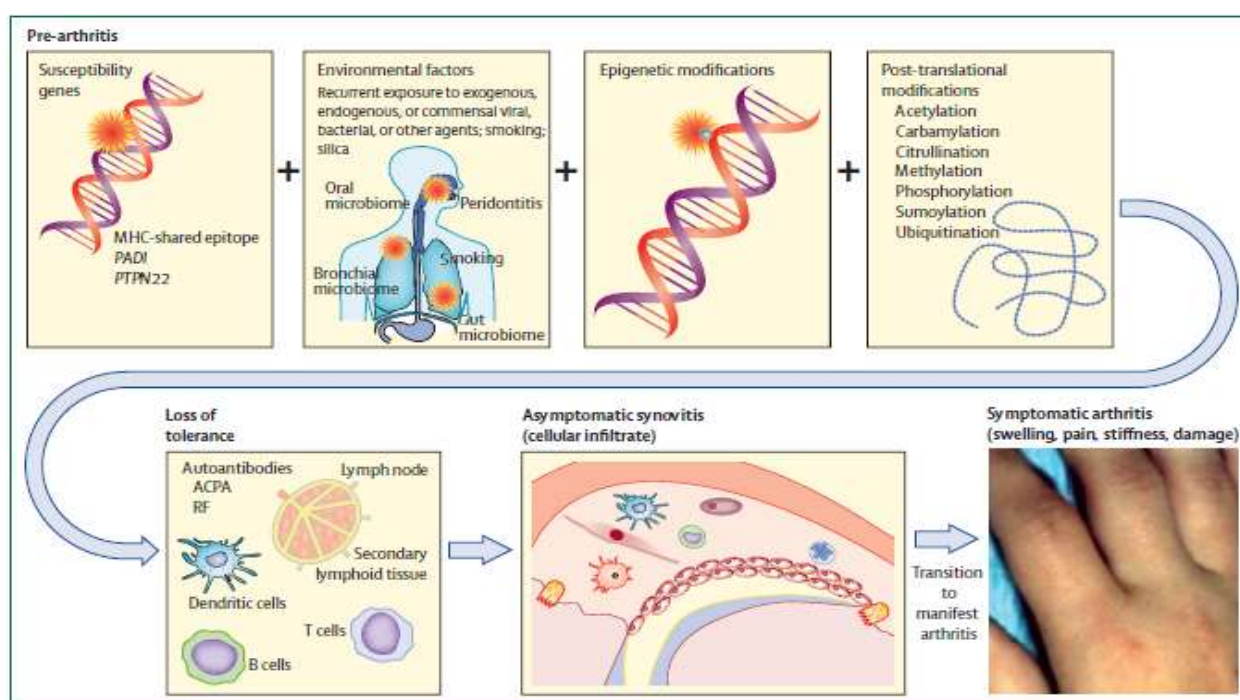
Figure 2: Pathways to RA in a genetically predisposed host with susceptibility genes, environmental insults, epigenetic modifications, and post-translational modifications can lead to loss of tolerance with subsequent asymptomatic synovitis, ultimately leading to clinically overt arthritis. Reproduced from Smolen et al., Rheumatoid Arthritis, Lancet, 2016.[13]

Sex hormones, as oestrogens and progesterone, have a complex influence in the T- cells balance with different cytokine profiles and may explain the differences between male and female prevalence of RA.[14] Smoking, birth weight, diet, alcohol intake, stress and socioeconomic status can modify the risk for RA.[3,14] Indeed, other infectious agents (eg, Porphyromonas gingivalis, Proteus mirablis, Escherichia coli, and Epstein-Barr virus) have been suggested to trigger RA, generally via molecular mimicry, however, these proposed mechanisms have not yet been substantiated.[13]

There is now considerable interest in the effect of the structure of the microbial community on disease risk and progression (Figure 2).[13] Gut microbiota in fact plays a crucial role in modulating innate and acquired immune responses and thus interferes with the fragile balance inflammation versus tolerance.

In the context of dysbiosis it is also important to remember that different environmental factors like stress, smoke and dietary components can induce strong bacterial changes and consequent exposure of the intestinal epithelium to a variety of different metabolites, many of which have an unknown function.[15]

A recent epigenome-wide association study identified differentially methylated positions that could promote genetic risk in RA as, altered histone acetylation and deoxyribonucleic acid (DNA) methylation (can regulate the biology of synovial fibroblasts and leucocytes) or, microRNAs (that represent an additional epigenetic aspect by targeting mRNA for degradation, thereby fine-tuning cellular responses).[13]

The human leukocyte antigen (HLA) system (particularly HLA-DRB1) remains the dominant influence, strongly implicating peptide (and self-peptide) binding in pathogenesis.[13] In particular, the DRβ1 chain, called 'shared epitope' (SE), is associated with the production of ACPA and with the RA disease.[3] Signal transducer and activator of transcription 4 (STAT4) is a member of the STAT family of transcription factors. This molecule has a key role for the IL-12 signaling in T- cells and natural killer (NK) cells, leading to the production of IFN-γ and the differentiation of Th1 and Th17 cells. Other candidate genes associated with RA are cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4), the α and β chain of the IL-2 receptor (IL-2RA and IL-2RB), IFN regulatory factor 5, the locus located between TNF receptor-associated factor 1 and C5 genes, the gene near TNF-α -induced protein (TNFAIP3), and the co-stimulatory molecules CD40 and CD28.[3]

The functional variant (R620W) in the intracellular protein tyrosine phosphatase N22 has recently been described as one of the examples of polymorphism susceptible to genetic transmission, with the risk of developing RA being twice as high in heterozygotes and four times as high in homozygous carriers of this polymorphism.[13] The presence of this polymorphism causes intracellular tyrosine phosphatase to regulate T-cell activity negatively (Figure 3).[13] However, polymorphisms are much less important in the transmission of RA.[13]
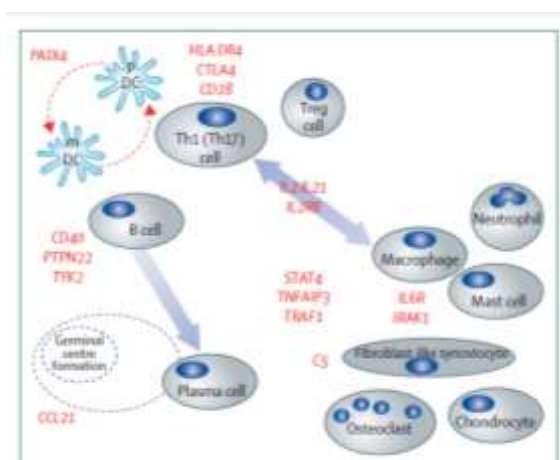
Figure 3: Important loci associated with risk and progression of rheumatoid arthritis.

Key immune cells implicated in the pathogenesis of rheumatoid arthritis. Th1=T-helper-1. Th17=T-helper-17. Treg=regulatory T. mDC=myeloid dendritic cell. pDC=plasmacytoid dendritic cell. Reproduced from Smolen et al., Rheumatoid Arthritis, Lancet, 2016.[13]

1.5 Diagnosis and Classification Criteria

The correct diagnosis of RA (especially early RA) remains a challenge. The challenge of treating early RA is the fact that new-onset arthritis can have numerous causes, often resolves spontaneously and persistent arthritis has many differential diagnoses to be considered in addition to RA or may even remain undifferentiated. Although, no formal criteria can replace the judgment and experience of the rheumatologist in the diagnostic setting.[1]

A clinical examination which finds joint swelling not caused by trauma or bony swelling suggests a diagnosis of early RA, especially if it includes involvement of at least two joints, early morning stiffness lasting 30 minutes or more and response to non-steroidal anti-inflammatories drugs (NSAIDs), will help differentiate between RA of many infectious, inflammatory, or malignant conditions.[1] Symmetric involvement of the hands is a hallmark of RA. Hand or foot involvement is common and in cases of early RA may be detected by a positive MCP or metatarsophalangeal (MTP) squeeze test.[1] Family history is also important for RA, psoriasis, and other autoimmune diseases. Laboratory investigations and imaging may be of additional benefit.[1]

Rheumatoid factor (RF) is a marker of persistence in patients with early inflammatory arthritis and a predictor of radiographic progression. ACPA testing may be of particular value in detecting patients with RA who are RF-negative. ACPA positivity has also been shown to be an independent predictor of radiographic damage and progression.[1]

Citrullination is the critical step for the recognition of several proteins (fibrin, vimentin, fibronectin, collagen type II), highly expressed in the synovial membrane during inflammation, by ACPA.[3]

Conventional radiographs, besides their low cost and availability, are not very sensitive for detecting change in early RA. Newer imaging modalities (eg, Magnetic Resonance Imaging (MRI) and Ultrasound (US) have been shown to be more sensitive for visualizing early inflammatory and destructive change in RA and predicting future radiographic damage. However, relatively high costs, long examination times, and low availability limit the widespread use of MRI. US, in comparison, is relatively inexpensive, non-invasive, and allows many joints to be assessed at any one time. The main disadvantage of this modality is its dependency on the skills of the operator and potential problems with reproducibility.[1]

Classification criteria of Rheumatoid Arthritis

Classification criteria may help to guide the rheumatologist in the difficult task of establishing a diagnosis. The 2010 RA American College of Rheumatology/ European League Against Rheumatism (ACR/EULAR) classification criteria replaced the 1987 American College of Rheumatology (ACR) RA classification criteria and are intended to classify RA earlier in the disease course.[16]

Patients must meet two mandatory requirements for the classification criteria to be applied. First, there must be clinical evidence of synovitis (i.e., swelling) in at least one joint. All joints of a full joint count

may be assessed for this purpose with the exception of the distal interphalangeal joints (DIP) joints, the first MTP joint, and the first carpometacarpal joint, as these joints are typically involved in osteoarthritis.[1]

Second, the synovitis should not be better explained by another diagnosis (e.g., Systemic lupus erythematosus, psoriatic arthritis, gout). Classification as definite RA is then based on achieving a total score of 6 or greater (out of 10) from individual scores in four domains. These are:[16]

• number and site of involved joints (score range 0–5);

• serological abnormality (score range 0–3);

• elevated acute phase response (score range 0–1); and

• symptom duration (score range 0–1).

As a caveat, patients with RA-type erosions on X-ray with a typical history of RA may also be classified as such and the scoring system need not be applied.[1]

Disease Activity Score in 28 joints (DAS28)

The Disease Activity Score in 28 joints (DAS28) is a combined index that measures disease activity in patients with RA.[13] It has been extensively validated for its use in clinical trials in combination with the EULAR response criteria. Its easy use also makes it possible to collect valuable information about the disease activity of the patient in daily clinical practice. Evaluation of response to a treatment can be made much easier and more objective using the DAS or DAS28. Just assess the number of swollen and tender joints and measure one inflammatory parameter (erythrocyte sedimentation rate or C-reactive protein) and may or may not include the overall disease assessment (from 0 to 100). The DAS will provide continuous numerical scales, between 0 and 10, reflecting disease activity (higher is worse), indicating how active the RA is at a given moment.[13] According to DAS28 it is considered that the person is in remission of the disease if the value is < 2.6 and that is in low disease activity if ≤ 3.2.[13]

1.6 Treatment

There is no cure to RA but, patients may reach a state of remission if optimal early and persistent intervention occurs.

Drugs form the mainstay of therapy in RA. Five main classes of drugs are currently used: analgesics, NSAIDs, glucocorticoids, non-biologic and biologic disease-modifying anti-rheumatic drugs.[17] However, despite optimal use of currently available anti-rheumatic agents, most RA patients live with chronic pain and severe functional decline because these therapies focus primarily on preventing joint inflammation and soft tissue swelling, but are not effective in preventing cartilage breakdown and the joint destruction associated with RA.[17]

NSAIDs

NSAIDs (including second-generation Cox-2 inhibitors) interfere with only a small cascade of the inflammatory steps, namely, prostaglandin production by cyclooxygenase (COXs), but not the underlying immuno-inflammatory reaction. Therefore, NSAIDs do not slow the progression of the disease and are incapable of preventing joint deformity. The major side effects of NSAIDs are their propensity to cause stomach ulcers, gastro intestinal (GI) bleeding and perforations and renal dysfunction.[18]

DMARDs

The therapy management of RA rests primarily based on the use of disease-modifying antirheumatic drugs (DMARDs), and practice guidelines instruct that DMARDs be initiated within the first three months of symptom onset for more favourable outcome and decreased mortality.[19] Cyclophosphamide, cyclosporine, D-penicillamine, glucocorticoids, gold, and minocycline are older DMARDs that are less frequently used because of high toxicity or decreased efficacy. Hydroxychloroquine, leflunomide, methotrexate (MTX), minocycline, and sulfasalazine are first-line agents, and a combination of two or three of these drugs may be used when appropriate.[19]

MTX is currently the DMARD of choice for initiation in patients with RA. This agent is an antimetabolite that interferes with DNA synthesis, repair, and replication in malignant cells.[19] Common side effects of MTX therapy are GI upset (nausea, vomiting, and diarrhoea), stomatitis, malaise, dizziness, and mild alopecia. Less common, more severe side effects include dose-related bone marrow suppression, liver toxicity, infections, rheumatoid nodules, leukopenia, pneumonitis, thrombocytopenia, and renal failure. MTX is contraindicated in pregnancy, pre-existing blood dyscrasias, alcoholic liver disease, severe hepatic or renal dysfunction, and hypersensitivity to the drug or any of its components. Caution should be exercised in women of childbearing potential or in patients with peptic ulcer or ulcerative colitis.[19]

Glucocorticoids

Current immunosuppressive therapies and glucocorticoids act on both the adaptive and the innate immunity leading to an improvement on disease outcome, though this is only a temporary solution. They have potent anti-inflammatory effects and are frequently include in the RA treatment regimen for approximately 3–6 months in order to minimize disease activity in patients with active RA while awaiting a clinical response to the given DMARD being applied.[17]

Corticosteroids exert a modulation of T-cell functions because of their effects on pro-inflammatory Th1-driven cytokines and on Th1/Th2 immune-mediated response.[3,20] However, severe adverse effects of glucocorticoid treatment, including loss of bone mass and increased risk of fractures, are common.[20]

Biologics

Recently, efforts have been focused on using the class of drugs called biologic agents (antibodies or soluble receptors for IL-1, IL-6 and TNF-a) frequently used in forms of RA that have suboptimal

response or intolerant to one or two traditional DMARDs and have acquired a prominent place in the management of rheumatologic conditions.[3,19]

Currently, anti-TNF agents such as infliximab, etanercept and adalimumab are the commonly used first line biologic followed by abatacept. It is usually combined with MTX. There is some evidence that tocilizumab is the most effective biologic as a monotherapy agent. Rituximab is generally not used as a first-line biologic therapy due to safety issues but still as effective as anti-TNF.[17]

The long-term data for the newer oral small molecule biologics such as tofacitinib is not available and hence used only as a last resort.[17]

Although these agents reduce inflammation and joint destruction, their long-term risks and benefits are not yet clear. Additionally, higher costs and the findings that they are not effective universally and severe side effects such as life-threatening infections and increased risk of malignancies limit the use of such agents in many populations.[3,17] Thus, a final assessment on the use of biologics for the treatment of RA, particularly with regard to risk of infections, malignancies and autoantibody production has to be carefully assessed.

Surgery

Arthroscopy will be a useful method where there is severe degradation of joint tissues.[1]

Gene Therapy

Up to half of the patients with rheumatoid arthritis continue to undergo symptoms of the disease. There is a need for additional therapies with "good tolerability and efficacy" profiles to use in patients who still experience inflamed joints despite previous treatment.

Suppressor gene locus of inflammatory mediators and matrix degrading enzymes were inserted into the affected area to reduce the disease progression. To overcome the raised by those therapies like side effects and expenses, phytocompounds have been investigated and certain compounds are proved to have anti-arthritic potential.[1]

Drugs that act on lipid/glucose metabolisms appear to confer an improvement on inflammatory features in RA patients. Clinical studies concerning the effect of drugs modulating insulin sensitivity (such as the peroxisome proliferator-activated receptor (PPAR)-γ agonists) are ongoing in order to provide new potential treatment to improve both the inflammatory status and the cardiovascular outcome in RA patients.[3]

ART-I02 is an investigational intra-articular gene therapy medication that could be a solution to provide local treatment for those with rheumatoid arthritis. This drug expresses interferon-beta (IFN-β), a protein that has the ability to reduce the production of other proteins that play a part in the development of rheumatoid arthritis. In pre-clinical studies, researchers found a single injection with IFN-β to be beneficial in mice and rhesus monkeys with induced arthritis. The ART-I02 drug has now moved on to a Phase I clinical trial in human subjects.[21]

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Chapter 2

Rheumatoid Arthritis
- Chinese Medicine overview

1. Contemporary understanding of Chinese Medicine: a Model of System Biology

Traditional Chinese Medicine (CM) has been recompiled since the 1950s–1970s in order to provide basic medical care for the population in China, which at that time was a developing country and was aimed at the rapid distribution of pragmatic concepts. The result was a reduction of its theoretical and diagnostic foundations.[1]

A more recent recompilation generated in cooperation with Chinese scientists is the so-called Heidelberg Model (HM) of CM. This model stands on mathematical principles applied to the vegetative regulation and on scientific conceptualization. Many of the key aspects of CM are explored in the oldest classical Chinese texts as the Yi Jin the Neijing Suwen or the Yi Jing. Particularly the *I Ching* presents what we would today refer to as a system view of life, health and society and has mathematic principles which are based on a system of binary numbers (*yin* and *yang* as 0 and 1, respectively), later on decoded by the mathematician Gottfried Wilhelm Leibniz (1646–1716) (Figure 1).[2] It is interesting to note that these numbers were largely replaced from the third century before Christ by the so-called phases: Wood (in the yang but still below = yang in yin), Fire (in the yang but still above = yang in yang), Metal ((in the yin but still above = yin in yang)), and Water (in the yin but still below = yin in yin) (Figure 1).
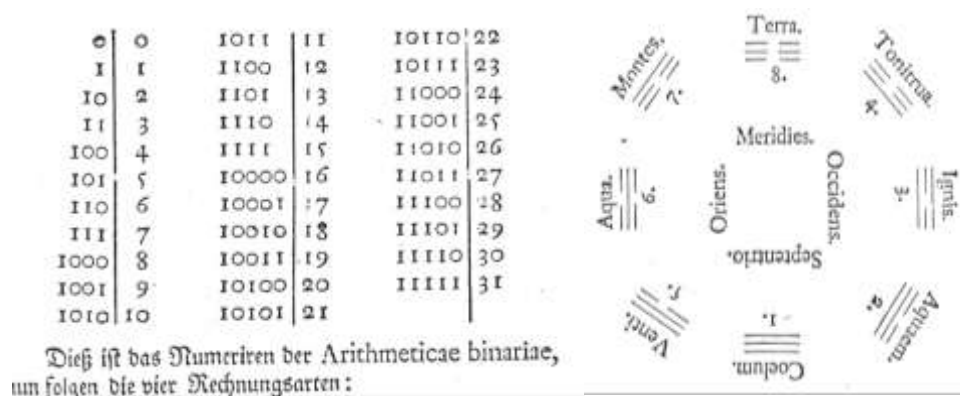
Figure 1: System of binary numbers decoded by the mathematician Gottfried Wilhelm Leibniz.

Left: extract from Leibniz' work showing the character of 0/I. He is quoting the arithmetic rules of binary numbers ("arithmeticae binariae") Leibniz. Right: the parts of a circle are represented, with bigrams in the center meaning the numbers 1,2,3,4 and, also the so-called Ba Gua with the application of binary numbers to divide a cyclic process. Reproduced from Greten, 2013.[1]

The phases (directions of movement) were therefore initially parts of a circular process. The Earth (axis of the system, the target value) by tradition is placed in the center of the movement, exerts a down-regulation in the first half of the movement and an up-regulation in the second half of it (Figure 2).[1]
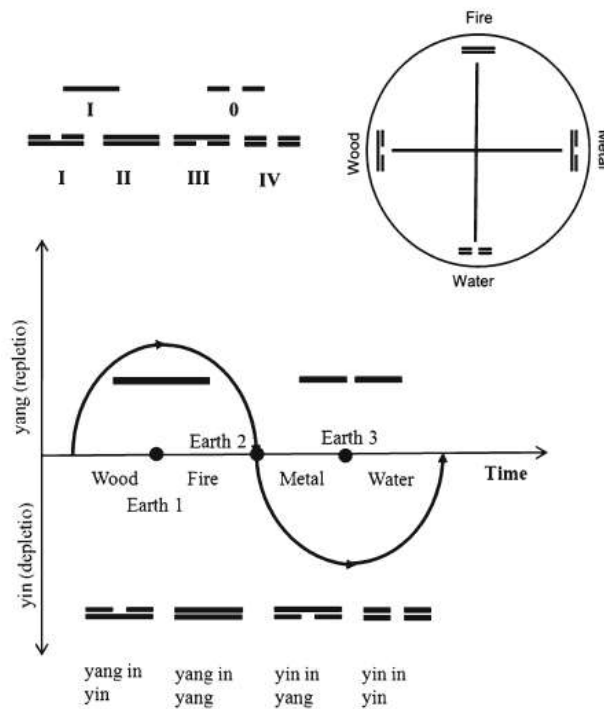
Figure 2: Phases as Part of a Circular Process.

Above left: I (solid line) and 0 (broken line) can be combined to form binary numbers. Above right: the quadrants of a circle can be described by them. Below: transformation into a sine curve which constitutes a simple model to represent periodic changes of regulated systems. The circular function with the quadrants I–IV (Wood, Fire, Metal, and Water) now describes the functional state of regulated systems. Yin, yang, and the phases are therefore regulative (cybernetic) terms. In the schematic representation the Earth (target value) is marked as a dot on the x-axis according to the axis of the cycle. Between Wood and Fire, the Earth is seen as down-regulation of excess values and between Metal and Water, as up-regulation. Reproduced from Greten, 2017.[3]

This regulation can be illustrated by the example of the temperature of a water basin or an incubator in a lab, regulated via a thermostat and an electric heater (Figure 3). A target value of for example, 37°C is adjusted, and periodic changes (up and downs) of the actual value as well as the vegetative system of the human body are mathematically explained by a sine wave or a projection of up- and downward circular movements (Figure 3).[3]
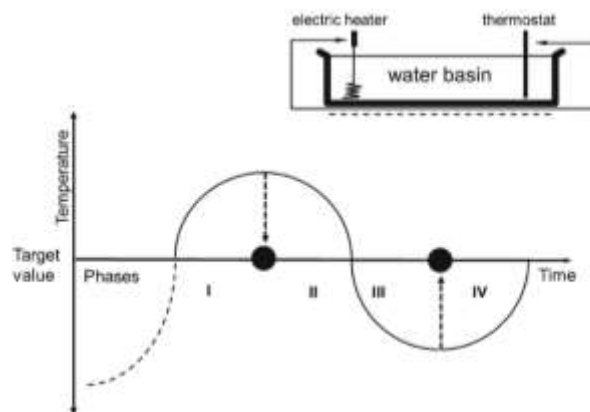
Figure 3: Fundamental aspects of regulation, according the HM of CM, using an incubator as example.

Reproduced from Greten, 2017.[3]

Therefore, it is possible to associate the system of phases as regulatory states of the body (sine wave) or uprising and descending energies (up and down) or circular processes with antagonistic parts of the movement (compass rose) (Figure 3).[1]

The writing as a cycle or sine wave can also be transferred to a common symbol, the fouqi (Figure 4). This emblem symbolizes regulatory (cybernetic) meanings of sine wave, yin and yang, the phases, circle and the target value of the function is then symbolized as a dot on the x –axis.[1]
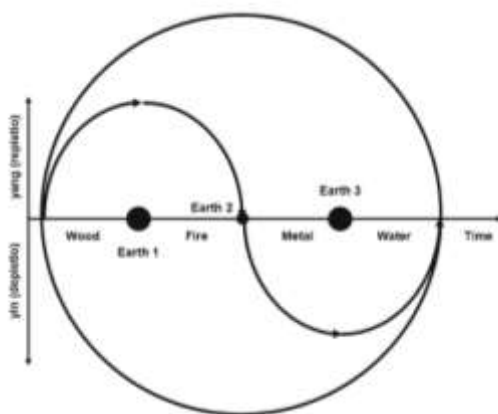
Figure 4: Taiji sign, foci sign, or yin–yang sign.

Both forms of writing a circle, the circle and the sine wave, are united in one symbol. The two dots show the target value of a regulated system. Reproduced from Greten, 2013.[1]

In Western medicine, the phases (vegetative functional tendencies) are described by a concert of vegetative transmitters, control circuits, and mechanisms (Figure 5). They are named after organ regions ("body islands" or "sensation region"). These body regions are part of the interior of the body and, in Western medical language, described as neuro-affective activation patterns of man. The "organs" or "*zang fu*" in CM are vegetative functional states, manifest clinical signs and have an emotional dimension which may become symptomatic in the organ region and reacts together with the skin regions (meridian or conduits).[1,3,4]
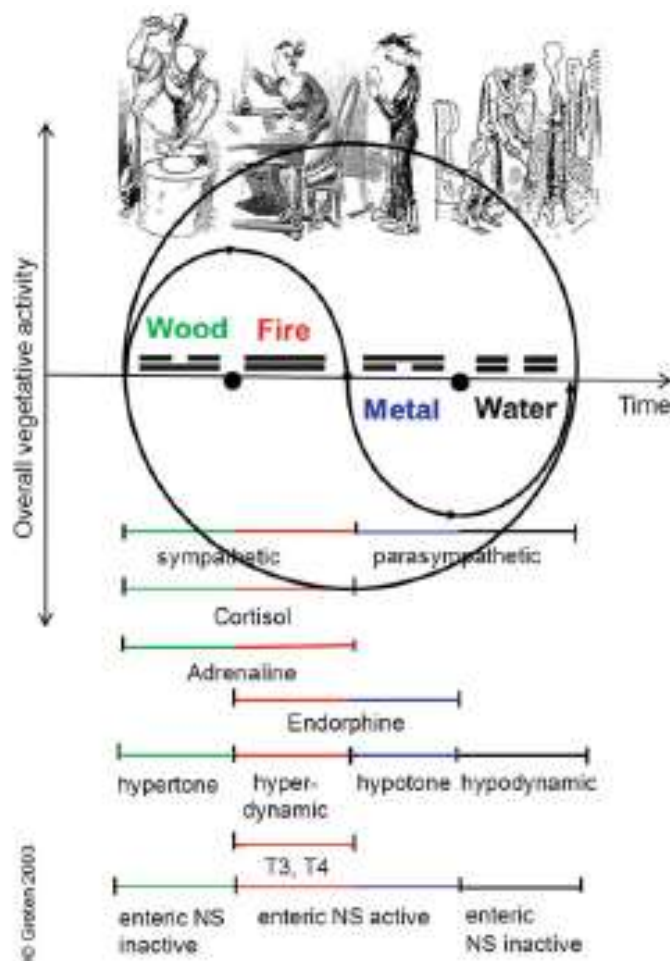
Figure 5. Phases and its concert of vegetative transmitters, control circuits, and mechanisms.

The phases Wood and Fire predominantly represent activating mechanisms, and the phases Metal and Water, deactivating and regenerative mechanisms which are known in Western medicine.[1] The upper part of the picture shows human functional states which can be differentiated by their key symptoms (diagnostically relevant signs). Such groups of key symptoms are called orbs in CM. The lower part of the picture shows a selection of vegetative functional mechanisms which in Western medicine are seen as the causes of these signs. The upper part shows the symptoms in the language of CM, the lower part shows the same symptoms in the language of Western medicine. For orientation, the yin–yang code (yin solid line, yang broken line) has also been included again in the form of bigrams.[1,3]

Contemporary CM could be regarded as a model of system biology with a holistic therapeutic purpose with emphasis on the integrity of the human body and the close relationship between a human and its social and natural environment.[1] In the cybernetic approach, CM takes the human body as a self-controlled system network (integrity) and external information should reflect something intrinsic.[1]

To better understand the next topics in this chapter, basic CM concepts need to be introduced here.

CM considers the existence and relation of different kinds of substances. Together "*qi*", "*shen*" and "*jing*" form the three known treasures of man.[3,4]

The neurovegetative auxiliary definition of "qi" is the vegetative capacity to function of a tissue or organ which may cause the sensation of pressure, tearing or flow.[3] Its functional power may be seen in functional and measurable physiological processes and aspects such as the increase of the peripheral

microcirculation, the subsequent increase of the skin temperature, the changes in acupoints' electrical potential and resistance, and even changes in the surrounding biomagnetic field.[5]

As the normal vegetative activation patterns take place automatically, "nothing special" happens, and the individuals in most of the cases do not have any extraordinary sensations. However, "non-normal," so to speak, "pathological" vegetative patterns of activation inside the body may be individually noticed as some sort of hard-to-describe movement, like a "whiff" or "breath," like a "cloud".

As "qi" may be perceived by the senses as a sensation of flow, tearing or pressure, the traditional Chinese concept of disease as a disturbance of the flow of "qi" in parts of the skin which goes along with functional symptoms can approximately be translated into Western physiology. All these analogues lead to the thesis that those symptoms which are called disturbance of "qi" in CM may be vegetatively induced symptoms, for example, in the depth of the tissue, which go along with sensory changes of skin areas.

In CM, "shen" represents the accumulation of "qi" and "xue" in the heart, which when sufficient, give rise to consciousness or spirit. Because "shen" is considered to have a material basis, its importance in medicine is not independent of the body. "Shen" is the capacity of the mind to form ideas, consciousness, memory, mental emotional balance, control of associability, mental coherence and control of motor functions.[3,6]

The model of vegetative regulation considers "jing" comparable to the clinical effects primarily caused by the nucleus of the cells (the primordial functional repertoire of the cell, which can be damaged by radiation, chemotherapy, age or genetic defects).[3] In this view, "jing" or innate essence (prenatal essence) is the original substance responsible for the construction and maintenance of the body structure, functions and generation of offspring, often linked to the reproductive essence stored in the kidney.[7]

In the context of neuro-immunology the concept of "xue" and "Jin ye" also needs to be explained. "Xue" is one of the four technical divisions of the yin (the structure).[3,6] "Xue" "moved structivity" or "blood," is a term which describes all fluids moving in the body and their effects, i.e. their functions (such as warming, moisturizing, creating of "qi" and nutrition of the tissue.[3] From a Western medical view, the clinical effects of "xue" can be comparable to the Western concept of the effects of microcirculation, including the functional relations of microcirculation blood cells, plasma factors, endothelium and parenchyma.[1,3] "Xue" is a substance and part of the yin, and at the same time, it is a form of energy (yang) with the above-mentioned effects.[3]

"Jin ye" or body fluids, is the general term for all the normal physiological fluids in the body, including internal fluids, which may be secreted by the "zang" organs, such as tears, saliva, sweat, normal nasal mucus, stomach or intestinal fluids, and also the fluids that act to moisten the various tissues within the body, such as skin, flesh, tendons, bones and marrow. "Jin ye" fluids are material substance (structure) sensitive to changes in the state of "qi" and "xue", changes in the orbs functioning, or changes in the

environment surrounding the body. Together with "qi" and "xue", body fluids form the only media of communication between the "zang fu" or orbs, and their related tissues and organs.[8]

2. Chinese Medicine diagnosis as the foundation of acupoint selection

The vegetative regulative processes are subject to the periodicity of homoeostasis, and the symptoms can be understood as part of an overall pattern of diagnostic signs which indicate the functional deviation pattern from the (individual) target value. Symptoms of the functional deviation tendencies, such as pain, develop as a deviation from the target value upward (yang) or downward (yin).[1,3,9]

Pathology or functional tissue disorders, according to the understanding of CM, are imbalances of the regulated body systems and closely associated with blockages of the normal "qi" flow of the vegetative sine wave for whatsoever reason (patient's constitution, pathogenic agents, social, emotional and natural factors).[1,3]

CM has a regulatory theory on vegetative activation which is quite compatible with Western physiology. As a general idea, CM analyses the physical sensations of the patient's body, as these sensations reflect a functional vegetative state, whereas Western physiology describes the single vegetative mechanisms underneath these sensations. Spatial patterns of activation may lead to the sensation or assumption of "flows" of "qi" which may be interpreted as spatial shifts of activation patterns and the vegetative capacity of defined tissues to function.[3]

The clinical information obtained by the CM analysis has an own specific process of understanding, by comprehensive analysis of the physiology, pathological changes and every aspect of the phenotype of a disease, obtained through observation, listening, questioning and palpation including the pulse form and tongue appearance are used as predictors of interventions selection, therapy outcomes and prognostic indicators.[10,11]

According to the HM, a CM functional diagnosis is invariably derived from the following components: constitution, agent, orb, and guiding criterion (GC) (Figure 6):[1,3]

1. The *Constitution* of a patient, in Western language describes the vegetative reaction type of the patient, including at the same time a behavioural and emotional typology, the "inner nature" of the patient. The constitution also significantly determines expressivity (including pain experience), body tension, and the guidance of joints by connective tissue (e.g. in hypermobile spine), and also bondage intensity up to bondage addiction, co-addiction, and a tendency to particular forms of compulsion (so-called pulmonary and renal compulsions).

2. The *Agent*/pathogenic factor, causes the dysregulated, symptomatic state of the patient. For example, in pain therapy the agent primarily determines the modalities of pain (e.g. worse with

cold, change of weather, and draught), and from that depends the stimulation technique of needling. External agents are vegetative reaction types of the defence type against cold, draught, humidity, etc.; internal agents are emotions; neutral agents are, for example, overwork, physical effects, and poisoning.

3. The *Orb* ("organ pattern" or "functional circle" or circle for short, Latin: orbs) is the current disturbance pattern which also includes the current main symptom (part of a group of predefined diagnostic signs) interpreted in the context of the regulatory overall status of the patient. These groups of symptoms/ signs are an expression of the body regulation and are named after organ regions (body islands) which can become symptomatic within the overall pattern. Examples are the hepatic orb, cardiac orb, pulmonal orb, and renal orb. They are manifestations of a vegetative functional tendency which is called phase.

4. The *GC* (overall evaluation of the regulatory status), also called the backbone of CM physiology, are four fundamental physiological models used (Table 1), along which CM physiology can be structured, like this: the status of the neurovegetative system (Figure 6 below left, outside); the humoro-vegetative system, i.e. the fluid phase with microcirculation pattern (Figure 6 below left); the neuroimmunological system (Figure 6 below right) and the functional tissue (Figure 6 below right, outside) is determined by using the key symptoms. This allows the healthcare practitioner to evaluate from what region of control the current symptom most likely results.
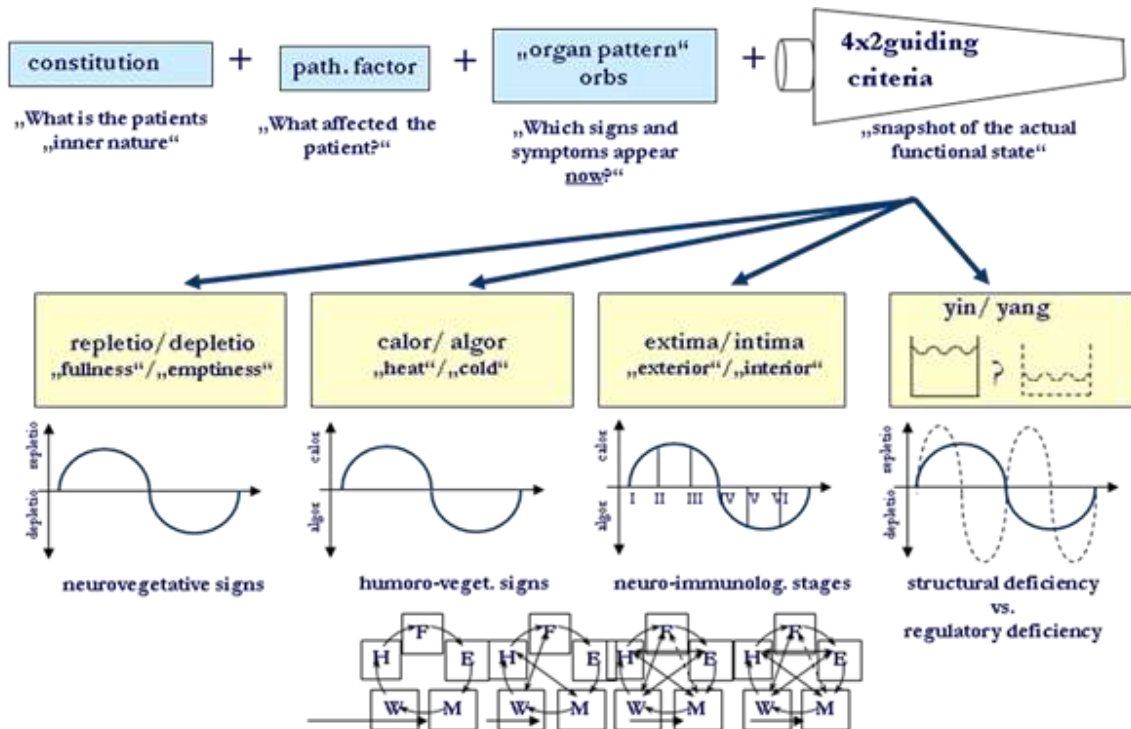
Figure 6: Components of diagnosis. Reproduced from Greten, 2013.[1]

Table 1: Guiding criteria and their significance in determining the overall regulatory status. Reproduced from Greten, 2013.[1]

Chinese guiding criterion	Level of regulation	Physiological process	Chinese perception
Repletion (over-fullness) *Depletion ("emptiness")* (the content of "qi")	1. Neurovegetative regulation	Increased activation by the nervous system. Decreased activation by the nervous system.	"To much capacity to function ('qi') in body and circuits" "Insufficient capacity to function ('qi') in body and circuits"
Calor/heat *Algor/cold*	2. Humorovegetative regulation and its up- and down-regulation of microcirculation ("interplay of blood cells, plasma, endothelium and parenchyma")	Increased microcirculation with pro-inflammatory effects and raised sympathetic tone. Decreased microcirculation with lack of inflammatory effects and sympathetic tone, reduced vigilance and unspecific defence reactions.	Excess activation of xue//blood (blood and its effects) and increased central nervous excitation. Insufficient activation of xue (blood and its effects).
Extima/outside *Intima/inside*	3. Neuroimmunological regulation	Early stages of disease. Late stages of disease.	Defence mechanisms active on the surface of the body. Defence mechanisms active in the depth of the body.
Yang (problem of the degree of unfolding function) *Yin (problem of the functional tissue or substrate)*	4. Cellular mechanisms	Control of functional tissue defect from outside. Defect in the cellular control of the functional tissue.	Problem on the levels named above. Problem resides in the cellular functional tissue, in the degree of hydration or in tissue supply.

Levels of regulation (in Western language) and their analogues in Chinese medical theory

The principle of diagnostics rests on an almost mathematical model of regulation and all components of diagnosis are exactly determined as part of a reflex pattern or vegetative functional state,[3] and from that depends largely the selection of acupoints and the stimulation technique chosed such as acupuncture, moxibustion and//or Manual Therapy, known as Tuina that can be combined with others CM therapeutic methods (cupping, Chinese herbs, dietetics, psychotherapy and mind-spiritual methods such as Qigong or Taijiquan).

3. Neuroimmunology and rheumatology, according to Chinese medicine

Autoimmune diseases such as RA show a participation of neurological-vegetative mechanisms as well as of the immune system. It is possible to associate the system of phases (regulatory states of the body), symbolized by the sine wave (uprising and descending energies), with (1) the neurological phenomena manifest in the system of the orbs and "qi" and, (2) the immunological functions and mechanisms in the reactions of the xue, which in CM are understood as the third GC.[1] This GC provides a deeper understanding of the complex symptomatology of RA.

According to this teaching, pathogen agents such as viruses, bacteria, toxic substances or cold, wind and humid environments, may change the surface of the connective tissue resulting in a dysbalance between the autonomic nervous system and an immune-activation and microcirculation disturbance.[3,6]

Within the language of CM, RA may be understood by the invasion of the body by external agents. If the aggression of the external agents overcome the six functional defence mechanisms layers, this process leads to systematic sequences of symptoms and manifestations in various parts of the channel and network vessel system from the skin and conduits//meridians (extima) to the body islands (intima), causing disturbances of aspects of bodily function that can be recognized by distinct constellations of signs and pulse conditions knowns as zhèng/"patterns".[3,6,12]

These defensive layers comprise six technically different forms of energy:[3,6,12]

- **defensive "qi"** ("wei qi"), which resides within the extima, outside the conduits and builds up a first barrier against external attacks;
- **conduit "qi"**, which is the "qi" within the conduits (also referred to as "cardinal qi", as the main conduits are the "cardinal conduits"). When an agent blocks the flow of "qi" in the conduits, this may primarily result in pain, and secondarily in functional disorders of the respective orb;
- **conduit "xue"**, which is driven by the conduit "qi" and warms the conduits, "nourishes" and "moisturizes" the tissues. The warming effect on the tissue is needed to drive out the agent algor;
- **body island "qi"**, which is the "qi" within the intima, a general name for the whole body's interior, where the functions of the orbs are generated in their respective parts of the body ("body islands");
- **body island "xue"**, which is a substantial yin part of the body islands with warming, functionally activating and enhancing properties;
- **yin**, which is the functional tissue; in Western terms the respective subpopulation of the cells, the substrate out of which functions (yang) develop.

In clinical practice, 90% of the RA symptoms and signs can be explained by the aggression of the external agent algor/"cold" which are characterized by six typical stages. If the aggression of the agent algor/"cold" persists, these stages may become chronic, and the "six stages" develop to disease patterns of their own.[1]

The Algor Leadens Theory (ALT) or Shang Han Lun (the Theory on Cold Damage) describes these six stages in detail and apparently contains speculations on the circular processes (sine wave). In principle, an attack on the body by algor (cold), the most important external agent in daily practice, evokes a neuro-immune mechanism defence reaction by the body, an increase of microcirculation also called calor (heat), along these functional powers (defence mechanisms layers) and associated with mainly two orbs (organ patterns).

3.1 Model of the six stages - Algor Leadens Theory (ALT)

The ALT is a specific way to interpret the GC extima/ intima: the stages I to III are extimal, stages IV to VI are intimal correlated (Figure 7). This model still combines the language of the orbs, which are signs and clinical symptoms indicating the functional neurovegetative state of the different body regions, with the language of the system of calor (heat) and algor (cold) that may stand for unspecific defence mechanisms and, in a Western sense, for effects of microcirculation as part of neuroimmunology.

	Stage I	Stage II	Stage III	Stage IV	Stage V	Stage VI
Name	Yang major/ Large yang (tai yang)	Splendor Yang/ Splendid yang (yang ming)	Yang minor/ small yang (shao yang)	Yin major/ large yin (tai yin)	Yin flectens/ yielding yin (jue yin)	Yin minor small yin (shao yin)
Conduits and orb/ functional circles involved	V-It/ B-SI	S-Ic/ S-Li	F-Tk/Gb-Tb	P-L/Lu-Sp	H-Pc/Lr-Pc	R-C/Ki-Ht
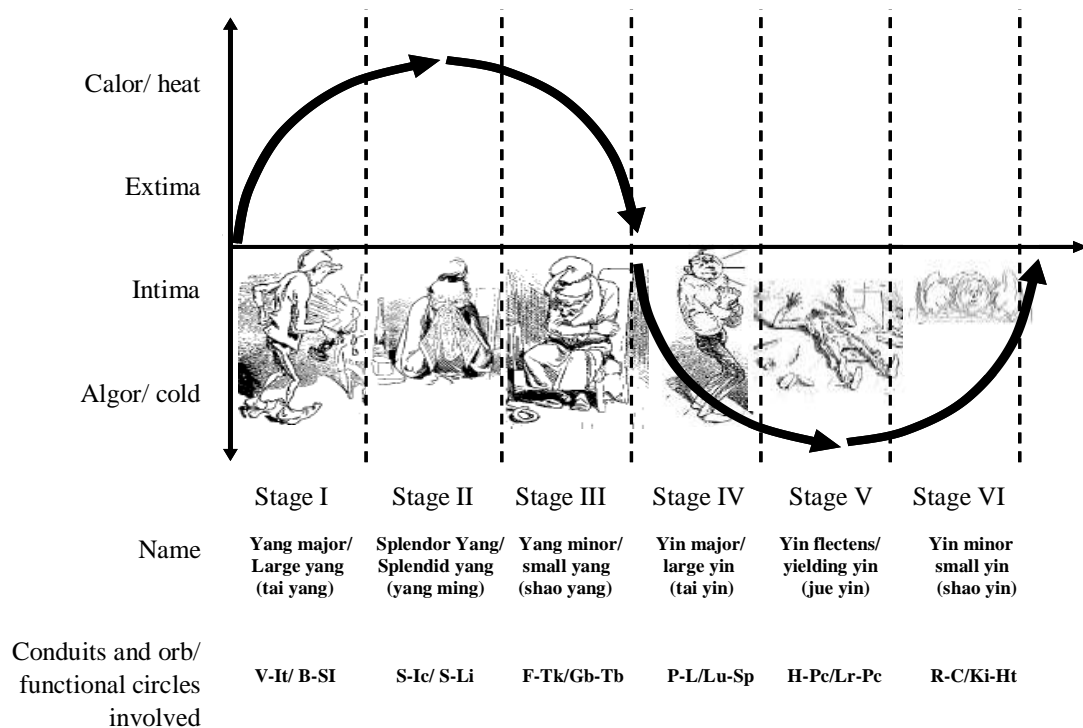
Figure 7: The teaching of the six stages (ALT) of the 3rd GC and Western diseases according to ALT stages. Reproduced from Greten, 2017.[1]

In Western terms, the invasion of the agent "cold/algor" may be roughly equivalent to "regional disturbance of microcirculation" and develops e.g. as a physiological defence reflex to cold; or immunologically e.g. by adhesion molecules and the coupling of complement and coagulation systems. The body reacts with a generalized increase in microcirculation (GC "heat"/calor) in order to eliminate the pathogen agent "cold"/algor. According to Western understanding, this reactive calor is comparable to generalized inflammation which is normally followed by activation of specific immunological mechanisms such as formation of antibodies, etc. If, however, the pathological factor algor invades further into the "interior"/intima, eventually a generalized decrease in microcirculation results (GC "cold"/algor) (Figure 7).[3]

This is an up and down (Figure 7) fluctuation, that can be described by a sine wave, of the temperature or the dynamics of xue, frequently indicating that there is some sort of immunological regulation involved manifested by neurovegetative dysregulatory signs. So, the six physiological stages of the ALT form a complete circle of stages that are seen as a model of neuro-immunomodulation or clinical neuro- or immuno-rheumatology.[3,12]

Stage I - Yang major//Taiyang:[3,12]

When the agent algor invades the skin, it "attacks" the defensive "qi" ("wei qi") inducing a localised regional deactivation of "xue", in Western terms a regional lack of microcirculation. If the body is able to specifically direct calor to the affected region, it produces generalised humoro-vegetative reactions with a general increase of microcirculation (GC calor), also known as "reactive heat",[13] as a generalised phenomenon to warm the conduits and the extima, thus trying to expel the invading algor. This correlates with typical pathophysiological changes as part of what is known as the "inflammatory response" in Western medicine.[13] The defensive "qi" does not sit in the conduits but in the skin surrounding the conduits and in all other tissues. Symptoms of the "wei qi" are various, but the clinically decisive one may be the symptom of a general sensation of cold shivering, induced by a deep-drawn sigh in the forearms. The skin may also be less compliant, cold and dry. This is what CM calls the "contracting" properties of algor. Algor, as a yin agent, diminishes the defensive "qi" like all other functional powers of the respective tissue. Algor, as a lack of microcirculation in Western terms, or as a de-activation of "xue" in Eastern terms, may affect firstly those conduits that contain more "xue" than "qi": the vesical (bladder) and tenuintestinal (small intestine) conduits.

In rheumatic disease, this stage tends to cause pain of the vertebral column (vesical conduit) or the joints of the head or shoulder pain (tenuintestinal conduit).

Affections of the vesical orb lead to retention of fluid resulting in humor (phlegm) in the extima (surface). In some patients there is a feeling of dull swollenness in the knees which is worse in the morning and contributes to morning stiffness which may also affect the feet.

Stage II - Splendor yang//yang ming:[3,12]

If expelling of algor fails, this agent may proceed to invading and blocking the qi of the conduits, thus causing tearing pain, functional disorders and calor which is generated as a reaction to expel the agent algor (cold from the conduit system). Then, the body activates "xue", which induces a reactive calor from the interior at a maximum to wash out algor within the conduits. When the agent algor enters the conduits, this leads to a regional block of "qi" and "xue" flow. "Qi" flow is blocked more easily than the flow of "xue", as "qi moves the xue". This is why phases and orbs depending more on "qi" and are most outside of the body are more prone to this affection.

"All depletion is a depletion of the centre" is an old rule of TCM, indicating that the centre is especially prone to a lack of "qi". The external conduit of Earth, the stomach conduit, is the extima of the orthopatic defence mechanisms. Therefore, the stomachal conduit is the most easily affected in this stage. The Crassintestinal (large intestine) orb belongs to Metal which controls the extima, and it is also easily affected.

At this stage, signs and symptoms could be described within an acute rhinosinusitis scenario. In case of rheumatic disease, e.g., this can be gonarthritis (course of the conduit) or prolapse of an intervertebral disk, as "the flesh cannot be held", with dull pain coexisting due to stomach orb function impairment. With the stomach orb affected, its functions of "bringing the turbid down", and of excreting humor (phlegm) are lowered. Therefore, humor and pituita accumulate mainly in the face, in the chest, in the knees and in connective tissue around the vertebral column resulting sometimes in back pain.

Stage III - Yang minor//Shaoyang:[3,12]

If the agent algor progresses further, then it invades the xue of the conduit. When the conduit xue is affected, it is natural that the outside orb of the phase Wood, which controls the flow of xue, is affected too. This is a special stage because the agent is sometimes already in the intima, and then is being expelled to the extima again, perhaps more accurately described as a "halfway pattern" since it is correctly conceived as disease located neither in the exterior nor in the interior, but between the two. So this is comparable to the door in a Wild West saloon. These doors open by swinging both inside and outside.

Though shaoyang disease is typically a halfway pattern, there may be a concurrent exterior pattern (manifest in heat effusion, mild aversion to cold, vexation pain of the joints and extremities, mild

retching, and propping bind below the heart) or an interior pattern (manifest in alternating aversion to cold and heat effusion, interior heat bind, persistent retching, distress below the heart, depression and vexation, and absence of stool). Other major signs are alternating aversion to cold and heat effusion, fullness in the chest and rib-side, taciturnity with no desire for food or drink, heart vexation, frequent retching, bitter taste in the mouth, dry throat, dizzy vision and white tongue. The pulse of shaoyang disease is one that is fine and stringlike. According Shang Han Lun, promotion of sweating and precipitation cannot be used, the appropriate treatment is harmonization.

The only constant thing in Stage III is the constant change of energies in the conduits, resulting in changes of symptoms. Another expression for this stage is the stage of the Turning Point (the hinge of a door) expressing:

a) The agent goes in and out, the only stable is the turning point
b) Mathematically speaking it is close to the axis of the function, which is a turning point too.

When the agent reaches the intima, this results in inner cold sensations, then again reactive calor is stronger than the agents and expels it to the extima, resulting in warm sensations of heat again. This scenario can be called cold-heat-cold-heat. In principle, this is a problem of exhaustion of intima capacity to develop heat, a capability linked to the xue.

"Xue" and "qi" comes from the interior and are lead through the system of conduits. If the agent algor overcomes "xue" flow within the conduit, this may lead to a reverse "xue" flow into the interior. Thus, algor reaches the interior, causing the sensation of inner cold. Often, "xue" from the inside (the yin) will be mobilised against the agent causing the sensation of internal heat again, or, if the agent algor is driven out, even temporarily, a sensation of external warming when reaching the skin (extima). The agent and "xue" flow within the conduit, drive each other in and out repeatedly. Mobilisation of internal heat is a feature of the phase Wood (mobilisation of potential), and, as this is still an extimal stage, leads to affection of the felleal (gall bladder) conduit. Also, this causes symptoms and signs of "imbalanced distribution" of energies, which is a main affection of the tricaloric (triple burner) orb. At this stage, signs and symptoms could be described within a hot-cold-nausea scenario.

The Shaoyang is often referred to as the "pivot", the central element of the three yangs. When a pathogenic agent enters the lesser yang (shaoyang), it causes inhibition of the pivot. Alternating aversion to cold and heat effusion, for example, is a manifestation of "right and evil struggling by turns". Aversion to cold occurs when the pathogen agent (evil "qi") prevails; heat effusion occurs when defence body mechanisms (right "qi") prevails, but right qi is unable to repel the evil through the exterior, and the evil qi is unable to advance into the interior. Thus in shaoyang, the disease, as it were, oscillates on the pivot. Basically, the pivot is one aspect of the "qi dynamic". Inhibition of the "qi" dynamic in the shaoyang

disease can have a variety of consequences, notably disturbance of spleen and stomach function. It is for this reason that retching is one of the main signs of shaoyang disease.[12]

In rheumatology and orthopaedics this is frequently seen as hip disease or lumboischialgia in the course of the felleal (gall bladder) conduit projecting to the sutures of your trousers.

In this stage the humor is not washed out, but may be transported into the inside of the body, as there is a contravection of qi flow by the agent algor. That is why in Stage III the humor begins to be present in the intima as well. This kind of humor often becomes chronic. By the relatively frequent calor constellation, the humor and pituita which are not cleared are consecutively dried out, they become hardened and by that made worse. Also, the tendons may be affected which tend to be swollen, hardened and painful as microcirculation cannot pass through the humor resulting in xue stasis and immense pain of various locations.

Stage IV - Yin maior//taiyin:[3,12]

From the fourth stage on, the main symptoms do not come from the conduits but more frequently from attack of the agent in the interior, the "body islands"; this will cause body island dysfunction inhibiting the physiologic processes in many ways. In Stage IV, cough and mucus are usual symptoms.

If calor is overwhelmed the agent algor can invade the interior, as the interior is then a zone of lack of microcirculation. All interior effects tend to start with a functional disturbance, as a consequence the body islands of the orbs are firstly affected in their function ("qi"), and in later stages in their "substance" "xue" (Stage V) and yin (Stage VI). When an agent affects the "qi" of the body islands, the lineal (spleen) and the pulmonal (lung) orbs are more often affected, as the Earth and Metal are sensitive to a diminished activity of "qi". At this stage, signs and symptoms could be described within a mucus and bronchitis scenario.

In rheumatic disorders this is often manifested in swollen joints, especially rhizarthrosis (pulmonal/ lung conduit) or in the knee (lineal/ spleen conduit).

The humor and pituita is now intensely accumulated and comes into the inside of the body. When algor blocks the pulmonary/ lung and lineal/ spleen orb, the amount of humor is dramatically increasing, therefore transforming and excreting humor by the lineal/ spleen orb is diminished and the clearing activity of the pulmonary/ lung orb is diminished as well.

Stage V - Yin flectens//Jueyin:[3,12]

The body island "xue" is a division of the yin, nourishing the yin thus providing the functional basis for the development of the yang. Therefore, this functional power is a necessity for the proper development of the qi of the body island. When the body island "xue" is affected by algor, qi and xue formation are interrupted as are all the functions associated with the xue. This may reach the lowest point of energy which is called the "flat-down" phase, like a car breakdown. At this point "xue" can even be used,

resulting in a lack of yin. This is the reason why this stage is called yin flectens, which means yin is vanishing. When algor affects "xue" within the interior, orb functions depending on "xue" are more easily affected than others. As the hepatic orb is considered to be the "mare xue" ("sea of blood"), the hepatic/ liver orb functions may be impaired together with the pericardic/ pericardium orb which is involved in pumping the blood and creating the pulse. At this stage, signs and symptoms could be described within a flat-down phase scenario (pneumonia).

In rheumatic disease this is frequently seen as tiredness and muscle weakness. There is an extreme weakness with no "qi", as "qi" to a certain degree is produced by the activity of "xue" ("xue is the mother of qi").

Stage VI - Yin minor//Shaoyin:[3,12]

The yin is both functional tissue and also a technical form of energy for the development of the functions (yang). When this energy is affected by algor, if the yin can defend successfully then we recover and keep up consciousness, but if the functional capacity of the yin is not strong enough to resist, the yin is functionally impaired, does not produce yang and renal/ kidney symptoms are most probable. Moreover, yang arises from the yin (in the language of the 4th GC), which is comparable by analogy to the process described in the technical terms of the 1st GC, as the development of "yang qi" upwards in a rapport with the cardiac "qi". This connection is also expressed in terms of a cardio-renal axis, in which the yin pole is the renal/ kidney orb and the yang pole is the cardiac/ heart orb. At this stage, signs and symptoms could be described within a convalescence scenario.

Also yin minor is a Turning Point stage as it approaches the axis of the mathematical function.

In rheumatic disorders weakness in the legs, weakness in the back and aching bones are observed. In this stage, all humor and pituita accumulation is still presented and the renal/ kidney orb is weakened too. The renal/ kidney orb reigns the lower caloric, where the humor is excreted. There is also humor from the renal/ kidney orb itself which controls the body fluids. This control of body fluids, as a general phenomenon, is not present as much as before. So humor and pituita reach high levels. When Stage VI arrives additional oedema is caused by the extreme weakness, by – according to Western medicine – congestive heart failure and pre-renal oedema formation. Therefore, the oedema (humor) is formed everywhere in the yin, and if not excreted the patient might even die.

Outside//inside hopping:[3,12]

The ALT stages are composed of specific signs of two orbs each. All conduits are coupled with a second conduit of the same phase. The connections between the extimal and intimal conduit of one phase are present between all points of a conduit which has the respective point on the other side. In the case that the heat and the functional powers of the intima are strong, the agent cannot invade the intima directly.

Alternatively, it may pass from an extimal conduit via the luo xue (foramina nexoria) connections to the coupled conduit of the same phase. This is assumed to occur via outside//inside hopping.

Outside/inside hopping is a new variant for new causes of disease. One of the consequences of the ALT is that, when algor has invaded, the original direction is sometimes reversed, because algor has changed the direction of the flow by overwhelming the course of the conduit.

Hopping stages: instead of seeing the copulated two conduits according to the phases, we can envisage them copulated in the order of the stages:

- Stage I to Stage VI: Geriatric (general and bone pain),
- Stage II to Stage IV: Chronic area diseases (Disease Pulmonar Obstrutive Chronic, bronchitis) (mucosa inflammation),
- Stage III to Stage V: Burnout, irritable stress.

Mathematically it is possible to create a model for qi and xue with two curves in which both curves create a ball, because both curves proceed vertically to each other.

In this case, every human manifestation would be mathematically like a ball in an optimum state of regulation (orthopathic, lineal). In cases of deviations from this regulated state the ball would look "like an egg" (heteropathic, sloping position).

We can also put the ALT model into the classical "compass rose" form (3) (Figure 8).
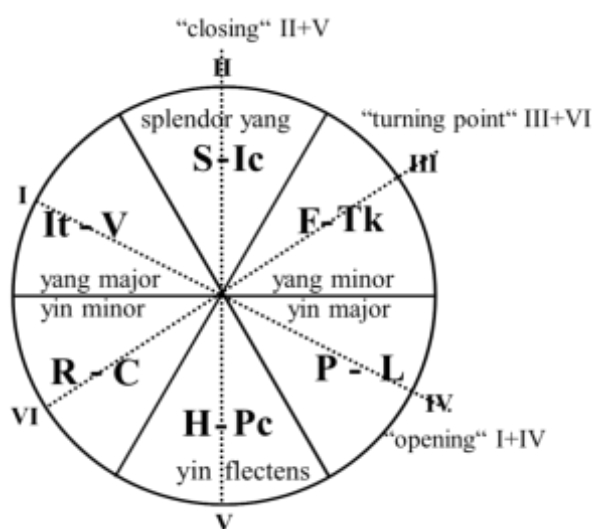
Figure 8 – Algor Laedens Theory expressed as "compass rose". Reproduced from Greten, 2017.[3]

Then we get a traditional classic version of the ALT in which we have a connection between the phases that are on opposite sides to each other. Therefore, we can divide the 6 stages into 3 x 2 stages:[3]

- Stage of the defence of attacks on the outside (Stage I) or defence originating from the inside (Stage IV) The curves mathematically open up to the top ("Opening Principle");

- Stage of the maximum of the symptoms (Stages II and V): "Closing Principle" which means that at the extreme points of the curves we already have the turn of the curve included. At all extremes we already have the opposite pole included, the yin only exists together with the yang. Therefore, the curve "closes" and proceeds into the direction of the target value;

- Stage of the decision, the "Turning point" stage (Stages III and VI). The curve is on its turning point, the point between inside and outside. Here it will be decided whether the agent algor will proceed into the intima or not (Stage III) or whether recovery will take place or not (Stage VI).

During the course of the ALT stages, analogous to the progress of the neuro-immune diseases process, stiffness (lack of microcirculation); dampness or turbidity (humor) and induced phlegm stagnation (xue stasis) will take place as the precipitating factors, which causes congelatio and concretio. Due to intermingled cold and/or heat from the exterior and due to deficiency and//or repletion in the interior, the zang-fu organs, qi and blood, yin and yang will be deficient and debilitated, and if the pathogen attack persists over time, the infection process may become chronic.[3] The main symptoms such as stiffness of the joints, retarded flexion and extension, deformity and contracture of the bones and muscles will appear.[14]

3.2 Understanding Rheumatoid Arthritis from a Chinese Medicine perspective

With regard to RA pathophysiology, Western and CM share some points. Both medicines consider that the innate immune system of the cholinergic anti-inflammatory pathway may predispose some individuals to excessive cytokine responses,[3,14] neuro-endocrine-immune (NEI) abnormality, autonomic nervous system – the sympathicus and parasympathicus – dysregulation, interaction between individual genetic background (for example HLA-DRB1 gene) and environmental risk factors (such as viral infections, smoking, diet and region of birth), all play a pivotal role in the pathogenesis of RA.[15] Symptoms as stiff joints, swollen joints, fever and pain with redness and swelling are commonly described by Western and CM.[14] However, in CM RA is not only a rheumatologic disease with its joint related symptoms.[16]

The signs and symptoms such as joint deformity, arthralgia, swelling, heavy sensation of the joints and migratory pain, are interpreted by CM as a disharmony between the functions of the orbs. The joint nonrelated symptoms, the disharmony between extrinsic and intrinsic factors, neurological vegetative manifestations, are part of the CM diagnostic and therapeutic parameters that might help finding specific indications for therapies.[3,16]

In RA neuronal pathways activation by inflammatory mediators are comparable to vegetative and sensory nerve functions caused by pain, and in CM are often explained by dysfunctional patterns like the orbs or the stages of the ALT or by patterns resembling the agents. For instance, the CM diagnosis for the inflammatory state is designed as calor (second GC) and all the characteristics of acute inflammation with swelling, reddishness or pulsating pain is defined as ardor (agent).[3]

Analysis of the symptoms and signs recognized in CM might point towards to different RA patients' subtypes:

(1) Bi-syndrome

In CM theory, RA is often classified as part of a group of syndromes, called the "Bi-syndromes" or occlusion syndrome.[17,18] The character "Bi" means blockage or obstruction of "qi" and "xue" (blood) in the conduits, as a result of invasion of muscles and bones by external pathogenic agents as wind, cold, dampness or heat on the conduits (meridians).[17] That block induces pain conditions, soreness or numbness of muscles, tendons and joints, heavy sensation, swelling of joints and limbs, limitation of movements, internal//general weakness of the body as well as the "wei qi" defences mechanisms, poor or deficient circulation of "qi" and "xue" (stasis).[19]

Distinction is made between three pattern types, each of which corresponds to a prevalence of one of those three evils:[48]

- wind impediment (or moving impediment) characterized by wandering pain and attributed to a prevalence of wind;

- cold impediment (or painful impediment) characterized by acute pain and attributed to a prevalence of cold;

- damp impediment (or fixed impediment) characterized by heaviness and attributed to a prevalence of dampness.

A fourth type, heat impediment, arises when the three evils transform into heat.

(2) Heat ("calor") and cold ("algor")

Heat and cold, classified as "calor" and "algor" in the HM, respectively, are medical classifications commonly used in Chinese medical schools. The clinical signs and symptoms indicating the presence of calor/"heat" and algor/"cold" can be explained today by physiological mechanisms (Table 2).[1]

Table 2: Symptoms of "heat" (calor") and "cold" (algor)

"Heat" (Calor)	"Cold" (Algor)	Differential symptoms
Reddish tongue with a yellow coating	Pale tongue	Calor: cardial repletion; Algor: lack of xue
Reddish skin; Flushed face; Fever	Pale skin; Cold feeling	Calor: ventus, ardor, aestus

Pulsus celer (rapid//fast)	Pulsus tardus (slow)	Calor: strong yin-(Fluids)-deficit
Scarce quantity of yellowish urine	Large quantity of light, clear urine (odourless)	
Dry constipation	Constipation or loose stools	Calor: depletion renalis; lack of fluids, yin deficiency
Tendency to body odour	Body smell unremarkable	Calor: aestus, repletion hepatic; algor: lack of xue, yin deficiency
Possibly thirst	Abcense of thirst	Calor: depletion stomachal; Algor: repletion stomachal
Dry mucosa of mouth, nose, airways	Moist mucosa of mouth, nose, airways	Calor: ariditas, Lack of fluids, possibly agent algor
Severe pain, worse under pressure and warm, generally relieved by applying cold to the joints.	Severe pain in a joint or muscle that limits the range of comfortable movement with localized and better under pressure.	Calor: ventus, repletion; Algor: agent algor, depletion
Pain may be burning (worse with warm).	Pain better with warmth and worse with exposures to a cold environment.	Calor: - ; algor: agent algor
Irritability, restlessness, reactive heat with yin affection.	Tiredness	Calor: repletion pericardial; Algor: depletion pericardial

According to the vegetative regulatory approach of the HM of CM, these two classic patterns are part of the four regulatory models of physiology and interpreted as humoro-vegetative (2nd GC) (see Table 1).[3]

In rheumatology the heat pattern is characterized by severe pain with hot, red, swollen and inflamed joints. Pain is generally relieved by applying cold to the joints. Other symptoms include fever, thirst, a flushed face, irritability, restlessness, constipation, deep-coloured urine, reactive heat with yin affection. The tongue may be red with a yellow coating, and the pulse may be rapid.[17]

On the other side is the algor/"cold" pattern distinguished by markedly diminished microcirculation, reduced vigilance and unspecific defence reactions (or the diminished dynamics, under-activity, "yin" on the understanding of CM).[3] The "cold" pattern can be described by severe pain in a joint or muscle that limits the range of comfortable movement with pain that does not move to other locations and is relieved by applying warmth to the affected area but, increases with exposure to cold.[17] Loose stools are characteristic of this pattern, as well as clear profuse urine and an absence of thirst.[17] A thin, white tongue coating is observable, combined with a wiry and tight pulse.[17]

Therefore, there is little controversy over how to classify patients into the two categories although patients can express both "cold" and "heat" symptoms at the same time. According to Zhang and colleagues, approximately half of the RA patients in the general population fall into the "cold" type while approximately 16% are classified as the "heat" type.[17]

(3) Deficiency pattern

The fourth partial teaching of CM (4th GC) is the theory of yin, the functional tissue or substrate to be regulated, and yang, the over- or undergrade function arising from it. It is a law of cybernetics that in a case of diminished substrate a labile actual//target curve results. This is comparable to the regulation of temperature in a laboratory incubator and the great fluctuations seen when the volume of water, i.e. the substrate to be regulated, is going to be used up. This complex theory leads to the mathematical speculation about the influence of constitutional factors on regulation.

The deficiency pattern is an analogous understanding of an insufficient cell population (yin deficiency),[3] categorized by deformity, inhibited bending and stretching in limbs; pain occurring or worsening during moodiness and numbness.[20] These symptoms clinically occur in the later stage of disease or later than other common articular symptoms such as pain with cold or hot feeling and swelling.[20] If the yin is in deficit (weak or insufficient cell population), it would then be stimulated in excess to temporarily augment the function. This function cannot be kept up, so a functional deficit will result. This is why, from a Western point of view, deficiency of body structure, results in changing symptoms caused by overstimulation or lack of function; these functions are difficult to understand without a regulatory theory.[3]

This deficiency pattern may be due to:

- Deficiency of the Renal//Kidney orb yin and yang that is the foundation of yang qi and mainly manifests as deficiency and cold of the whole body.[11] According to the theory of CM, the kidney masters the bones which has close relationship with the pathogenesis of RA. The kidney-yang deficiency pattern was an overall performance of multisystems and organs dysfunction of nervous system, endocrine system, and immune system.[11] The signal transduction abnormalities among cells may play a key role in the development and progression of RA. Various common signal molecules and receptors in nervous, endocrinology, and immune system are the molecule structure basis of NEI network.[11]

- Deficiency of the liver (yin and yang deficiency).

- Deficiency of the qi, xue and yin.

3.3 Rheumatic pain

The functions of the body are in a constant diligence equilibrium, which we describe in the CM as the phases or the qi of the orbs.

Successively, the functional principles of the phases become effective in the body. From this follows the sequence wood-fire-earth-metal-water and a continuous flowing change of the vegetative functions (qi) associated with these phases. The sequence of the phases is accompanied by an increased vegetative activation of certain body parts ("organs"). In the terms of Western medicine, this can be interpreted as a successive neuro-vegetative activation and activation of the body regions. This activation is always

accompanied by other functional changes in the body that correspond to the inter-limiting regulatory function of the phases.[3]

Disturbances of functional vegetative transitions becomes sensorily detectable or "unnormal" to the individual and therefore appears to be symptomatic, for example, symptoms such as pain develop. "Something is wrong within the body" but this is sometimes hard to express verbally for the patient. The individual symptomatic function emerges from the continuum of the innumerable processes within the body. This is interpreted as an obstacle, and this can be translated into Western functional categories as a block of vegetative functional transitions. According to the fact that vegetative functions are mirrored by the skin, this leads to functional changes in skin areas which are called conduits or meridians.[1]

According to the HM, there are four main approaches that may lead to functional disorders:[3]

1. **Problems of transition between the phases**, characterized by a lack of transformation in the body. This may be due to an insufficiency of Earth phase, the transforming power within the wheel of phases.

2. **Over-eliciting of an agent,** the continuous stimulation of a pathological agent, leading to an excess of the respective vector (over-initiation of a phase). Pathogen agents include: exterior agents (like algor/ "cold", ventus/"wind", humor/"phlegm, ariditas/"dryness", aestus/"summer heat", ardor/"hot"); interior agents (emotions such as anxiety, stress, anger, fear or grief) or neutral agents (like stress, poor nutrition, weather conditions, hereditary factors, infections and trauma).[21]

3. **Imbalance and instability of antagonists** on the phase system and correspondent vector, leading to an imbalance.

4. **Yin deficiency** characterized by a lack of body substance or structure, which causes an extreme course of the regulatory circular function.

Functional deviation pattern or disorders occurs when a non-transition of the wave from one part to the other of the body occurs. So, the transition from one tissue to the next of this vegetative action does not take place.

Three aspects should be emphasized here:

1. Tissue Activation

The increased tissue activation (in CM: more qi, "fullness" or repletio) of a target tissue of the body can be explained as a purely sensory phenomenon in which the functional increase in microcirculation may contribute to the sensation of expansion.[1] In Western terms neuro-impulses which should evenly

distribute over the tissues then concentrate on one tissue, a site of the body that finally is felt as painful.[22] Activated tissue will need more oxygen and more blood flow in the capillaries and corresponds to hot (calor) patterns or GC. For rheumatic pain therapy, this primarily means that pain increases on pressure. According to the classical rules, such conditions require deactivating interventions at the sensitive skin areas, such as the needling technique of "dispelling" (dispulsion) to lowering the sympathetic activation pattern within a tissue that depends on a certain point.[22]

On the contrary, the "emptied" points of the skin are associated with decreased tissue activation (in CM: less qi, "emptiness" or depletio) of the target tissue. It may be explained, in a Western sense, by the fact that after the site of blocked transition (region posterior) of the spatial wave of neuroactivation there is a lack of sympathetic action and a relative over-representation of vagal and de-activating stimuli.[22] De-activated tissue will show less blood flow and corresponds to cold (algor) patterns.[1] For pain therapy, this means that pain, one of the key symptoms which go along with this functional deactivation, becomes better on pressure, for example, when a patient intuitively presses his aching stomach with his hands. Such conditions demand stimulating interventions on these rather indolent skin areas such as the needling technique of suppletion which is also sometimes called tonification. This effect may be explained by a stronger perception of the dependent area by the central nervous system resulting in a regulation of the feedback mechanism of vegetative impulses.[22]

2. *Spatial Pattern of Sensations*

The functional finding of palpation and, by that, the functional state of the skin therefore correlate – comparable to Head's concept – with a vegetative functional state of the tissue within the interior of the body.[22]

Accordingly, the related sensations of "over-fullness" or "emptiness" principally correlate with the picture of vegetative activation. CM holds that not all regions of the body (body islands) have the same degree of activation (content of qi) at the same time but that there are different regions that are regularly activated in specific sequences.[22] This is a functional picture, quite analogous to the vegetative activation patterns of Western physiology in which, according to certain functional necessities, certain tissues may be activated according to the functional challenges of life.[22] For instance, the region of the heart will be stimulated by the sympathetic nervous system during physical exercise, and the region of the heart (the body island) may be felt more intensely than before.

According to this principle, even less dramatic challenges like keeping up with the regular homoeostasis of vegetative functions may be seen as a complex pattern of a spatial activation of parts of the body resulting in a spatial shift of activation and therefore minute sensations of "fullness" and "emptiness".

As most vegetative functions work on a subconscious level, this may not regularly be "felt" unless irregular patterns of activation take place. Consecutive spatial changes in the skin lead to the thesis of a "flow of qi" or activation patterns.

CM has a regulatory theory on vegetative activation which is quite compatible with Western physiology. As a general idea, CM describes physical sensations of the patient, whereas Western physiology describes the single vegetative mechanisms underlying these sensations. Spatial patterns of activation may lead to the sensation or assumption of "flows" of qi which may be interpreted as spatial shifts of activation patterns and the vegetative capacity to function of defined tissues.[22]

3. Qi Flow in the Conduits

If the qi flow is blocked for a longer time, even xue will not flow, resulting in xue stagnation and finally xue stasis.[22] Stagnation of xue is comparable to a slight venous congestion of microcirculation and the main clinical signs, according the CM, are livid tissues and tissues that show dark blood flowing out of the point into which you have inserted a needle. The stagnation blood flow, of xue, can be enhanced and ascend for what CM call acute xue stasis, typically manifested by acute pain of a stabbing nature. Outflow of dark red blood from punctured sites is an important sign of this acute stasis. So we have something like a microcapillary microthrombosis. Therefore, the reaction of surrounding tissue is to dissolve this microthrombosis, this intravascular coagulation.[22]

According to CM, the root cause of pain is mainly due to the stagnation, full or partial blockade of the normal neurovascular flow in regions of human body and abnormal impedances.[23] In the case of RA, stagnation in the joints will produce arthritis pain but if the stagnation or blockade of the neurovascular flow in that part of the body is removed, then the pain syndrome will also disappear.[23]

In chronic rheumatic pain the basic idea is that the brain with its plasticity always adapts to function and malfunction. In the case of pain this may mean that malfunctioning vegetative circuits and pathways are engrammed by the build-up of synapses and thereby are stabilized and used preferentially.

As these pathways in chronic pain are used in preference to the natural and pain-free circuits, the pain process becomes self-determined and independent, like a vicious circle. Pain may cause the onset of a neuronal pathway. The neuronal pathway then is stabilized by synapse formation and in certain cases even myelinisation and metabolic and transmitter changes which cause pain again. The Western model of pain therefore gives us an explanation why some cases of chronic pain are hard to treat and the pain mechanisms have to be interrupted at various levels simultaneously.[23]

4. Complementary and alternative medicine used by patients with RA – effectiveness and safeness

Almost 60–90% of arthritis patients unsatisfied with conventional Western medicine use Complementary and Alternative Medicines (CAMs), including acupuncture.[24,25,26] Pharmacotherapy, manual therapy (tuina), specific exercises like the methods of qigong or taiji of CM, or the autogenic training of Western medicine, psychosomatic treatment, lifestyle changes, and other concepts.

The American College of Rheumatology (ACR) supports rigorous scientific evaluation of all modalities that improve the treatment of rheumatic diseases and the integration of those proven to be safe and effective by scientifically rigorous clinical trials published in the biomedical peer review literature. However, the ACR understands that certain characteristics of some CAMs and some conventional medical interventions make it difficult or impossible to conduct standard randomized controlled trials (RCTs). For these modalities, innovative methods of evaluation are needed, as are measures and standards for the generation and interpretation of evidence. In the absence of such rigorous clinical trials, the ACR recommends advising patients that potential harm can occur from unproven or alternative therapies and thus advises caution in the use of unproven treatments.[27]

4.1 Acupuncture as a West–Eastern Reflex Therapy

Acupuncture is part of Chinese medical methodology and is generally one of the most popular sensory stimulation techniques of CM, originating in China more than 3,000 years ago,[28] and is currently flourishing in the United States and in Europe as primary and adjunctive therapy for a variety of chronic conditions.[29]

Classically acupuncture is described as the insertion of a metallic needle into specific body areas (acupoints located on the meridians/conduits or in extra-meridian acupoints), or in specialized approaches, known as microsystems, such as hand-foot acupuncture, auricular and scalp acupuncture.

Acupuncture as a reflex therapy can therefore be regarded as a functional vegetative therapy. Western medical language calls this vegetative spatial distribution of neuro-vegetative impulses, whereas the Chinese explanation is qi flow.

The effect of acupuncture as a reflexology phenomenon is also determined by the kind of swift stimulation until the appearance of the qi phenomenon or *de qi* (acquisition of energy, i.e., a mixed sensation of soreness, numbness, swelling, sinking, and hot sensation appears in acupoints). As physiology knows, the kind of stimulus for sensory organs and structures, the diversity of the effects which may be elicited by acupoints, according to CM and Western physiology, may even unfold

opposite effects according to the kind of stimulation and may or may not have an effect, depending on the stimulation frequency.[1]

The most important kinds of stimulation are:[1]

– Vegetatively activating techniques, which are called "suppletive" or tonifying methods, which replenish the functional capacities ("energies").

– Deactivating techniques, which are called "dispulsive" methods, distribute the functional capacity of an over-reactive target tissue and thereby return it to normal.

– Warming techniques, for example, moxibustion increases microcirculation within the target tissue and thereby treats the most frequent origin of pain encountered in daily practice, the so-called algor/"cold" reflex.

– Cupping, bloody cupping and bloody needling. They all have an effect on the content of fluid within a tissue and seemingly affect the venous outflow of microcirculation.

– Manual techniques of Chinese manual therapy (tui na an mo). There are more than 50 different methods to influence target tissues, zones of the connective tissue and acupoints.

– Physical stimulation techniques like the application of electric current in various frequencies, laser stream or the application of magnetic balls (the so-called Gecko Ball).

– Pestle acupunture is an interesting application of stimulatory metal pestles of various kinds.

– Scratching or scraping which is frequently combined with different oils, partly with etheric components.

– Tapping

– Application of ointments and injection of various substances like V-poison, ant venom, or homoeopathic substances (sino-homoeopathy).

The neurophysiological mechanisms of acupuncture

The effects of acupuncture can nowadays be well explained by neurophysiological mechanisms that underly this kind of therapy. One can divide them into peripheral and central effects.

– *Peripheral effects* of acupuncture are those effects which directly affect the symptomatic target tissues involved. They include improvement of microcirculation, relaxation of muscles, and activation and deactivation of tissue functions such as peristalsis or effects on nasal and bronchial secretions and other functions of mucous membranes, etc.[1]

– *Central nervous effects* are those effects of acupuncture which have been shown within the brain or the spinal cord and which are believed to change the functional perception of the body and by doing so, change the symptoms. These functions include the release of endogenous opioids (encephalin, dynorphin, β-endorphin and endomorphin) and serotonin (5-HT) in acupuncture-mediated analgesia, the

stimulation of complex pain suppression mechanisms, for example, as part of the gate-control theory of pain and other mechanisms.[1]

Acupuncture has influence on neurohumoral mechanisms of regulation. For example, increased vagal stimulation by acupuncture may down-regulate macrophage activation and suppress synthesis of tumor necrosis factor (TNF) and other peripheral pro-inflammatory cytokines (Figure 8). Some important effects take place on the level of spinal cord where C-fibres mediate sensations on the laminae 3 and 4, which lead to further mechanisms of pain reduction in the periaqueductal grey and are especially important for the perception of pain.[1]

Studies with positron emission tomography have shown increments in the binding of μ-opioids to receptors in the brain after several days of acupuncture.[30] Functional Resonance Magnetic Imaging research has correlated acupuncture with activation of the basal anterior brain, limbic system and other areas of the brain related to affective and somatosensory functions.[31]
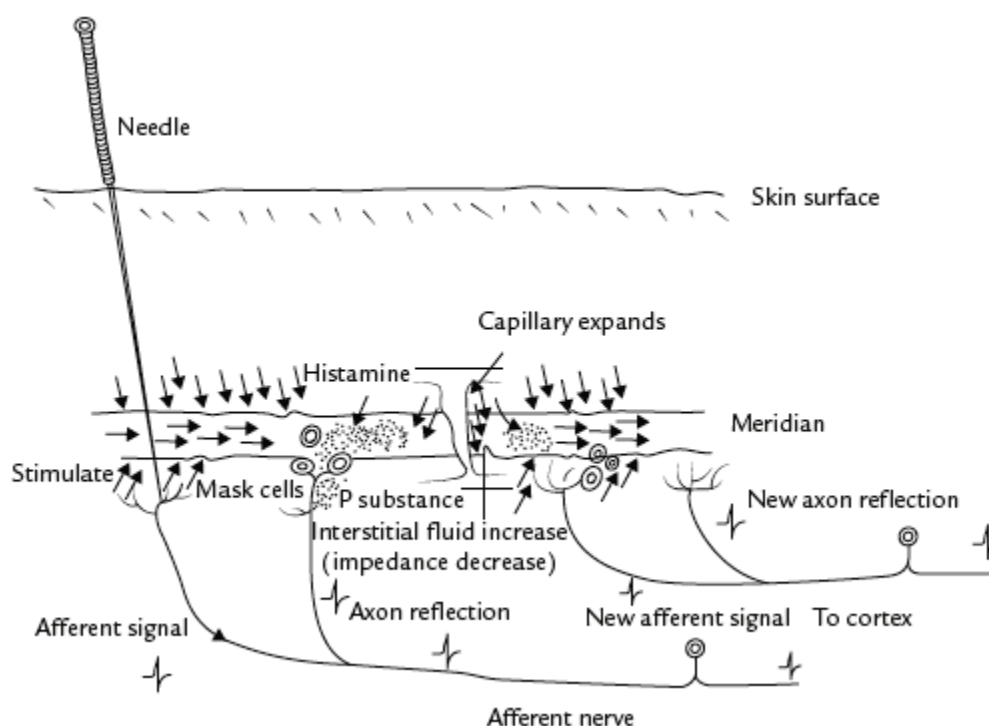
Figure 9 – Proposed mechanism for the effect of acupuncture along meridians.[32]

The neural hypothesis behind acupuncture in pain treatment action could be described as follows: the acupuncture needle activates a sensory receptor inside the muscle, and this sends impulses to the spinal cord via the cell type II and III muscle afferent nerves (small diameter myelinated afferents).[33] Type II afferents are thought to signal the numbness of *de qi* needling sensations and type III the fullness (heaviness and mild aching) sensation. These send impulses to the spinal cord and activate three centres (spinal cord, midbrain, and hypothalamus/pituitary) to cause analgesia. The spinal site uses enkephalin

and dynorphin to block incoming messages with stimulation at low frequencies, and other transmitters (perhaps gamma-amino butyric acid, or gamma-aminobutyric acid) with stimulation at high frequencies. The midbrain or mesencephalom uses enkephalin to activate the raphe descending system, which inhibits spinal cord pain transmission by a synergistic effect of the monoamines, serotonin and norepinephrine. The midbrain also has a circuit, which bypasses the endorphinergic links at high frequency stimulation. Finally, at the hypothalamus/pituitary centre, the pituitary releases β-endorphin into the blood and cerebrospinal fluid to cause analgesia at a distance. In addition, the hypothalamus sends long axons to the midbrain and activates the descending analgesia system via β-endorphin. This third centre is not activated at high frequency stimulation but only at low frequency. Also, the small afferent nerve fibres have numerous peptides around their terminals, including cholecystokinin, somatostatin, neurotensin, bombesin, calcitonin gene-related peptide, angiotensin, substance P, and vasoactive intestinal peptide, which may play a role in acupuncture, acting like the opiate antagonist naloxone to block endorphin-mediated acupuncture analgesia.[33]

Unspecific and Specific Effects of Acupuncture

– *Unspecific effects* of needling are effects which may basically be induced by penetration of a needle by any kind on any part of the skin. They consist of a bunch of physiological and also suggestive effects, for example, the momentary elevation of the sympathetic tone, release of adrenalin and changes in vigilance by stimulation of the reticular arousal system (formatio reticularis). Some of these mechanisms may also lead to a phenomenon that is sometimes called peripheral counter-stimulation, which is understood as a way of masking a sensation by eliciting a second one which, within our perception, covers the first one and hides sensations like pain and others.[1]

– *Specific effects*, which can only be elicited by the stimulation of acupuncture points, may be seen as a local enhancement of peripheral microcirculation, control of heart rate (up- and down-regulation), of blood pressure, effects on peristalsis and the vagal tone, of peripheral pain, and numerous other vegetative functions which may affect the local origins of pain and also induce functional changes in specific areas of the brain.[1]

Acupuncture studies – methodological shortcomings and contradictory data

The data supporting efficacy of acupuncture are controversial. For example, many clinical trials and experimental studies claim that verum acupuncture and needling of unspecific skin points (non-acupoints) or sham acupuncture had only minor differences in the success of treatment.[34] Sometimes this is interpreted in the sense that the sham acupuncture is as effective as verum acupuncture. This

interpretation, however, contradicts the numerous animal experiments and clinical data in which specific acupuncture effects were already objectively recognized.

The proof of efficacy in human studies reveals some methodological difficulties:

- There is no real placebo which means a placebo without any physiological effects.[48]

- Some of the so-called sham acupunctures as used in some of the main studies have putative effects on the symptomatology by segmental mechanisms, the zones of Head, and other mechanisms.[35]

- A considerable number of acupuncture studies have no standard sham acupuncture control and many other factors can affect the clinical effect. These factors include needle retention time, treatment frequency, and the total number of treatments needed for satisfactory results, and all can change the clinical effect.[36]

- Lack of blinding and double-blinding is a specific problem of acupuncture research, as especially in studies with a lot of participants even single-blinding ended up in premature unblinding.[37]

It is still too early to conclude that sham acupuncture is as effective as traditional Chinese acupuncture. If we look at the selection criteria of the points, in the majority of existing acupuncture treatment studies the allocation of acupoints for the treatment depended largely on Western diagnoses without prior definition of the key symptoms and the guiding findings of CM.

According to tradition, the selection of points and the selection of the kind of stimulation are made on the basis of key symptoms arising from the patient's history and examination. These key symptoms are then ordered according to an objectifiable hierarchy – at least in the scientific form of CM.[3] The vegetative functional status is derived from one order of key symptoms, i.e. the (pathological) reflexological state in which the patient presents. This is the basis for selecting the point and the stimulation pattern for healing reflexes (acupuncture) in each individual case.[1]

How acupuncture treats RA

As many factors are involved in the pathogenesis of RA, including susceptibility genes, disease-causing immune cells, cytokine, and signal transduction networks, the treatment of RA has always been a challenge. The mainstream of the management regarding RA is the use of nonsteroid anti-inflammatory drugs, disease-modifying antirheumatic drugs (DMARDs), analgesics, and biological agents. But concerns may arise when taking the accompanying side effects and toxicity into consideration.

Given the fact of the expanding awareness of unwanted side effects of pharmaceutical treatment, there has been an increased utilization of acupuncture as a contemporary healthcare option which has been reported as a kind of safe management. Some countries have decided to pay for acupuncture by the

social security system for certain indications which further augments its position in the multimodal concept of integrative therapy.

Discrepancy exists between previously conducted investigations and reviews regarding clinical efficacy of acupuncture for RA.

The actual mechanism by which acupuncture works also remains controversial. Among all the proposed mechanisms, anti-inflammatory effect has been the most often mentioned which was supposed to provide non-analgesic effects via suppression of inflammatory response, improvement of blood flow, or relaxation of muscle tone, but they are still largely conjectural. Others include the reduction of erythrocyte sedimentation rate and c-reactiv protein, lower TNF-α and vascular endothelial growth factor (VEGF) in peripheral blood and joint synovia after acupuncture in RA subjects,[38] regulation of the plasma adrenocorticotropic hormone, serum cortisol levels, activity of synovial nuclear factor (NF)-κB, and the release of endorphins.[38]

Other possible mechanisms could be attributed to the antioxidative effect, such as inducing the increased activities of superoxide dismutase and catalase in the serum of RA, alleviating oxidative stress and inflammation, and improving antioxidant and energy metabolic status.[38]

Results of a systematic review show that there are 120 acupuncture prescriptions and 143 acupoints selection to treat RA.[39] The selection of acupoints has not been very unanimous according to the authors' clinical experience and CM theory applied. Some investigations used single acupoint while some used more than 10 acupoints.[38]

Local acupoints are mainly used for disease locations. Zusanli (Stomach 36) is the most frequently used acupoint followed by Yanglingquan (Gallbladder 34), Hegu (Large Intestine 4), Kunlun (Bladder 60) and Xuanzhong (Gallbladder 39).[38]

Lim et al. found that the anti-inflammatory effects of Zusanli (Stomach 36) rely on the vagus nerve pathway.[40] Manual acupuncture stimulation relieves systemic inflammation, by downregulating TNF-α, which implies the direct involvement of the vagus nerve in the modulation of TNF-α. However, electroacupuncture has the opposite effect when applied to Zusanli (Stomach 36). By testing the effects that a splenic neurectomy and vagotomy have on TNF-α levels in the spleen and the brain, the researchers found that TNF-α induced in the spleen and the serum after lipopolysaccharides administration may be modulated by acupuncture stimulation.[40]

A systematic review was developed which aimed to analyze the most recent state of scientific evidence-based worldwide published studies and possibly identify scientific findings which could enable evaluation of whether acupuncture is effective in pain relief, physical function (PF) and Health Related Quality of Life (HRQoL) improvement in patients with RA (see Chapter 3). Results of the systematic review suggested that acupuncture interventions may have a positive effect in pain relief, PF and HRQoL in RA patients. However, due to the heterogeneity and methodologic limitations of the studies included in this systematic review, evidence was not strong enough to produce a best practice guideline.

4.2 Nutritional intervention

There is a strong rationale from laboratory studies suggesting that dietary nutrients, patterns, and intakes could influence RA disease activity.

Studies reporting significant effectiveness and safety of dietary and nutritional interventions in the treatment of RA included:[27]

- supervised fasting (200–300 kcal/day) during 7–10 days, produces a decrease in pain and inflammation in RA patients. However, the inflammation reappears when the patient starts his/her normal diet.[27,41]

- Mediterranean diet (small amount of meat, fish, high quantities of olive oil, fruits, vegetables, whole cereals and legumes, which are good sources of the antioxidant vitamins A, C and E and are associated with anti-inflammatory effects.[42,43] A Mediterranean diet has been proved to reduce blood pressure; improve glucose metabolism, the lipid profile, and lipoprotein particle characteristics and decrease inflammation and oxidative stress. In RA patients, a Mediterranean diet decreases pain, morning stiffness, the number of swollen joints and also improves the Health Assessment Questionnaire score, Disease Activity Score 28 (DAS28) and disease patient perception. Three systematic reviews stated that a Mediterranean diet decreased pain in RA patients. Moreover, the Mediterranean diet has been recommended for cardiovascular diseases and osteoporosis (frequent RA comorbidities).

- Nutritional elements:
    - o *Fish oil* rich in omega-3 polyunsaturated fatty acids (PUFAs) (eicosapentaenoic acid and docosahexaenoic acid), at dosages >2.7 g/day in the diet for >3 months reduces NSAID consumption in RA patients which have been associated with reduced expression of TNF-α and interleukin-1 and contributes to reduce the occurrence of cardiovascular disease events in RA patients with coronary artery disease. Although not necessarily clinically significant, when prescribing omega-3 PUFAs, rheumatologist should be aware that high dose omega-3 PUFAs are not recommended in patients who may be susceptible to increased bleeding (e.g., patients taking warfarin), because they may increase coagulation times.[27]
    - o *Virgin olive oil* contains numerous compounds that exert potent anti-inflammatory and antioxidant actions and its action may be increased when associated with fish oil supplements.[27]
    - o *Vitamin D* plays a role in the maintenance of the homeostasis of the calcium and phosphorus metabolism. It is considered an immune system regulator. It intervenes in the innate and acquired immune systems. In vitro, vitamin D inhibits the activation of IL-2, IL-12, IL-6,

interferon gamma, and TNF-α. Instead, vitamin D promotes monocyte differentiation into macrophages. Moreover, vitamin D has anti-inflammatory qualities through its capacity to regulate the production of prostaglandins.[27]

o *Probiotics* may play a therapeutic role in chronic inflammatory diseases. A recently reported randomized, double-blind, clinical trial study showed beneficial effects of *Lactobacillus casei* in pain, tender and swollen joint counts and DAS28, in RA women patients. It also showed amelioration in PCR, TNF-α, IL-12 e IL-10 levels.[44]

o Various phytochemical constituents of **ginger** have potential therapeutic roles in amelioration of RA symptoms and even possibly RA itself. It is expected that further elucidation of the molecular mechanisms behind the action of these phytochemicals will not only lead to discovery of new drugs for symptomatic relief of RA conditions like inflammation and pain, but also may make it possible to stop further progress or even reverse the damage caused by RA.[45]

o **Turmeric** and **curcumin** can be safely used as a therapeutic agent for arthritis. A recent systematic review and meta-analysis provided scientific evidence that 8–12 weeks of standardized turmeric extracts (typically 1,000 mg/day of curcumin) treatment can reduce arthritis symptoms (mainly pain and inflammation-related symptoms) and result in similar improvements of the symptoms as ibuprofen and diclofenac sodium. However, the sample sizes (45–124) of the studies included in this review were insufficient to be conclusive, and some studies represented moderate quality. Further high-quality RCT studies with more subjects are needed to confirm the therapeutic efficacy of turmeric and curcumin for arthritis.[46]

o **Astragalus** polysaccharides may also deter the accumulation of inflammatory cells in the synovial tissues in RA. Animal models of RA show reduced concentrations of TNF-α and interleukin-1-beta in the joints of rats when treated with *Astragalus*.[47]

o **Pepper** possesses various active components such as piperine and capsaicin which help in the management and treatment of the arthritic condition. These compounds act as anti-inflammatory, analgesic and immunomodulatory agents and can also improve the blood circulation throughout the body. All the evidence suggests that pepper can be developed into a natural, potent therapeutic agent with minimum side effects for helping patients suffering from arthritis.[48]

o **Cinnamon** supplementation can be a safe and potential adjunct treatment to improve inflammation and clinical symptoms in patients with RA.[49]

o **Onions, Garlic, Leeks** and **Shallots** are pungent vegetables and members of the allium family, which are rich in a type of antioxidant called Quercetin. Researchers are investigating quercetin's potential ability to relieve inflammation in diseases like RA and

they assumed that Quercetin may be an adjuvant natural drug for treatment of RA. The possible mechanism is through regulation of NF-κB, to inhibit the transcription of joint synovitis factors, hinder the generation of inflammatory factors, and inhibit the inflammatory reaction; through inhibiting the activities of VEGF, bFGF, MMP-2 and other cytokines, to inhibit angiogenesis in multiple links and inhibit synovial pannus formation.[50]

Fresh and biological sources of proteins may contribute to nourish the yin, xue and to increase the body resistance to exterior cold.[3]

4.3 Pharmacotherapy

Some herbal medicinal products have been shown to interact with the mediators of inflammation and, therefore, may be used in the treatment of RA. These products can also act as free radical scavengers, and through other mechanisms. However, few high-quality clinical trials have yet been carried out to substantiate the safety and efficacy of herbal medicines, which are not free of potentially serious side effects.

Anti-inflammatory and immunosuppressive *Tripterygium wilfordii* Hook F extracts (TEs) have been used for the treatment of a wide spectrum of autoimmune and inflammatory diseases, including RA. Based on their bioactivity, TEs, which function as a type of "herbal DMARD", appear to have the same effects as synthetic DMARDs. Meanwhile, the most common adverse effects of TEs should be assessed periodically, as with synthetic DMARDs. Considering the low methodological quality of the randomized trials, more RCTs are needed before TEs could be recommended to either replace synthetic DMARDs or to be combined with them.[51]

It has also been suggested that plants such as *Borago officinalis*, *Oenothera blennis* and *Ribes migrum* which contain a high grade of acid gamma linolenic (AGL), an essential fatty acid precursor of prostaglandin E1 with anti-inflammatory and immunomodulatory properties, may improve pain and disease activity in RA patients.[52]

The total glucosides of peony (TGP), a powdery substance extracted from *Paeonia lactiflora* pall root, have been recognized as a valuable Chinese herb used in the treatment of RA. A systematic review evaluates the efficacy of TGP combined with MTX, and another when combined with an immunosuppressant for RA. The results show the combination therapies are better than biomedicine monotherapy. High-quality and large-scale RCT are needed to further prove the results because of the limited quality of the included studies.[53]

Guizhi-Shaoyao-Zhimu decoction (GSZD) has been extensively used for RA therapy. Marked therapeutic efficacy of GSZD acting on RA has been demonstrated in several long-term clinical trials

without any significant side effects.[54] GSZD is composed of nine Chinese herbs, including *Ramulus Cinnamomi* (Guizhi), *Paeonia lactiflora* (Shaoyao), *Radix Glycytthizae* (Gancao), *Herba Ephedrae* (Mahuang), *Rhizoma Zingiberis Recens* (Shengjiang), *Rhizoma Atractylodis Macrocephalae* (Baizhu), *Rhizoma Anemarrhenae* (Zhimu), *Raidix Saposhnikoviae* (Fangfeng) and *Radix Aconiti Lateralis Preparata* (Fuzi). Clinical studies have revealed that the clinical cure rates of GZSD on treatment of patients with RA may range from 87.5–95.8%, superior to those of indometacin, tripterygium glycosides and prednisone.[54] Modern medical research has shown that GSZD may partially attenuate RA by reversing inflammation-immune system imbalance and regulating the HDAC1-HSP90AA1-NFKB2-IKBKB-TNF-α signaling axis. GSZD can alleviate RA progression by restraining osteoclast differentiation and activation, reducing synovial cell proliferation, and increasing synovial cell apoptosis.[54]

Yiyiren Decoction from the Leizhengzhicai is a classic prescription in the treatment of RA induced by cold and dampness.[55] Yiyiren (Coicis) Decoction from the Leizhengzhicai is composed of 11 Chinese herbs, in which Yiyiren (*Coicis Semen*) and Cangzhu (*Atractylodes Rhizoma*) can tonify spleen and dehumidify; Duhuo (*Angelicae Pubescentis Radix*), Qianghuo (*Notopterygh Rhizoma et Radix*) and Fangfeng (*Saposhnikoviae Rdix*) can dispel wind and overcome dampness; Chuanwu (*Aconiti Radix*), Mahuang (*Ephedrae Herba*) and Guizhi (*Cinnamomi Ramulus*) can warm and activate meridians, dissipate cold and dispel dampness; Danggui (*Angelicae Sinensis Radix*) and Chuanxiong (*Chuanxiong Rhizoma*) can nourish the blood and promote blood circulation and promote the circulation of qi; Shengjiang (*Zingiberis Rhizoma Recens*), and Gancao (*Glycyrrhizae Radix et Rhizoma*) can invigorate spleen and regulate the middle warmer, avoid evil and preserve substantial vital energy. All herbs combined can dissipate cold, dispel dampness and relieve pain and this formula has shown advantages in alleviating clinical symptoms and laboratory index of RA patients.[55]

It is reported that Yiyiren Decoction can significantly inhibit the ear inflammation caused by xylene, and significantly reduce the permeability of capillaries and the PGE2 content of inflammatory tissue, which has good anti-inflammatory and analgesic effect. Yiyiren (*Coicis Semen*) is sweet, tasteless, and cold in nature, which can clear damp, promote diuresis, invigorate the spleen, stop diarrhea, treat rheumatism, and expel pus. Studies indicated that Yiyiren's active ingredient coixenolide can increase the proportion of Foxp3+, CD4+, CD25+, and Treg in collagen-induced arthritis mice, which may have an immunoregulation in RA (55). Wuteng Ercao decoction is effective in patients with active RA and it can reduce the levels of IL-6 and TNF-α.[56]

4.4 Physical activity

According to the latest evidence, physical activity has not been associated with harmful effects on RA disease activity, pain or radiological damage, and probably provides additional benefits. For example, it decreases the risk of fracture and loss of bone mineral density and increases muscle mass, strength, power and intrinsic neuromuscular activity.[57]

Based on the evidence, Hurkmans et al. suggested that aerobic capacity training combined with muscle strength training is recommended as routine practice in patients with RA.[58] However, physical activity should be of low joint impact in order to avoid pain and musculoskeletal injuries.[57] Specific exercises like the methods of qigong or taiji which may be considered as concentrative breathing and movement exercises seem to be adequate for RA patients.

Qigong exercises

Qigong is an ancient component of traditional CM, predominantly involves non-strenuous slow-motion breathing exercises, meditation, and gentle slow body movements.[57]

Qigong is a method of gentle self-healing exercises, which may reduce sympathetic nervous system stimulation, inefficiencies in upper thoracic breathing, and can help to strengthen the body's musculoskeletal system and cognitive function even if only practiced for 15 minutes per day. It can be applied in sitting, walking, standing, or even when reclining and may be beneficial for the physical activity of RA sufferers, joint flexibility, motor function, movement coordination, hand grip strength, pain control, emotional well-being, as well as posture and balance.[57]

Taiji exercises

Taiji is a Chinese martial art that combines meditation with slow, gentle, graceful movements, as well as deep breathing and relaxation.[57] Taiji was associated with improvement in terms of RA disease activity, without RA exacerbation or adverse events. However, the evidence remains limited and inconclusive.[57]

Yoga and Pilates

Yoga modulates sweating response to dynamic exercise and improves respiratory muscle strength, handgrip strength, handgrip endurance and flexibility.[57]

Pilates is an exercise system focused on improving flexibility, strength, and body awareness, without necessarily building bulk.

There is very low evidence of the role yoga or Pilates plays in RA patients because of the few number of studies and poor methodological quality of the studies, due to lack of patient blindness or low sample sizes.

Meditation and Mindfulness

Meditation incorporates a diverse range of techniques that help to focus attention and bring a state of self-awareness and inner calm. Meditation may improve pain, anxiety, and depression in RA patients. However, no evidence is known on any potential impact on RA disease activity.[57]

Balneotherapy/hydrotherapy

Balneotherapy/hydrotherapy/ involves the use of the mechanical and thermal effects of water in treatments and is one of the oldest forms of therapy for patients with arthritis.[59]

The main aims of balneotherapy are to maintain or improve functional mobility, soothe pain and let patients feel well. Most studies report positive findings but provide insufficient evidence to support their claims. The quality of the evidence of the effectiveness of balneotherapy for RA patients is very low mainly because of the low number of participants in the studies and concerns about study designs.[59]

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Chapter 3

The effectiveness of acupuncture on pain, physical function and health-related quality of life in patients with Rheumatoid Arthritis

The effectiveness of acupuncture on pain, physical function and health-related quality of life in patients with Rheumatoid Arthritis: a protocol for a systematic review of quantitative evidence

ABSTRACT

Introduction

Rheumatoid Arthritis (RA) is a systemic inflammatory disease characterized by functional disability, pain and has a significant impact on health-related quality of life. Although acupuncture is widely used, Western acupuncture studies on RA have shown no conclusive positive results.

This systematic review aims to analyse the available studies stating quantitative data related to the effectiveness of acupuncture in the quality of life of patients with Rheumatoid Arthritis (RA).

Methods and analysis

We will perform a comprehensive search of 12 Western and Chinese databases and reference lists/ studies published in English, Portuguese, German and Chinese. Studies will be included from their inception up to 2015.

This review will comprise randomized controlled trials in which human patients suffering from RA - classified accordingly to the American College of Rheumatology - were treated with needle acupuncture (with or without electrical stimulation or moxibustion), laser at precise locations for the purpose of therapy or auricular acupuncture.

The primary outcome measure will be assessed by the health-related quality of life, pain and physical function. The secondary measure includes the symptom evaluation (morning stiffness and functional impairment); number of joints affected by RA, assessed by a Tender Joint Count (TJC); serum concentrations of inflamatory markers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level, cortisol, interleukins, anti-CCP, Rheumatoid factor, autonomy or any adverse effects likely to be related to RA.

The study quality will be assessed by two independent reviewers using the standardized critical appraisal instruments from the Joanna Briggs Institute Meta-Analysis of Statistics Assessment and Review Instrument (JBI-MAStARI).

Conclusion

This review intends to collect factual scientific evidence of possible positive effects of acupuncture in quality of life, physical function improvement and pain relief in RA patients.

Keywords: Acupuncture, rheumatoid arthritis, quality of life, pain, physical function, randomized controlled clinical trial.

BACKGROUND

Rheumatoid Arthritis (RA) is a chronic inflammatory, multisystemic and autoimmune disease manifested by symmetrical, persistent inflammatory synovitis, involving destructive polyarthritis of the synovium.[1] According to the World Health Organization data, approximately 1-2% of all people in the world suffer from RA and its prevalence is about 0.2 to 0.5% in Portuguese population.[2] The social-economic impact is high on the individuals as well as on the Health System.[3]

The conventional treatment of RA is dominated by the use of Non-Steroidal Anti-Inflammatory Drugs, including second-generation Cox-2 inhibitors, Disease Modifying Anti-Rheumatic Drugs, and analgesics. Recently, the use of biological agents has been started.[3] The treatments or surgical interventions are associated with higher costs, unwanted side effects, toxicity and limited efficacy.[4,5] These and other limitations led almost 60-90% of unsatisfied arthritis patients to use Complementary Alternative Medicine, including acupuncture.[4,6]

Acupuncture is one of the most popular sensory stimulation techniques of Traditional Chinese Medicine (TCM), originating in China more than 3,000 years ago.[7] It is known that acupuncture stimulates the nervous system and thereby causes the release of neurochemical messenger molecules as well as biochemical changes that influence the body's homeostatic mechanisms.[8]

This review will consider as inclusion criteria the classical definition for acupuncture which describes the insertion of a metallic needle in TCM points located on the meridians or conduits. However, simple acupuncture can be performed in extra-meridian acupoints and still cause a stimulus on the nervous system. The simple acupuncture can be performed with added electrical stimulation where the impulse is provided directly on the needle through an electric conductor attached to the external cable of the needle. Moxibustion can be also an adjuvant method where heat is applied directly on TCM designated acupoints. Other form of action on the acupoints can be done by laser stream instead of the classical needle insertion. The auricular acupuncture is described to be a microsystem within Chinese Medicine, based exclusively on the use of needles insertion on the auricular pavilion.

There are forms of acupuncture that will be considered as exclusion criteria on our systematic review these being Bee venom acupuncture (injection of this substance on acupoints), transcutaneous electrical nerve stimulator (TENS), TuiNa (Chinese massage therapy) and mesotherapy (sub cutaneous injection of chemical and biological compounds).

The acupuncture in RA can decrease the pro-inflammatory cytokines Interleukin 1 and interleukin 6 and increase the inhibitory cytokines interleukin 4 and interleukin 10;[9] induce vasoactive intestinal peptide expression, an anti-inflammatory neuro-peptide;[10] inhibit the function of synovial mast cells and

upregulate plasma adrenocorticotropic hormone, down regulate serum cortisol levels and synovial nuclear factor-kappaB/p 65 immune-activity, and restore the hypothalamus-pituitary-adrenal axis.[11]

By stimulating the nervous system, acupuncture may lead to the release of endorphins and other neurohumoral factors, as well as to changes in the processing of pain in the brain and spinal cord and to an increase of local microcirculation that helps the dispersal of swelling. [12,13]

The main reason for pain is assumed to be a systemic inflammation although psychosocial factors, peripheral and central pain processing mechanism, such as loss of descending analgesic activity and central pain augmentation or sensitization, are intricately entwined.[14]

Untreated RA leads to joint destruction and severe disability. Main features of RA are acute and chronic rheumatic pain, physical function (PF) limitation and the significant impact on health-related quality of life (HRQoL).[15]

This systematic review will provide a detailed summary of the current state of scientific evidence-based for the effects of acupuncture for pain relief as well as PF improvement and improving HRQoL in patients with RA.

The International Association for the Study of Pain defines pain as an unpleasant sensory and emotional experience which we primarily associate with tissue damage or describe in terms of such damage.[16] However, pain is more than a sensation, or the physical awareness of pain, it also includes perception, the subjective interpretation of the discomfort.[16]

Acute pain is the body's normal response to damage such as a cut, an infection, or other physical injuries. It is often sudden in onset, as it is usually the direct result of a noxious stimulus. It often goes away in a few weeks or months if treated properly. Acute pain can become chronic when the cause is difficult to treat.[17]

Chronic pain is, by definition, present for at least 3 months. It can be affected by physical, environmental, and psychological factors. Chronic pain often cannot be treated or cured, it can only be managed. Chronic pain may persist because the original inciting stimulus is still present and/ or because changes to the nervous system have occurred, making it more sensitive to pain.[18] Therefore, chronic pain in RA may reduce quality of life (QoL), well-being, and the ability to function over the long term.[17]

According to TCM, the meridian system or neurovascular network per se can conduct and transmit nerve signals irrespective of whether it is pain or not. The root cause of pain is mainly due to the stagnation, full or partial blockade of the normal neurovascular flow in regions of human body and abnormal impedances.[19]

In the case of RA, stagnation in the joints will produce arthritis pain but if the stagnation or blockade of the neurovascular flow in that part of the body is removed, then the pain syndrome will also disappear.[19]

Pain relief can be achieved by acupuncture through adjusting the impedances of the meridian system, which is connected internally with viscera and externally with limbs and sensory organs. Initially, the injury around the acupoint is produced, then the magneto-electric inductive effects along the meridian

system will be triggered, and finally the analgesia/pain relief can be obtained via the impedance matching/mismatching with pain source/brain.[19]

The negative consequences of RA on the PF of patients are multidimensional, involving decrease in muscle strength and endurance and restricted range of joint movement.

The PF domain is theoretically composed of four subdomains that are conceptually related but distinct: mobility (lower extremity), dexterity (upper extremity), axial or central (neck and back function), and complex activities that involve more than one subdomain (instrumental activities of daily living). In practice, the subdomain assignment may sometimes be arbitrary, as many tasks involve more than one part of the body.[20] PF scales are used in the majority of clinical trials to assess the effectiveness of treatment and have become established instruments for assessing health outcomes in clinical practice and observational studies as well.[21]

Consequently, PF is a key component of patient-reported outcome assessment in rheumatology and includes specific tasks being evaluated in a standardized manner using predetermined criteria such as time, number of repetitions, force and degrees of movement.[22]

Patients with RA have reduced levels of physical function, body pain, fatigue, substantially lower mental HRQoL, levels of vitality, social functioning and global health in comparison with other health conditions.[23]

Quality of life is a ubiquitous and multidimensional concept that has different philosophical, political and health-related definitions.[24] HRQoL self-reports comprise physical, functional, social and emotional well-being, as well as the biological integrity, of individuals.[25]

Measurement of HRQoL is supported by the National Institute for Health and Care Excellence guidelines and is potentially useful for several reasons. Many patients value HRQoL more than disease-related variables such as inflammatory biomarkers or joint counts; reduced HRQoL in RA patients is associated with increased use of healthcare resources and with increased levels of depression.[25]

With the aim to determine the efficacy of acupuncture for pain relief in patients with RA, Wang et al led a systematic review.[7] They have concluded that questionable evidence exists in placebo-controlled trials concerning the efficacy of acupuncture for RA.[7]

The systematic review led by Lee et al concluded that the evidence for the effects of acupuncture to treat RA was not convincing.[4] The number, size and quality of the RCTs are too low to draw firm conclusions. These systematic reviews showed methodologic concerns and questionable conclusions regarding the effects of acupuncture in the treatment of RA.[4,7] The evidence is limited due to methodological considerations, such as the type of acupuncture, the site of intervention, the sample size, the long-term benefits that remain unknown, inappropriate randomized-control or blind interventions, and scarce use of validated outcome measures. Our systematic review will be based on previous published studies and therefore will comprise the same limitations.

A systematic review comparing different therapies to treat rheumatic diseases include RA, shows that acupuncture was the therapy that had the most significant evidence.[5]

Acupuncture is often advocated for the treatment of RA.[26,27, 28, 29] In order to understand the specific evidence of the potential benefits or possible impairment of acupuncture on the HRQoL in RA a thorough survey was conducted in several databases (Prospero, CINAHL, Medline, Cochrane, JBI Library). Relatively few rigorous clinical trials have been published, the recent scientific evidence is scarce and the most recent systematic review for this topic is over 5 years old.

This review will benefit patients and practitioners and lead to new requirements in the field of traditional and complementary medicine therapies.

REVIEW QUESTION/ OBJECTIVE

The objective of this review is to identify and synthesize the best available evidence regarding the effectiveness of acupuncture on pain, physical function and health-related quality of life in patients with Rheumatoid Arthritis (RA).

More specifically, the review questions are:

Is needle acupuncture effective in improving health-related quality of life in patients with RA?

Is acupuncture effective in relieving pain in patients with RA?

Is acupuncture effective in improving physical function in patients with RA?

INCLUSION CRITERIA

Types of participants

The review will consider studies that include patients (regardless of gender, age, race, ethnicity) suffering from RA classified according to the American College of Rheumatology.

Type (s) of intervention(s)

The review will consider all studies regarding patients with RA that were treated with needle acupuncture with or without electrical stimulation, laser at precise locations for the purpose of therapy, auricular acupuncture, or moxibustion on the body as the sole treatment or as an adjunct to other treatments. Animal trials will be excluded.

The trials of acupuncture that exclude patients being submitted to Western therapy or where only immunological or biological parameters are assessed will be excluded.

Comparator

In our review we will include trials comparing acupuncture with placebo or sham acupuncture as also acupuncture versus conventional Western treatments. Studies will be excluded if they compared the use

of TCM acupoints with Transcutaneous Electrical Nerve Stimulator (TENS), bee venon acupuncture, TuiNa or Mesotherapy but are not really using any of the acupuncture techniques.

When acupuncture is used as a complementary therapy it is expected that the control group received the same conventional treatment as the acupuncture group.

Types of outcomes

This review will consider studies that include the following outcome measures:

<u>Primary outcomes</u>

(1) Health-related quality of life (HRQoL)

   Measurement tools:[23,24]

   36-item Short-Form Health Survey (SF-36),

   Arthritis Impact Measurement Scales,

   Health Assessment Questionnaire Disability Index,

   Health Assessment Questionnaire (HAQ),

   Rheumatoid Arthritis Quality of Life instrument (RAQoL).

(2) Pain

   Measurement tools:

   Visual Analogue Scale (VAS),

   Numeric scale,

   Faces Scale,

   Qualitative Scale.

(3) Physical function (PF)

   Measurement tools:[27,30]

   Item Response Theory,

   Visual Analogue Scale and Computerized Adaptive Testing,

   Disease-specific HAQ,

   Groningen Activity Restriction Scale (GARS),

   McMaster Health Index Questionnaire (MHIQ).

<u>Secondary outcomes</u>

(1) Symptoms (morning stiffness and functional impairment) following the ACR criteria.

(2) Measurement by its duration to maximum improvement and by its severity on a VAS.

(3) The number of joints affected by RA, assessed by a Tender Joint Count.

(4) Serum concentrations of inflammatory markers such as erythrocyte sedimentation rate and C-reactive protein level, cortisol, interleukins, anti–citrullinated protein antibodies, Rheumatoid factor.

(5) Adverse effects.

(6) Autonomy

(7) Measurement by self-reported survey directly or indirectly in the survey defined to other outcomes as for example HRQoL.

Types of studies

The review will consider experimental study designs including randomized controlled trials, non-randomized controlled trials, quasi-experimental, before and after studies.

SEARCH STRATEGY

The search strategy aims to find both published and unpublished studies. A three-step search strategy will be utilized in this review. An initial limited search of MEDLINE and CINAHL will be undertaken followed by an analysis of the text words contained in the title and abstract, and of the index terms used to describe the article. A second search using all identified keywords and index terms will then be undertaken across all included databases. Thirdly, the reference list of all identified reports and articles will be searched for additional studies. Studies published in English, Portuguese, German and Chinese will be considered for inclusion in this review. Studies published from databases inception up to 2015 will be considered for inclusion in this review.

Dissertations and abstracts will be included if they contain sufficient detail.

The searched databases will be:

Medline, Cochrane Central Register of Controlled Trials (CENTRAL), AMED, British Nursing Index, CINAHL, China Academic Journal, Century Journal Project

The search for unpublished studies will be:

China Doctor/Master Dissertation Full Text DB, China Proceedings Conference Full Text DB), Proquest, RCAAP, Open Grey

Initial keywords to be used will be:

Acupuncture; Rheumatoid arthritis; Quality of life; Pain; Functional impairment; Physical function; Randomized controlled clinical trial.

ASSESSMENT OF METHODOLOGICAL QUALITY

Quantitative papers selected for retrieval will be assessed by two independent reviewers for methodological validity prior to inclusion in the review using standardized critical appraisal instruments from the Joanna Briggs Institute Meta Analysis of Statistics Assessment and Review Instrument (JBI-MAStARI). Any disagreements that arise between the reviewers will be resolved through discussion, or with a third reviewer.

Patient blinding will be assumed in cases where the control intervention is indistinguishable from acupuncture, even if the word 'blinding' did not occur in the report.

The quality of acupuncture will be assessed by the reviewers by answering the question, 'how would you treat the patients included in the study?'. The answer will be related with the quality of the studies (randomized, blind or not) as also the type of treatment (standardized treatment or individual treatment) and as the possible five categories including (1) exactly or almost exactly the same way', (2) similarly, (3) differently, (4) completely different or (5) could not assess due to insufficient information (on acupuncture or on the patient).

DATA COLLECTION

Quantitative data will be extracted from papers included in the review, by two independent reviewers, using the standardized data extraction tool from JBI-MAStARI. The data extracted will include specific details about the interventions, populations, study methods and outcomes of significance to the review question and specific objectives.

In order to find any missing data, the authors of included primary studies will be contacted.

DATA SYNTHESIS

Quantitative papers will, if possible, be pooled in statistical meta-analysis using JBI-MAStARI. All results will be subjected to double data entry. Effect sizes expressed as odds ratio (for categorical data) and weighted mean differences or standardized mean differences (for continuous data) and their 95% confidence intervals will be calculated for analysis.

Heterogeneity will be assessed statistically using the standard Chi-square and also explored using subgroup analyses based on the different quantitative study designs included in this review.

If the data is available, we will conduct subgroup analyses to explore the heterogeneity between the studies. Subgroups will include the following:

(1) Type of Acupuncture,

       Acupuncture vs penetrating or non-penetrating sham acupuncture

       Acupuncture or acupuncture plus moxibustion vs conventional drugs

(2) type of control,

(3) Duration of RA;

(4) Laterality of RA - bilateral RA versus unilateral RA.

Where statistical pooling is not possible, the findings will be presented in narrative form including tables and figures to aid in data presentation if necessary.

CONFLICTS OF INTEREST

There is no conflict of interests.

ACKNOWLEDGEMENTS

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Appendix I: Appraisal instruments

MAStARI Appraisal instrument

JBI Critical Appraisal Checklist for Randomised Control / Pseudo-randomised Trial

Reviewer _____ Date _____

Author _____ Year _____ Record Number _____

	Yes	No	Unclear	Not Applicable
1. Was the assignment to treatment groups truly random?	☐	☐	☐	☐
2. Were participants blinded to treatment allocation?	☐	☐	☐	☐
3. Was allocation to treatment groups concealed from the allocator?	☐	☐	☐	☐
4. Were the outcomes of people who withdrew described and included in the analysis?	☐	☐	☐	☐
5. Were those assessing outcomes blind to the treatment allocation?	☐	☐	☐	☐
6. Were the control and treatment groups comparable at entry?	☐	☐	☐	☐
7. Were groups treated identically other than for the named interventions	☐	☐	☐	☐
8. Were outcomes measured in the same way for all groups?	☐	☐	☐	☐
9. Were outcomes measured in a reliable way?	☐	☐	☐	☐
10. Was appropriate statistical analysis used?	☐	☐	☐	☐
	☐	☐	☐	☐

Overall appraisal: Include ☐   Exclude ☐   Seek further info. ☐

Comments (Including reason for exclusion)

_____

_____

_____

Appendix II: Data extraction instruments

MAStARI data extraction instrument

JBI Data Extraction Form for Experimental / Observational Studies

Reviewer _____ Date _____

Author _____ Year _____

Journal_____ Record Number_____

Study Method

RCT	☐	Quasi-RCT	☐	Longitudinal	☐
Retrospective	☐	Observational	☐	Other	☐

Participants

Setting

Population

Sample size

Group A _____ Group B _____

Interventions

Intervention A

Intervention B

Authors Conclusions:

Reviewers Conclusions:

Study results

Dichotomous data

Outcome	Intervention ( ) number / total number	Intervention ( ) number / total number

Continuous data

Outcome	Intervention ( ) number / total number	Intervention ( ) number / total number

Effectiveness of acupuncture on pain, physical function and health-related quality of life in patients with Rheumatoid Arthritis: a systematic review of quantitative evidence

ABSTRACT

Objective

To identify and synthesize the most recent available evidence of effectiveness of acupuncture on pain, physical function and health-related quality of life (HRQoL). HRQoL in patients with rheumatoid arthritis (RA).

Methods

A comprehensive search of 12 Western and Chinese databases was undertaken, from their inception up to end of 2016. Randomized controlled trials (RCTs), concerning patients with RA treated with needle acupuncture, written in English, Portuguese, German or Chinese were included. Primary outcomes: pain, physical function and HRQoL. Secondary outcomes: morning stiffness; functional impairment; number of tender and swollen joints and serum concentrations of inflamatory markers. Methodological quality was assessed by three independent reviewers using the standardized critical appraisal instrument from the Joanna Briggs Institute Meta-Analysis of Statistics Assessment and Review Instrument.

Results

Twenty-two studies met the inclusion criteria. Of those, nine studies were excluded after assessment of their methodological quality. The remaining 13 original RCTs included 974 patients. Ten of these studies, and published in China, showed favorable statistically significant effects of acupuncture in relieving symptoms of RA compared with controls.

Conclusions

Evidence suggests that acupuncture interventions may have a positive effect in pain relief, physical function and HRQoL in RA patients. However, due to the heterogeneity and methodologic limitations

of the studies included in this systematic review, evidence is not strong enough to produce a best practice guideline.

Keywords: acupuncture, rheumatoid arthritis, quality of life, pain, physical function, randomized clinical trial

BACKGROUND

Rheumatoid arthritis (RA) is a chronic inflammatory, multisystemic and autoimmune disease manifested by acute and chronic rheumatic pain, symmetrical persistent inflammatory synovitis, involving destructive polyarthritis of the synovium.[1] Untreated RA leads to joint destruction, physical function (PF) limitation and severe disability.

The worldwide prevalence is estimated at 1%.[2] Reduced Health-Related Quality of Life (HRQoL) in RA patients,[3] particularly increased levels of depression, lack of vitality, social functioning and global health, is associated with high social-economic impact and increased use of healthcare resources.[4-6]

The conventional treatment of RA is dominated by the use of non-steroidal anti-Inflammatory drugs (NSAIDs), glucocorticoids, disease modifying anti-rheumatic drugs, analgesics and biological agents.[3] These treatments are associated with higher costs, unwanted side effects, toxicity and limited efficacy.[7,8] These and other limitations led almost 60%-90% of unsatisfied arthritis patients to use complementary and alternative medicine, including acupuncture.[7,9,10]

Pain and inflammation relief can be achieved by acupuncture through adjusting the impedances of the meridian system,[11-13] connected internally with viscera and externally with limbs and sensory organs.[14-16]

Acupuncture is often advocated for the treatment of RA.[17-19] Relatively few rigorous clinical trials have been published, the recent scientific evidence is scarce and the most recent systematic review for this topic is over five years old.[7-9] These systematic reviews showed methodologic concerns and questionable conclusions regarding the effects of acupuncture in the treatment of RA.[7,9]

Our objective is to analyze the most recent state of scientific evidence-based of worldwide published studies and possibly find scientific finding which enable us to conclude if acupuncture is effective in pain relief, PF and HRQoL improvement in patients with RA.

METHODS

Inclusion Criteria

We considered randomized clinical trials (RCTs), regarding patients suffering from RA classified according to the American College of Rheumatology (ACR),[20] that were treated with acupuncture. Acupuncture, one of the most popular sensory stimulation techniques of Chinese medicine (CM), can be performed with metallic needle in specific acupoints or by laser stream instead of the classical needle insertion and combined with moxibustion or electrical stimulation.[7,9,10]

Exclusion Criteria

Animal studies, acupuncture trials that exclude patients being submitted to western therapy, studies that used phytotherapy or Chinese herbs, bee venom acupuncture, transcutaneous Electrical Nerve Stimulator, tuina (Chinese massage therapy) and mesotherapy. We also excluded studies relating Chinese herbs and acupuncture because they do not isolate the possible different mechanism associated with each technique.[21]

Outcomes

Primary Outcomes

(1) pain (measurement tools: Visual Analogue Scale (VAS), Numeric scale, Faces Scale, Qualitative Scale); (2) physical function (measurements tools:[17] item response theory, VAS and Computerized Adaptive Testing, Disease-specific Health Assessment Questionnaire, Groningen Activity Restriction Scale, McMaster Health Index Questionnaire); (3) health-related quality of life (measurement tools:[5,20] 36-item Short-Form Health Survey (SF-36), Arthritis Impact Measurement Scales, Health Assessment Questionnaire Disability Index, Health Assessment Questionnaire (HAQ), Rheumatoid Arthritis Quality of Life instrument).

Secondary Outcomes

(1) symptoms (morning stiffness and functional impairment) following the ACR criteria;[20] (2) the number of tender and swollen joints (assessed by a disease activity score 28 (DAS28) and tender joint count (TJC)); (3) serum concentrations of inflammatory markers (erythrocyte sedimentation rate (ESR), C-reactive protein level, cortisol, interleukins, anti–citrullinated protein antibodies and rheumatoid factor (RF)).

Search Strategy

Studies published in English, Portuguese, German and Chinese were considered, from their inception up to end of 2016. The search was done between January and May to 2017.

The searched databases (DB) included were: Medline; Cochrane Central Register of Controlled Trials (CENTRAL); AMED; CINAHL; China Academic Journal, Century Journal Project. The search for unpublished studies were: China Doctor/Master Dissertation Full Text DB, China Proceedings Conference Full Text DB), Proquest, RCAAP and Open Grey.

Initial keywords to be used were: acupuncture, rheumatoid arthritis, quality of life, pain, functional impairment, physical function, randomized controlled clinical trial.

Method of the Review

After duplicates were removed manually through the extracted search strategy results into a Microsoft Excel spreadsheet, all identified studies were assessed for relevance based on title and abstract. Whenever the title and abstract lacked data to make a decision, the inclusion criteria described above were verified in full-text papers.

Assessment of Methodological Quality

As originally outlined in the review protocol,[22] the papers selected for retrieval were methodological assessed by two independent reviewers (SS and DM). BN and SS reviewed the Chinese papers with

the help of JG. BN and JG have high-level proficiency of Chinese language. Any disagreements between the reviewers were resolved through discussion, or with a third reviewer (DC).

To exclude studies with high risk of bias, the reviewers established that a study required "yes" answers to at least five questions in the standardized critical appraisal instrument from the Joanna Briggs Institute Meta-Analysis of Statistics Assessment and Review Instrument (JBI-MAStARI).[23]

RESULTS

Description of the study selection process

The searches yielded 420 potentially relevant studies. Of those, 77 were duplicates and 299 were excluded after title and abstract assessment. From the 47 remaining articles, 15 of them, all written in Chinese, proved impossible to gain access to the full-text papers and respective references. We tried different strategies to access the articles including contacting the authors and requesting the papers from national and international libraries. So far, our emails have been unanswered and the libraries (University of Coimbra, University of Porto, Hospital of the University of Coimbra in Portugal; University of Roma Tor Vergata in Italy; University of Heidelberg and the School of Chinese Medicine in Heidelberg, in Germany; Taiwan Joanna Briggs Institute, in Taiwan) were unsuccessful with the search.

Methodological quality of included studies

After methodological quality assessment, we decided to include 13 RCTs: nine adopted a two-armed parallel-group design,[19,24-31] three a three-armed parallel group design[32,33,35] and one was a cross-over trial (see Figure 1).[34] The methodological quality of the included studies was low to moderate (see supplementary information online).
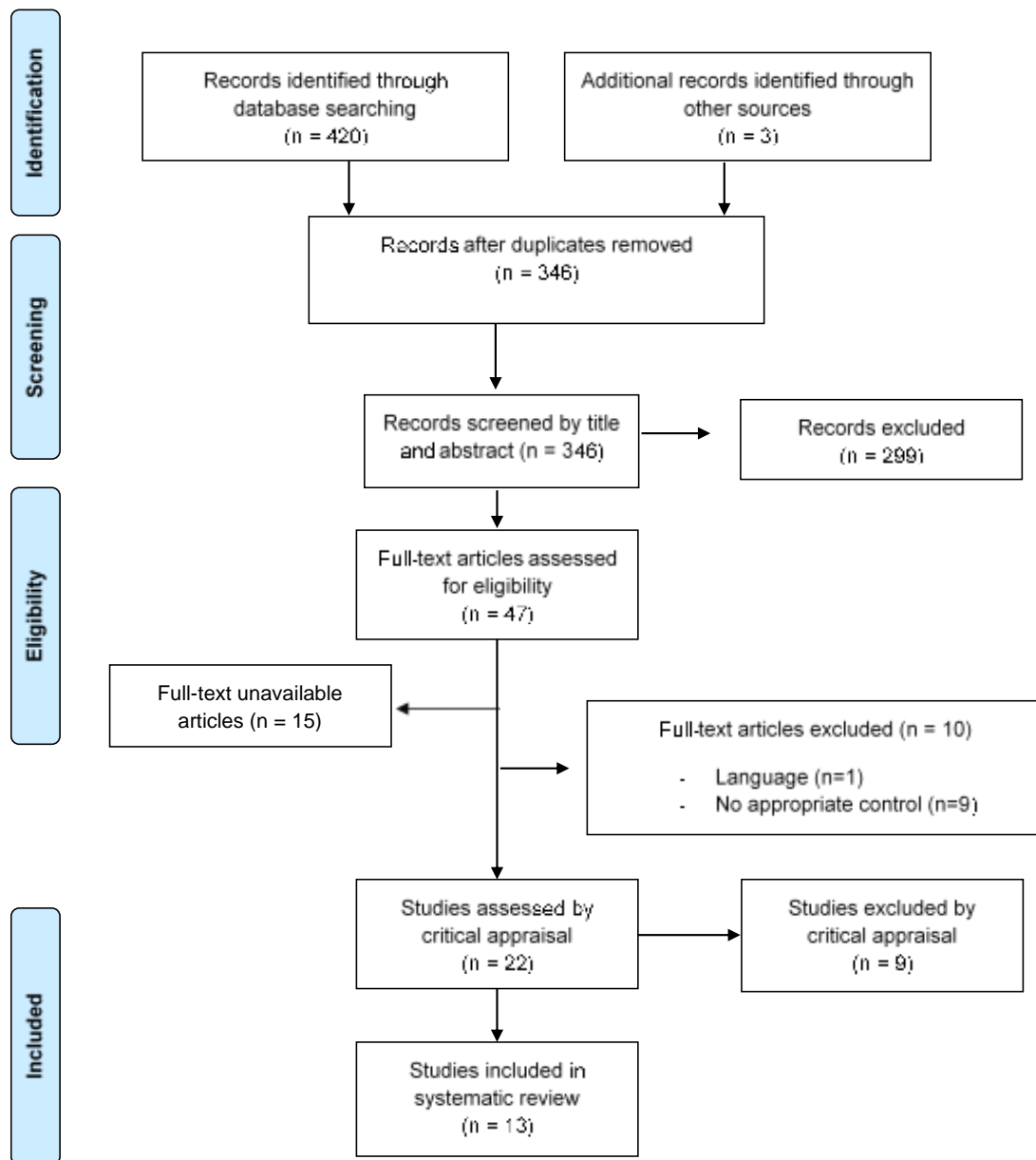
Figure 1: Flowchart for the search and study selection process. From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097

Acupuncture was always the main intervention chose however, the studies showed high clinical heterogeneity (interventions, instruments to assess the outcomes, for instance, the dose/intensity of

the treatments, the duration variations, the number of sessions and the fluctuations time elapsed between sessions) and methodological heterogeneity (designs).

The studies included in the review were published between 1999 and 2015. Ten of them reported data found in Chinese population; one was developed in United Kingdom; one in Brazil and one in Germany. Five of the studies were written in English and eight in Chinese. The remaining 13 RCTs included 974 patients, aged between 25 and 77 years. Sample sizes ranged from 36[32] to 150[30] participants and disease duration between 3 months and 35 years. All studies showed similarity at baseline between the groups. Details related to participants, interventions and possible limitations reported by the authors are presented in Table 1.

Three placebo-controlled trials employed sham acupuncture[19,32,34] but, did not give promising results for acupuncture treatments and reported conflicting evidence. The results found by Zanette and colleagues showed that traditional acupuncture (TA) seems promising but does not reach, on most of the parameters, statistical significance and TA were not superior to placebo.19 Tam and colleagues suggested that electroacupuncture (EA) or TA significantly improved TJC compared with placebo, but the results were no better than sham acupuncture in terms of changes in the pain score. David et al, reported no significant differences between traditional and sham acupuncture in pain relief or inflammation.[34]

Ten[24,25,26,27,28,29,30,31,33,35] of the 13 included RCTs showed favorable and statistic significant results of acupuncture treatments in relieving RA clinical symptoms and health status, as described below.

Table 1. Summary of studies included

Study	Group/ Intervention	Sample size (M/F)	Age (years) (Mean±SD)	Results	Needle Manipulation	Measured outcomes	Notes/ Remarks
Tam, et al, 2007[32]	Group A Electroacupuncture	12 (1/11)	56.4±8.5	Reduction of the physician's global assessment (p = 0.04) and number of tender joints (p = 0.03).	Manual manipulation.	VAS, ACR20, DAS Index, HAQ ESR, CRP Standardized acupuncture. LI 11, TE 5, ST 36, GB 34, GB 36, GB 39. EA.	A foam cube was applied around the acupuncture point, needles were inserted through the cube to avoid seeing the level of entry of the needle. 20 sessions of 40 min, needles retained 30 min
	Group B Traditional Chinese Acupuncture	12 (2/10)	58.1±12.0	Reduction of the physician's global assessment and number of tender joints (p = 0.01).			
	Group C Sham	12 (4/8)	57.6±8.3	Reduction of the physician's global assessment (p = 0.03).			
Wang, et al, 2014[35]	Group A Acupuncture	30 (10/ 20)	53. 50 ± 7.02	The range of motion improve (p < 0.05).	Standardized treatment	Joint tenderness and swelling, grip strength, pain.	Compared with Acupuncture group, moxibustion group can significantly improve joint tenderness (p<0.05), Acupuncture group combined with moxibustion group can significantly improve joint swelling in patients with dual grip strength ($P<0.05$ or $P<0.01$) and pain scores compared with moxibustion group.
	Group B Moxibustion	30 (9/ 21)	58.06 ± 12.57	The joint tenderness and pain scores improve (p < 0.05).			
	Group C Acupuncture combined with moxibustion	30 (8/ 22)	60.02 ± 12.68	Clinical efficacy, patient's primary and secondary disease, range of motion and pain scores improve (p < 0,05).			
Sun, et al, 2009[33]	Group A Midnight-noon ebb-flow acupuncture	40 (19/ 21)	47.3 ± 2.5	11 cases obviously improved; 11 cases improved; 9 cases slightly improved; 9 cases ineffective.	Manual manipulation.	Curative effects in RA signs and symptoms, Lysholm Knee scale.	Treatments once a day, 6 times per week; duration of 4 weeks.
	Group B Acupuncture by differentiation of symptoms and signs	40 (18/ 22)	47.8 ± 2.4	10 cases significantly improved, 11 improved, 11 moderate improved, 8 ineffective.			
	Group C Integrative group of midnight-noon ebb-flow acupoint selection and acupuncture by differentiation of symptoms and signs	40 (16/ 24)	48.1 ± 2.3	15 cases significantly improved; 13 cases improved, 10 cases moderate improved; 2 cases ineffective.			

Zanette, et al, 2008[19]	**Group A Acupuncture**	20 (3/17)	53.1±12.44	8 cases (40%) reached ACR-20 standard. Physician global assessment of the disease activity (p < 0.012) and physician (p < 0.003) and patient (p < 0.011) assessment improve.	Manual manipulation.	ACR20, VAS, DAS, HAQ, PGADA, ESR, CRP EX 1, EX 27, CV 6, CV 12, L 14, CV 4, GV 14, LR 3, PC 6, SP 6, ST 36, BL 11, BL 20, BL 22, BL 23, BL 60.	Small sample size. Standardized acupuncture
	Group B Control acupuncture (sham)	20 (0/20)	46.5±9.9	2 cases (10%) reached ACR-20 standard.			
Bernateck, et al, 2008[24]	**Group A Auricular Electroacupuncture**	19 (5/14)	51.05±13.18	VAS reduced between morning evaluations at baseline and after 3rd week of treatment (4.6±1.64 vs 3.26±1.42, p=0.002). PDI significantly reduced between baseline and after 2nd treatment week (29.16±12.66 vs 22.63±12.25, p=0.028). DAS28 decreases after 3rd treatment (3.63±1.20 vs 2.89±0.97; p<0.001).	EA manipulation.	VAS, PDI, DAS28, TAS, CGI	Randomization method unclear. The PDI at baseline had a significant intergroup difference (p=0.036) After the 6th treatment, patients in EA group assessed their outcome to be significantly more markedly improved than patients in the AT group (1.32±1.25 vs 0.39±1.34, p=0.035).
	Group B Autogenic training	18 (2/16)	52.22±11.19	VAS reduced between morning evaluations at baseline and 1 week after 6th treatment week (4.37±1.37 vs 3.14±1.94, p=0.021). PDI was significantly reduced between baseline and after 5th treatment week (20.89±10.18 vs 15.28±9.14; p=0.022). DAS28 decreases after 3rd treatment (3.58±1.14 vs 3.07±0.94; p=0.022).			
Bing-bin, 2015[25]	**Group A Acupuncture (Observation)**	30 (7/23)	45.5±2.3	Morning stiffness duration, joint tender index, joint swelling index and ESR improved after intervention (p<0.01). The total effective rate was 93.3%.	Manual manipulation (using reinforcing-reducing manipulation	Joint swelling and tender index, Morning stiffness ESR	10 days as a treatment course, 3 courses in total with an interval of a week between two courses. Major points (GV 14, GV 11, GV 9, GV 4, EX B2, GV 20, GB 20, GB 21). Control group: points selection by syndrome differentiation. Topical points were selected depending on the affected joints.
	Group B Control	30 (5/25)	44.2±2.2	Morning stiffness duration, joint tender index, joint swelling index and ESR improved after intervention (p<0.01). The total effective rate was 76.6%.			
David, et al, 1999[34]	**Group A Acupuncture treatment (sequence A)**	29 (gender not referred)	61	Thirteen outcome variables were assessed and the only significant difference between the 2 sequence groups was GHQB anxiety (p=0.02).	Manual manipulation (needles were left in situ for 4 min and manipulated	VAS, VASG, DAS28, GHQ	At baseline there were no significant differences between the 2 group's. GHQB anxiety (p=0.02) was different between the 2 groups

	Group B **Placebo treatment** **(sequence B)**	27 (gender not referred)	57		manually at 2 min for 5 s).		
Wan and Xioung, 2012[26]	**Group A** **Acupuncture**	40 (13/27)	25-68	The results suggest that acupuncture group improved symptoms of finger joint pain in comparison with usual care.	Manual manipulation.	VAS, Clinical symptoms and signs, ESR, CRP	There was no significant difference between the two groups in general data (p>0.05).
	Group B **Western medicine**	40 (11/29)	26-69				
Zhu, Y, 2014[27]	**Group A** **Acupuncture**	20 (3/17)	56.8±20.5	DAS28 and HAQ scores improved significantly (p<0.05 or p<0. 01).	. Manual manipulation.	HRQoL, DAS 28, the clinical efficacy TBilateral Fungchi, Yangchi, Quchi, Yangxi, Heding, Xuehai, Yanglingquan, calf nose, knee and the local Ashi point.	Standardized acupuncture treatment.
	Group B **Western medicine**	20 (4/16)	57.3±19.8				
Ouyang, et al, 2010[28]	**Group A** **Electroacupuncture**	32 (9/23)	49.52 ± 12.89	Improvement of clinical symptoms, activity of pathological condition, and health status improvement after treatment. Quality of life improved (p<0,05). Somatic function, physical functions, somatic pain and mental health were better (p<0,05).		ACR 20 and ACR 50, TNF-α, VEGF, SD	3-5 acupoints selected; needles retained 30 min. Patients changed to prone position to execute needling on dorsal acupoints and needles were retained for more 15 min. Treatments carried out once a day, for 10 times as one course (total of three courses.
	Group B **Control (Acupuncture)**	31 (9/22)	50.49 ± 13.23	13 cases (41,94%) reached ACR-20 standard and 4 cases (12,90%) reached ACR-50 standard. Overall health, somatic function, somatic pain, vitality and social functions (p<0,05) improved.			
Zhou and Zhu, 2000[29]	**Group A** **Acupuncture**	30 (5/25)	45±5	Total effective rate 83,3%. The number of painful joint, number of swelled joint, duration time of morning stiffness and grip strength showed significant improvement. ESR, titer of RF, activity of SOD and level of LPO decreased and the level of LEK increased.	Manual manipulation	Number of painful and swollen joints, Morning stiffness, Grip strength, ESR, Titer of RF, SOD, LPO Level of LEK	Standardized treatment.
	Group B **Control**	15 (3/12)	44 ± 7.3	The number of painful and swollen joints, duration time of morning stiffness and grip strength showed significant			

				improvement. ESR, titer of RF, activity of SOD and level of LPO decreased.			
Wang, et al, 2014[30]	**Group A Acupuncture plus Moxibustion**	75 (26/49)	54±7	VAS scores decrease (p<0.05). Total effective rate 93.3%.	Manual stimulation,	VAS, Clinical sign grades and scores	Standardized treatment. Statically significant difference were found between the two groups (p<0.05).
	Group B Acupuncture plus TDP lamp	75 (27/48)	55±6	VAS score and the clinical sign scores improved (p<0.05). Total efficacy rate 78.7%.			
Xie, et al, 2015[31]	**Group A Acupuncture (observation)**	70 (gender not referred)	48.4±10.5	Total effective rate 91.43%. Tender joint count, swollen joint count, PLT, ESR and DAS28 better than those of the control group (p<0.05). Quality of life scores significantly higher than those of the control group [(70.5±15.2) vs (64.3±14.4); (81.6±15.5) vs (71.6±14.3), p<0.05].	Manual stimulation.	Range motion, PLT, ESR, DAS28, HRQoL	Standardized modified mild suspension acupuncture therapy (Kidney Yu, Liver Yu, Spleen Yu, Vital Point and the Hegu, Zusanli, Taichi points).
	Group B Control (usual care)	80 (gender not referred)	48,4±10.5	The range of motion improved significantly (p<0.05).			

Notes: ACR: American College of Rheumatology; AT:Autogenic training; CGI: Clinical Global Impression; CRP: C: reactive protein: level of lipid peroxidation; PDI: pain disability index; PLT: total effective rate platelet; PGADA: patient's global assessment of disease activity; RF: rheumatoid factor; SD: satisfaction degree; SOD: activity of superoxide dismutase; TAS: tellegen absorption scale; *TC:traditional Chinese;* TCA: traditional chinese acupuncture; TCM: t*raditional Chinese Medicine;* VAS: visual analogue scale; VASG: visual analogue scale of patient's global assessment.

Primary Outcomes

Effectiveness of Acupuncture on Pain in Patients with RA

Regarding pain relief assessed with the VAS, evaluation between patients treated with auricular EA and autogenic training (AT), significant differences between groups in favor of EA group were found after the 4th treatment week.[24]

Wang, et al[35] in a three-armed parallel study, concluded that the total effective rate of acupuncture treatments with moxibustion were significantly higher than when acupuncture or moxibustion are used alone. Wan et al. compared the effectiveness of acupuncture treatments with the conventional current RA medication and found that the acupuncture group improved symptoms of finger joint pain better than the group treated only with western medicine ($p < 0.05$).[26]

Zhou and Zhu[29] showed that the number of painful joints decreased after treatment with acupuncture ($p < 0.05$).

Effectiveness of Acupuncture on Physical Function in Patients with RA

Xie and colleagues found that after the acupuncture treatments the total effective rate, the TJC, swollen joint count and DAS28 were better than the results showed to the patients treated only with western medicine ($p < 0.05$).[31]

Zanette, et al[19] also demonstrated a significant improvement in physician global assessment of the disease activity ($p < 0.012$), physician ($p < 0.003$) and patient ($p < 0.011$) global assessment after the acupuncture treatment.

Effectiveness of Acupuncture on HRQoL in Patients with RA

Zhu[27] found that, after the acupuncture treatments, symptoms affecting the HRQoL, DAS28 and HAQ scores improved significantly and the results were better than the patients treated only with western medicine ($p < 0.05$). Xie and colleagues showed that after the treatment and four months of follow-up, HRQoL scores of the group treated with acupuncture were significantly higher than those of the control group [(70.5 ± 15.2) vs (64.3 ± 14.4); (81.6 ± 15.5) vs (71.6 ± 14.3), $p < 0.05$].[31]

Ouyang and collaborators compared the effects of acupuncture with or without electro-stimulation and the overall effect of EA was better than acupuncture alone.[28] All HRQoL parameters were significantly improved ($p < 0.05$) except emotional functions. Somatic function, physical functions, somatic pain and mental health were better to the patients treated with EA than the control group ($p < 0.05$).[28]

Secondary Outcomes

Zanette and collaborators[19] showed that eight of the participants (40%) of the group treated with acupuncture reached ACR-20 standard in comparison with only two cases (10%) reached ACR-20 standard to the control group.[19]

For Tam and colleagues,[32] the ACR score to patients treated with EA showed significant reduction of the physician's global assessment ($p = 0.04$) and number of tender joints ($p = 0.03$), as also to the patients treated with TA ($p = 0.01$). The group treated with sham acupuncture, ACR score showed reduction of the physician's global assessment ($p = 0.03$) where all other components remained unchanged.[32]

Comparison of auricular EA with AT showed that DAS28 score had a more marked decrease in the EA group, the clinical global impression was successful in both groups but after the 6th week of treatments, symptoms and clinical outcomes were better in the EA group than in the AT group (1.32 ± 1.25 vs 0.39 ± 1.34; $p = 0.035$).[24]

Two of the Chinese studies compared acupuncture treatment using different CM treatment approaches.[25,33] One of them chose a selection of major acupuncture points for Bi-Syndrome. The results showed that the morning stiffness duration, joint tender index, joint swelling index and ESR significantly improved after acupuncture treatment using major acupuncture points ($p < 0.01$) and the total effective rate was 93.3%.[25] To the group treated with acupuncture in acupoints selected to the Bi-impediment syndrome due to wind, the total effective rate was 76.6%.[25] The difference of the total effective rate between observation group and control group ($p < 0.01$, Chi-square) indicated that the therapeutic effect of the group that used major points was higher than the control group.[25]

Another CM approach showed that the results of the integrative group were better than the other two groups ($p < 0.01$), besides the midnight-noon ebb-flow method had an positive therapeutic effect on RA clinical signs, which could improve the effect combining with dialectical therapy.[33]

Studies that compared acupuncture treatment with western medical treatment showed that RA symptoms, DAS28, HAQ scores and HRQoL improved significantly more in the acupuncture group than in the Western medicine group ($p < 0.05$ or $p < 0.01$).[26,27,31]

Zhou, et al[29] showed an effective rate of 83.3% for the acupuncture group. The number of painful joints, number of swollen joints, duration time of morning stiffness and grip strength significantly improved ($p < 0.05$). ESR, titer of RF, activity of superoxide dismutase (SOD) and level of serum lipid peroxide (LPO) decreased after treatment with acupuncture.[29]

Ouyang and collaborators[28] showed that 22 cases (68.75%) in the EA group reached ACR-20 standard and 6 cases (18.75%) reached ACR-50 standard. Clinical symptoms, activity of pathological condition, DAS28 and health status tended to improve after the acupuncture treatments and the results were better than to the patients treated only with western medicine ($p < 0.05$).[31] Patients treated only with usual care showed that 13 cases (41.9%) reached ACR-20 standard and 4 cases (12.90%) reached ACR-50. ESR and C-reactive protein improved in both groups ($p < 0.01$).[31]

DISCUSSION

RA has major, diverse effects on patients's HRQoL, spanning both physical and mental domains.[36] Given the complexity of the therapeutic used in RA, acupuncture has been heavily advertised with broad, attractive claims.

Ten of the 13 RCTs pointed out that acupuncture was effective in relieving pain, PF and HRQoL in patients with RA compared to controls.[24-31,33,35] A particularity of these studies it is that they were published in China and variation between east and western cultures cannot be denied. Chinese clinical trials combined acupuncture with other CM techniques as moxibustion, acupoints chosen according to specific CM theories and patients were treated according to a litany of symptoms interpreted from a CM perspective and not just in a western medicine point of view.

Three placebo-controlled trials employed sham acupuncture[19,32,34] and reported no statistically significant results for treatments using real or verum acupuncture in terms of RA symptom. The lack of evidence reported is subject of few interpretations. It is doubtful whether the acupuncture treatment administered was ideal. The results could be related to the type of intervention, the number of treatment sessions could have been too small to generate a significant effect; possibly insufficient stimulation; unsuitability of the protocol for treating RA. Different levels of expertise in acupuncture interventions and differences in methodologic considerations, such as lack of a real double-blind, higher doses (intensity and duration), the type of acupuncture (acupuncture combined with moxibustion or acupuncture versus EA), the site of intervention, the small sample size and the lack of a CM differential diagnosis might had influenced the lack of efficacy of acupuncture.

Some of the RCTs followed the specific CM concept of an individual diagnosis.[24,28,33] The acupuncture points selection is based on a specific group of symptoms of RA patients that lead to the CM diagnosis specificity. By integrating the CM diagnosis as an inclusion criterion, it is distinguishable by the homogenization of biomedical parameters and classification of CM diagnosis, gives clear evidence about the importance of synergy that must exist between the diagnosis in CM and respective selection of acupoints[6,37] and, it's essential for clinical practice because it might allocate interventions more adequately to the patient complaints.[15,16]

Studies that do not work on the basis of a well collected CM diagnosis but instead use a form of scientific acupuncture with standardized points, showed contradictory conclusions and may underestimate the effects of acupuncture in the treatment of RA.[19,32,34]

It is necessary to determine the specific effects of acupoints when treated by different CM techniques but, it can only be shown if the intervention using real acupoints is maximally effective in comparison to unspecific and suggestive effects of the false or placebo acupoints (control groups). Therefore, the CM diagnosis as an inclusion criterion is the way to allocate the correct points to the studies

participants and to improve efficacy of acupuncture treatments. The suggest effects of acupuncture can only be excluded by double-blinding acupuncture.

Questionable it is also the type of sham acupuncture used by the authors.[19,32,34] The use of placebo is essential for differentiating non-specific from specific treatment effects but exist several kinds of sham acupuncture (non-penetrating needles, needle insertion into random points rather than acupoints, needle insertion at least 5cm away from the acupuncture points and their connecting meridians and avoid painful pressure points,[36] superficial puncture of 2mm and then the needle is quickly withdrawn using acupoints[32]).

The key point to remember when performing sham acupuncture is that it is absolutely critical that the patient is unaware if they are receiving sham or true acupuncture. The method and time of puncture, number of needles must be the same on all groups, as well as same depth of insertion, but point selection is based on using areas that are external to the meridian channel to avoid the puncture in acupoints.[36]

We consider to exist consequences for the control intervention to be chosen. Trials using streitberger placebos, shallow 2mm needlings or pyonex controls, the dosage of penetration is zero or low. The use of different numbers of needles in verum and control intervention, lead the searchers to compare high dosage of needling in the verum versus low dosage of penetration in controls.

Acupuncture seems to be promising when compared with conventional current RA-medication. The groups treated with acupuncture showed better results to pain relief, DAS28, HAQ scores and HRQoL than the groups treated only with western medicine.[26,27,31] Only one study showed non-significant results between acupuncture and western medicine alone, but acupuncture had effects on early RA with lower side effects and the mechanism of anti-inflammation and analgesia of acupuncture may be related to SOD and LPO.[29]

The studies from Asian countries tend to have positive results. However, the long-term benefits remain unknown and the results must be carefully interpreted because of the risk of methodological limitations, as well as unclear information about the methods of random assignment, inappropriate control interventions (non-comparable), no double-blind interventions and no real placebo.

Acupuncture combined with moxibustion to treat RA had significant immunomodulatory effects and can improve the physiological function as the morning stiffness duration, joint tender index and joint swelling index indicating that the therapeutic effect of the groups treated with acupuncture combined with moxibustion is higher than the control groups.[25,30,31,35] Acupuncture combined with the synergetic effects of heat from moxibustion, might induce a comparison of the acupuncture effects to the analgesics, which claim to reduce pain through a stimulation of the serotonergic, noradrenergic and opioid system.[7]

Association of different strategies seems to be promissory. The study conducted by Bing-bin and colleagues, combining major points choice plus moxibustion.[25] The results intended to have marked

systemic affects believed to be caused by the choice of points based on the syndrome differentiation and local ashi points.[25] The integration of midnight-noon ebb-flow acupoint selection and acupuncture by differentiation of symptoms and signs group, combining points with systemic and local actions, showed better results (a total effective rate of 95% and P<0.01), than the application of each strategy alone.[33]

Despite the promising results of ten of the 13 studies included,[24-31,33,35] evidence displayed on these is limited due to methodological considerations.

Lack of data on power analysis and effect sizes providing information about the impact of the acupuncture intervention is a limitation to most studies. This could explain how much difference the intervention had made and to assist clinicians and policy makers in making informed decisions about the appropriate acupuncture use.

The studies are difficult to compare, as it is necessary to determine and record the qualification level and experience of the acupuncturists in both eastern and western countries, the optimum dose/intensity (effective evidence-based dose/intensity including number of acupuncture points, difference of effects of acupuncture on acupoints and painful points, frequency of acupuncture sessions, intervention duration, appropriate needle insertion and manipulation techniques) of acupuncture treatments in order to homogenize the samples and to develop a standardized, generalize and optimized treatment protocol.

The ability to access articles on Chinese databases might have yielded further information pertaining to our topic. We included Chinese databases, as acupuncture is originated in China and there are many studies published in Chinese. However, we recognize that to search English words in Chinese database may inevitably lead to omissions. China Academic Journal and Century Journal Project are part of CNKI and no inclusion of other Chinese biomedical literature database may lead to no identification of potential papers. Besides that, we were limited by the unavailability to access the full-text of 15 studies. The difficulty to access the Chinese literature was related to the fact that articles might not be indexed to conventional databases and also that access to local journals might be restricted. These facts might have resulted in an overestimation or underestimation of the effect of acupuncture interventions.

No meta-analysis could be performed due to clinical heterogeneity (acupuncture interventions, instruments, the dose/intensity of the treatments, the number of sessions and the fluctuations time elapsed between sessions) and methodological heterogeneity (designs) whereby, evidence is not strong enough to produce a better practice guideline.

Future high-quality studies are justified as research priorities and should be designed with the potential to provide opportunities for better treatment outcomes by targeting western or CM treatment to specific groups of patients, by using validated outcome measures, applying appropriate randomized-control or blind interventions and by knowing long-term benefits.

Future RCTs with more prevailing high-quality designs, larger-scale samples, validated longer-term outcome measures for RA, appropriate control groups, appropriate sham methods, real double-blind and applying the CONSORT guidelines are required to strengthen the current evidence base on acupuncture treatments and to further understand its long-term effects in RA.

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Supplementary material

Appendix 1: Search strategy

- **Pubmed – searched in January 5ᵗʰ, 2017**

Search formula	Results
Search (((((((((acupunc*[Title/Abstract]) OR Acupuncture Therapy[MeSH Terms]) OR Acupuncture[MeSH Terms]) OR Acupuncture Points[MeSH Terms]) OR Acupuncture Analgesia[MeSH Terms]) OR Acupuncture, Ear[MeSH Terms]) OR electroacupuncture[MeSH Terms])) AND ((("Rheumatoid Arthritis"[Title/Abstract]) OR "inflammatory arthritis"[Title/Abstract]) OR Arthritis, Rheumatoid[MeSH Terms])) AND (((((((((((pain[Title/Abstract]) OR "quality of life"[Title/Abstract]) OR "physical function"[Title/Abstract]) OR "health-related quality of life"[Title/Abstract]) OR "life quality"[Title/Abstract]) OR pain[MeSH Terms]) OR acute pain[MeSH Terms]) OR arthralgia[MeSH Terms]) OR Chronic Pain[MeSH Terms]) OR Pain Measurement[MeSH Terms]) OR Pain Management[MeSH Terms]) OR Quality of Life[MeSH Terms])	89
Search (((((((((((pain[Title/Abstract]) OR "quality of life"[Title/Abstract]) OR "physical function"[Title/Abstract]) OR "health-related quality of life"[Title/Abstract]) OR "life quality"[Title/Abstract]) OR pain[MeSH Terms]) OR acute pain[MeSH Terms]) OR arthralgia[MeSH Terms]) OR Chronic Pain[MeSH Terms]) OR Pain Measurement[MeSH Terms]) OR Pain Management[MeSH Terms]) OR Quality of Life[MeSH Terms]	804123
Search (("Rheumatoid Arthritis"[Title/Abstract]) OR "inflammatory arthritis"[Title/Abstract]) OR Arthritis, Rheumatoid[MeSH Terms]	125583
Search (((((((acupunc*[Title/Abstract]) OR Acupuncture Therapy[MeSH Terms]) OR Acupuncture[MeSH Terms]) OR Acupuncture Points[MeSH Terms]) OR Acupuncture Analgesia[MeSH Terms]) OR Acupuncture, Ear[MeSH Terms]) OR electroacupuncture[MeSH Terms]	23199
Search Quality of Life[MeSH Terms]	131012
Search Pain Management[MeSH Terms]	22568
Search Pain Measurement[MeSH Terms]	65775
Search Chronic Pain[MeSH Terms]	5462
Search arthralgia[MeSH Terms]	9059
Search acute pain[MeSH Terms]	893
Search pain[MeSH Terms]	321623
Search "life quality"[Title/Abstract]	4245
Search "health-related quality of life"[Title/Abstract]	27462
Search "physical function"[Title/Abstract]	7887
Search "quality of life"[Title/Abstract]	174062
Search pain[Title/Abstract]	458151

Search Arthritis, Rheumatoid[MeSH Terms]	97405
Search "inflammatory arthritis"[Title/Abstract]	3323
Search "Rheumatoid Arthritis"[Title/Abstract]	85185
Search electroacupuncture[MeSH Terms]	2809
Search Acupuncture, Ear[MeSH Terms]	307
Search Acupuncture Analgesia[MeSH Terms]	1074
Search Acupuncture Points[MeSH Terms]	4576
Search Acupuncture[MeSH Terms]	19297
Search Acupuncture Therapy[MeSH Terms]	18654
Search acupunc*[Title/Abstract]	16795

- **CINAHL - searched in January 5th, 2017**

Search strategy	Results
S25 AND S27 AND S31	38
S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S28 OR S29 OR S30	263, 384
(MH "Arthralgia")	1,791
AB "health-related quality of life"	7,611
AB "life quality"	809
S1 OR S2 OR S26	17,993
AB "inflammatory arthritis"	511
S3 OR S4 OR S5 OR S6 OR S7 OR S8	12,019
(MH "Physical Activity (Omaha)")	1
(MH "Physical Activity")	23,774
(MH "Functional Assessment Inventory")	44
(MH "Functional Assessment")	12,788
(MH "Functional Status")	15,422
(MH "Quality of Life (Iowa NOC)")	2
(MH "Quality of Life")	66,368
(MH "Pain Management (Iowa NIC)")	6
(MH "Acute Pain Control (Saba CCC)")	1
(MH "Acute Pain (Saba CCC)")	1
(MH "Chronic Pain")	13,476
(MH "Pain Measurement")	35,146
(MH "Pain")	52,829
AB "Physical function"	2,952
AB "Quality of life"	46,914

AB Pain	86,261
(MH "Electroacupuncture")	912
(MH "Acupuncture Analgesia")	285
(MH "Acupuncture Points")	1,749
(MH "Acupuncture, Ear")	136
(MH "Acupuncture")	9,559
AB acupunc*	3,926
(MH "Arthritis, Rheumatoid")	15,385
AB "Rheumatoid Arthritis"	7,237

- **Cochrane Central Register of Controlled Trials - searched in January 5th, 2017**

Search strategy	Results
acupunc*:ti,ab,kw (Word variations have been searched)	8349
"Rheumatoid Arthritis":ti,ab,kw (Word variations have been searched)	7072
MeSH descriptor: [Arthritis, Rheumatoid] explode all trees	4207
MeSH descriptor: [Acupuncture Therapy] explode all trees	3254
MeSH descriptor: [Acupuncture] explode all trees	154
MeSH descriptor: [Acupuncture Points] explode all trees	1120
MeSH descriptor: [Acupuncture Analgesia] explode all trees	253
MeSH descriptor: [Acupuncture, Ear] explode all trees	131
MeSH descriptor: [Electroacupuncture] explode all trees	490
Pain:ti,ab,kw (Word variations have been searched)	83792
"Quality of life":ti,ab,kw (Word variations have been searched)	38239
"Physical function":ti,ab,kw (Word variations have been searched)	3456
MeSH descriptor: [Pain] explode all trees	33829
MeSH descriptor: [Chronic Pain] explode all trees	462
MeSH descriptor: [Acute Pain] explode all trees	90
MeSH descriptor: [Pain Measurement] explode all trees	15333
MeSH descriptor: [Pain Management] explode all trees	1737
MeSH descriptor: [Arthralgia] explode all trees	931
MeSH descriptor: [Quality of Life] explode all trees	15428
"health-related quality of life":ti,ab,kw (Word variations have been searched)	5616
"life quality":ti,ab,kw (Word variations have been searched)	1180
"inflammatory arthritis":ti,ab,kw (Word variations have been searched)	143
#2 or #3 or #22	7771
#1 or #4 or #5 or #6 or #7 or #8 or #9	8515
#10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21	121934

#22 and #23 and #24	31
#22 and #23 and #24 in Trials	24

- **China Academic Journal - searched in January 5th, 2017**

Search strategy	Results
AB (Rheumatoid Arthritis AND acupuncture)	192

- **Century Journal Project - searched in January 5th, 2017**

Search strategy	Results
AB (Rheumatoid Arthritis AND acupuncture)	9

- **China Doctor/Master Dissertation Full Text DB - searched in January 5th, 2017**

Search strategy	Results
AB (Rheumatoid Arthritis AND acupuncture)	17

- **China Proceedings Conference Full Text DB - searched in January 5th, 2017**

Search strategy	Results
AB (Rheumatoid Arthritis AND acupuncture)	16

- **ProQuest – Nursing and Allied Health Source Dissertations - searched in February 18th, 2017**

Search strategy	Results
ab(acupunc*) AND ab("rheumatoid arthritis" OR "inflammatory arthritis")	4

- **RCAAP – Repositório Científico de Acesso Aberto de Portugal - searched in January 5th, 2017**

Search Strategy	Results
AB ("Rheumatoid Arthritis" OR "inflammatory arthritis") AND AB (Acupuncture OR acupunc*)	2

- **AMED - searched in June 6th, 2017**

Search Strategy	Results
exp Pain measurement/ or exp Pain/ or pain*.mp. or exp Arthralgia/ or arthralgia.mp.	30925
exp "Activities of daily living"/ or activities of daily living.mp. or (adl or functionality).mp. or physical function.mp.	7332

exp "Quality of life"/ or "quality of life".mp. or "life quality".mp. [mp=abstract, heading words, title]	11212
or/1-3	45430
exp Arthritis rheumatoid/ or rheumatoid arthritis.mp. or inflammatory arthritis.mp.	2332
4 and 5	827
exp acupuncture therapy/ or acupuncture/ or "therapeutic acupuncture".mp. or "acupuncutre therapy".mp. or acupunctur*.mp. or electroacupunct*.mp. [mp=abstract, heading words, title]	10554
6 and 7	29

Appendix 2: Assessment of the methodological quality of included Randomized Control Trials

Citation	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10
Zanette et al.[19]	Y	Y	U	U	N	Y	Y	Y	Y	Y
Tam et al. [32]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Bernateck et al.[24]	U	U	U	N	U	Y	Y	Y	Y	Y
Bing-bin[25]	Y	U	U	Y	U	Y	Y	Y	Y	Y
David et al.[34]	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
Wan and Xioung[26]	U	U	U	Y	U	Y	Y	Y	Y	Y
Zhu, Y.[27]	U	U	U	Y	U	Y	Y	Y	Y	U
Wang et al[35]	U	U	U	Y	U	Y	Y	Y	Y	Y
Sun et al.[33]	U	U	U	Y	U	Y	Y	Y	Y	Y
Ouyang et al.[28]	Y	U	U	Y	U	Y	Y	Y	Y	Y
Zhou and Zhu[29]	U	U	U	Y	U	Y	Y	Y	Y	Y
Wang et al.[30]	U	U	U	Y	U	Y	Y	Y	Y	Y
Xie et al.[31]	U	U	U	Y	U	Y	Y	Y	Y	Y
%	46.15	23.1	15.4	76.9	23.1	100	100	100	100	92.3

Q1 (Was the assignment to treatment groups truly random?); Q2 (Were participants blinded to treatment allocation?); Q3 (Was allocation to treatment groups concealed from the allocator?); Q4 (Were the outcomes of people who withdrew described and included in the analysis?); Q5 (Were those assessing outcomes blind to the treatment allocation?); Q6 (Were the control and treatment groups comparable at entry?); Q7 (Were groups treated identically other than for the named interventions?); Q8 (Were outcomes measured in the same way for all groups?); Q9 (Were outcomes measured in a reliable way?); Q10 (Was appropriate statistical analysis used?); Y = yes; N = no; U = unclear.

Chapter 4

Understanding Chinese Medicine patterns of Rheumatoid Arthritis and related biomarkers

Understanding Chinese Medicine patterns of Rheumatoid Arthritis and related biomarkers

ABSTRACT

Introduction

A considerable number of Rheumatoid Arthritis (RA) patients only experience side effects from treatment, with little to no actual pain relief. The combination of disease diagnosis in biomedicine, and multi-disciplinary integrative approaches such as Chinese Medicine (CM), can help to identify different functional diagnosis of RA in the context of biomarker discovery.

Objective

To analyze CM patterns in RA and their biomarker profiles.

Methods

Four electronic databases (web of science, CINAHL, Scopus and Pubmed) were searched. The reference list of all identified reports and articles were searched for additional studies. All study designs were included, and no date limits were set. Studies were considered if they were published in English, and explored the possible biomarkers profiles in RA patients, classified according to the American College of Rheumatology, and categorized in CM as either cold, heat/hot or deficiency patterns. Methodological quality of included studies was assessed using checklists adapted from the ©Critical Appraisal Skills Programme by two independent reviewers. A narrative synthesis was conducted, using thematic analysis.

Results

A total of 10 articles were included. The studies examined 77 healthy volunteers and 1,150 RA patients categorized as cold, heat/hot or deficiency pattern, and related biomarkers were identified individually or concomitantly.

Conclusions

CM pattern differentiation based on clinical signs and symptoms showed a diverse range of biomolecules, proteins and genes from RA patients correlated well with cold, heat/hot or deficiency phenotype-based CM patterns, and could be used as diagnostic biomarkers for early detection, disease monitoring and therapeutic targets.

Keywords: Rheumatoid Arthritis; Biomarkers; Traditional Chinese Medicine; Patterns

INTRODUCTION

Rheumatoid Arthritis (RA) pathogenesis is a multistep process between the dysregulated neuro-immune system, abnormal neuro-endocrine-immune and the individual's genetic background (for example the HLA-DRB1 gene) that may predispose some people to excessive cytokine responses.[1,2,3,4] As a multifactorial complex chronic inflammatory disease with heterogeneous clinical manifestations, RA is characterized by functional disability and pain with a high social-economic impact on the individuals, as well as on the Health System.[5,6] Quality of life has improved for RA patients due to new therapeutic options, however 20-40% of the patients have seen no satisfying solutions.[7] Due to the side effects, high costs and limited therapeutic response to the available treatments, it could be helpful to stratify patients in order to identify those who would benefit from a particular therapy.[7]

Chinese Medicine (CM) uses an individualized approach based on the unique combination of symptoms and signs of each patient (named syndromes, patterns, or *Zheng*).[8]

CM pattern diagnosis is an approach that takes into account a broad spectrum of symptoms and signs.[9] Constitutional, behavioral and social aspects are also considered in both the diagnosis and in the selection of treatment.[9,10]

In CM clinical practice, patients with the same disease can be divided into different groups according to their syndromes.[11,12] Some studies suggest that CM pattern differentiation may help to identify different subsets of RA patients which respond differently to biomedical treatments with biomarkers based on the integrated and interactive network of genes, proteins and biochemical reactions of the body system.[8,13,14,15]

RA patient subtypes described according CM may fall into Bi Zheng, a syndrome characterized by obstruction of *qi* and *xue* (blood) in the conduits (meridians) and collaterals.[16] Cold, heat/hot or deficiency syndromes are also very well described in RA patients not taking nonsteroidal anti-inflammatory corticosteroid drugs.[17] These syndromes can be found isolated but RA patients often show mixed features.

The cold pattern is described as an attack from the external pathogen agent algor/"cold",[1] showing symptoms such as a cold feeling in the limbs and joints; stiffness or pain in a joint or muscle which is relieved by applying warmth and increases with the patient's exposure to cold; local reduction of the microcirculation; thin white tongue coating; wiry and tight pulse; facial pallor; loose stools; clear profuse urine; and absence of thirst.[18,22,24]

The heat or hot pattern is related with hot, red, swollen and inflamed joints; severe pain generally relieved by applying cold to the joints; red tongue with a yellow coating; pulse may be rapid; flushed face; constipation and deep-colored urine; thirst; and irritability.[17,23] The deficiency pattern normally

occurs in the later stages of the disease and is characterized by deformity; inhibited flexion and extension of the limbs.[17]

Thus, identification of new biomarkers with key roles in CM patterns may represent different stages of diseases and may be a subject of interest for RA treatment, allowing prevention of the condition and appropriate intervention in the context of a personalized medicine.[20]

The purpose of this review is to analyze cold, hot and deficiency CM patterns in RA patients, and their biomarker profiles. This may be useful for the evaluation of the effects of biomedical combination therapy and CM in the context of biomarker discovery.

METHODS

This review was conducted in line with PRISMA guidelines.

Search strategy and screening

Four electronic databases (Web of Science, CINAHL, Scopus and PubMed) were searched. The reference lists of all the identified reports and articles were further searched for additional studies.

The keywords used were a combination of the following: (("rheumatoid arthritis" OR rheumatoid) AND (genomics OR biomarker* OR marker*) AND (syndrome OR pattern OR zheng) AND (cold OR hot OR defici* OR excess OR phlegm) AND (TCM or "Chinese medicine" OR acupuncture OR moxibustion OR moxa)).

Titles and abstracts of articles retrieved were screened for eligibility against the inclusion criteria (see below) to determine the population being studied, outcome measures, and study design. Whenever the title and abstract lacked data to make a decision the article was then sourced for full-text reading. The reference lists of any articles deemed eligible for inclusion after full-text reading were also reviewed, screened and potentially eligible articles retrieved. This process continued until no new articles were identified.

Inclusion criteria

Inclusion criteria to determine which studies would be reviewed were developed using the PICOS acronym (Participants, Intervention, Comparator, Outcome Measures, Study Design). Studies were considered if they were published in English, and no date limits were set.

Participants: Patients that met the American College of Rheumatology criteria (ACR)[21] for RA for at least one year, classified as functional Class I, II, or III based on their current physical functioning level and, at the same time, they were categorized as having CM cold, heat/hot or deficiency patterns according the patient's symptoms.

Intervention: Any intervention, where applicable.

Comparator: Either another intervention, or no intervention (i.e., usual care practice or care), where applicable. Animal trials and studies exclusively testing the effects of Chinese herbs were excluded.

Outcome Measures: Any tissue sample, technique or physiologic health outcome in relation to identifying a candidate biomarker.

Study Design: Any. To include randomized controlled trial, cohort studies, cross-sectional surveys, and qualitative studies.

Assessment of methodological quality and data extraction

The papers selected for retrieval were assessed by two independent reviewers (SS and GF) for methodological validity prior to their inclusion in the review using standardized critical appraisal instruments from the ©Critical Appraisal Skills Programme (CASP) checklists (www.casp-uk), as there are qualitative and quantitative versions to enable appraisal across different study designs.

The reviewers established minimum criteria for the inclusion of a study in the review, that is studies where relevant information was clearly reported and that scored a "yes" to the first two questions in the standardized critical appraisal instrument (CASP) (see supplementary file).

A narrative synthesis was conducted, using thematic analysis.

RESULTS

The database search yielded 48 papers, while an additional 176 papers were identified through other sources. After assessing these for eligibility and eliminating duplicates, 10 articles met the inclusion criteria (eight qualitative studies,[17,22,23,24,25,26,27,28] one randomized clinical trial[29] and one non-randomized study[30]). Figure 1 illustrates the study selection process.
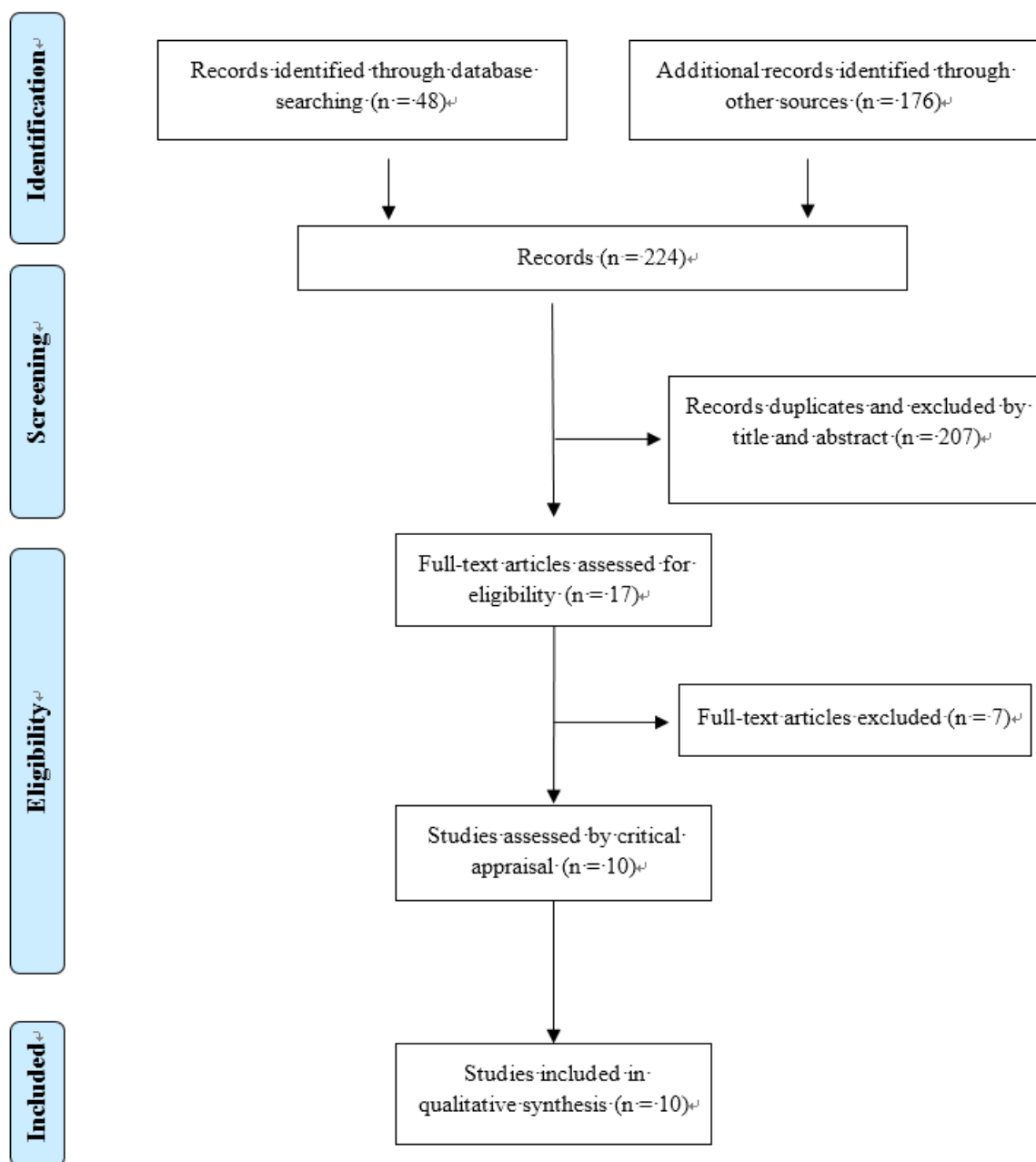
Figure1: Flow chart of the study selection process

The studies included in the review examined 1,150 patients who fulfilled the ACR criteria for RA, and 77 healthy volunteers. The patients had an age range between 12 and 70 years. Sample sizes ranged from 20 to 398 participants.[22,29] Continued Western medication therapy was an exclusion criteria in four studies,[17,22,24,27] while three studies were unclear about this aspect.[23,25,28] Three studies allowed participants receiving nonsteroidal anti-inflammatory drugs, corticosteroids, or both if they had been on stable doses.[26,29,30]

The cold, hot, and deficiency patterns are key in RA patients, and they can be identified individually or concomitantly, such as deficiency-cold, deficiency-hot, or intermingled cold and hot patterns.[17,22,23,24,25,26,27]

The cold pattern can be described as cold intolerance, feeling cold in the limbs and joints, and/or severe fixed pain in a joint or muscle that limits the range of comfortable movement.[17,22,24] Pain is relieved by applying warmth to the affected area, and increased with exposure to cold.[23] Chills, fear of cold, facial pallor, pale tongue and white greasy tongue coating, slow or stagnant pulse, loose stools, clear profuse urine and absence of thirst can be part of the profile.[17,22,23,24,25,26,27]

The hot pattern is characterized by severe pain with hot, red, swollen and inflamed joints.[17,22,24] Pain is relieved by applying cold to the affected area.[17,22,24] The tongue may be red with a yellow coating and the pulse may be rapid. Other symptoms include fever, thirst, a flushed face, irritability, restlessness, constipation and deep-colored urine.[17,22,23,24,25,26,27,28]

Deformity, inhibited bending and stretching in limbs; pain occurring or worsening during moodiness, and numbness were categorized in the deficiency pattern.[17] These symptoms clinically occur in the later stage of disease or subsequent to other common articular symptoms such as pain with cold or hot feeling, and swelling.[17]

Logistic regression analysis showed that the parameters erythrocyte sedimentation rate, white blood cell count, C-reactive protein, joint pyrexia, joint cold, thirst, sweating, aversion to wind and cold, and cold extremities were statistically useful to discriminate hot from cold syndrome.[27]

The CM patterns show both unique and common features at a genomic, proteomic, and metabolomic levels in RA patients (Table 1). Figure 2 summarizes the biomarkers and pathways of the CM syndromes described in RA patients.

Table 1. Included studies

Ref.	Sample size (m/f) Age (years)	Methods/ Outcomes Tissue Sample Technique Verification/ Validation	Remarkable results in RA patients				
			TCM pattern	TCM Signs/ symptoms	Identified candidate Biomarkers	Implication	Target disease
Lu et al[22]	0/20 RA patients [Cold and Hot (1:2)] Age: 12 to 68	Qualitative study Blood sample (8 ml) RNA isolated from CD4+ T cell Microarray; PPI; IPCA; Cytoscape; BiNGO Databases: BIND, BIOGRID, DIP, HPRD, MINT	Cold	- no color change in joint; - severe pain in cold condition	1. Up-regulated genes: TLR4 2. TLR signaling pathways	1. Remarkably elevated expression of a spectrum of genes involved in collagen VI, pathogen recognition and activation of innate immunity in CD4+ T cell 2. Induction of persistent expression of immune and inflammatory genes (such as TNF-α, Type I interferon, NF-κB)	Inflammatory response is more pronounced (higher effective rate of anti-inflammatory drugs)
			Hot	- red joint; severe pain in hot condition	1. Up-regulated genes: 1.1 TRPC3, CABLES1, VWOX, IFI27 2. Pathways: 2.1 Calcium signaling; CAMs 2.2 PPAR signaling, nuclear hormone receptors 2.3 Fatty acid metabolism	1. 1.1 Genes participated in proliferation and/or differentiation, cholesterol efflux, regulation of cellular functions, regulation of protein sorting and membrane trafficking, immuno-regulatory processes 2. 2.1 T cell interaction (activation, proliferation, and secretion) 2.3 Activated by fatty acids and their derivates	1. Signature of induction of apoptosis 2.1 Regulation of signal transduction mediated by adhesion molecules on T-lymphocyte interactions (possible effective way to control the pathological inflammatory process) 2.3 PPAR and FFA
Chen et al[23]	0/ 33 RA patients [n=21 cold, n=12 hot] Age: 42.8±9.9	Qualitative study Blood sample RNA isolated from CD4+ T cell Microarray; PPI; IPCA; BiNGO Databases: BIND, BIOGRID, DIP, HPRD, MINT)	Cold	Cold intolerance, cold feeling in the limbs, cold feeling in the joints	1. Genes highly expressed: 1.1 GABRA6; EGR1; SLC15A3; ZNF24		Hormones are predominant factors
			Hot	Thirst, vexation, fever and turbid urine	1. Higher expression of: 1.1 TIAM1 1.2 ALOX5 1.3 H2AFX and LIG1	1.1 Small G protein signaling pathways activated 1.2 Lipid inflammatory mediators increased/ oxidation-reduction in fatty acid metabolism increased 1.3 T cell proliferation increased	Predominance of immune factors Oxidation-reduction in fatty acid metabolism increased

Study	Sample	Methods	Pattern	Symptoms	Biomarkers	Pathways	Notes
Lu et al.[24]	0/ 45 [RA patients: n=21 cold, n=12 hot] [12 healthy volunteers] Age: 18 to 70	Qualitative study Blood sample RNA isolated from CD4+ T cell Microarray; PPI; IPCA; BiNGO DAVID; GeneSpring Databases (BIND, BIOGRID, DIP, HPRD, IntAct MINT)	Hot and Cold common points		1. six genes shared (MMGT1, TDRD7, GTF3C6, BCL2A1) 1.1 CTLA4 1.2 PSMD8 1.3 RNA splicing	1. Five pathways: CAMs, T cell receptor signaling pathway, proteasome 1.1 CTLA4 (up-regulated) participates in the pathways of autoimmune thyroid disease, CAMs and the T cell receptor signaling 1.2 PSMD8 (down-regulated) – imply down-regulation of protein ubiquitination in the cell cycle	- CTLA4: negative regulator in autoimmune diseases; down-regulation effect on TNF-α and Il1-β production - Protein ubiquitination, RNA splicing, proliferation and apoptosis related to the cell cycle
			Cold	Severe fixed pain in a joint or muscle; pain relief upon warming and worse upon cooling; white tongue coating	1. Significant gene biomarkers: 1.1 EIF4A2 1.2 CCNT1 1.3 IL16 1.4 IL7R	1. Pathways: up-regulation of cell proliferation, GPI anchor biosynthesis, arachidonic acid metabolism, ABC transporters, pentose and glucoronate interconversions, and axon guidance. 1.1 Regulation of translation and cell biosynthetic processes 1.2 RNA transcription and protein ubiquitination (CD4+ T cell and macrophages) 1.3 T cell regulation 1.4 The Jak-STAT signaling cascade; hematopoietic cell lineage; primary immunodeficiency; cytokine-cytokine receptor interaction; T cell regulation. Can block apoptosis and promote the proliferation of CD4+ T cells	Regulation of translation and the Jak-STAT cascade IL7R, candidate marker (simple, minimally invasive pharmacodynamics assay for RA treatments directed at the NF-κB pathway)
			Hot	Severe pain, hot, red, swollen and inflamed joints; pain relief upon cooling and worse upon warming, fever, thirst, restlessness, deep-colored urine, red tongue with yellow coating.	1. Significant gene biomarkers: 1.1 CAMP 1.2 PRKAA1 1.3 HSPA1A 1.4 HSPA8 1.5 LSM6	1.1 T cell regulation and cell proliferation 1.2 mTOR signaling; adipocytokine signaling; regulation of autophagy; HCM; insulin signaling; FFA metabolism 1.3 spliceosome, antigen processing and presentation, endocytosis, MAPK signaling, T cell regulation; complement and coagulation cascades; I-kB kinase/ NF-κB cascade 1.4 spliceosome, antigen processing and presentation, endocytosis, MAPK signaling; I-kB kinase/ NF-κB cascade 1.5 Spliceosome; RNA degradation, hematopoietic cell lineage	FFA metabolism and the I-kB kinase/ NF-κB cascade
Gu et al.[25]	0/57 [RA patients: n=28 cold, n=29 hot], [n=23 healthy volunteers] Age: 12 to 68	Qualitative study Plasma samples; LC-MS GC-MS Database: NIST	Cold	Severe pain in a joint or muscle, pallor, intolerance of cold, absence of thirst, loose stools, clear profuse urine, pale tongue and slow pulse.	1. Metabolites perturbations in: 1.1 Inositol metabolism 1.2 Lipid metabolism 1.3 Amino acid metabolism 1.4 Glucose metabolism 1.5 Ascorbate metabolism	1.1 Inositol is up-regulated in RA patients – this could modulate intracellular signaling systems and further induce the production of inflammatory mediators, and finally might affect other metabolic pathways. 1.2 Lipid metabolism/ FFA prominently up-regulated (e.g. arachidonic acid) and may reflect the activation of the immune system.	Rates of fat and protein mobilization may be higher

			Hot	Inflamed, red and swollen joints, flushed face, fever or feverishness, thirst, irritability, restlessness, constipation, deep-colored urine, reddened tongue and rapid pulse.	1. Metabolites disorders: 1.1 Elevated plasma concentrations of glycochenodeoxycholate, proline, saturated and mono-unsaturated PC 1.2 Decreased levels of urea, FFA and polyunsaturated PE.	Presence of oxidative stress and the excess reactive oxygen species production could disturb the redox status, damage macromolecules and exacerbate inflammation.	Oxidative stress and collagen destruction may be more severe.
Van Wiet mars chen et al.[26]	0/39 [RA patients: n=20 cold, n=19 hot] Age: Cold pattern 51±13 Hot pattern 54±11 CH: n=36	Qualitative study Clinical symptoms. Blood, urine and plasma. Clinical chemistry measurement, metabolite measurement. Database: HMDB	Cold	Cold feeling, aversion to cold	1. Levels of 11 acylcarnitines were lower; 2. Lower DHEAS.	2. More suppressed HPA axis function (associated with a decreased stress response which results in an inadequate response to stress factors and consequently autoimmune and inflammatory disorders)	1. Carnitine and acylcarnitine supplementation might be beneficial for Cold RA. CRP and RF showed a low variance accounted between the cold and hot RA sub-type.
			Hot	Warm feeling, pain worsens with warmth and movement; red, warm, swollen joints; dull pain	CCP levels higher	More joint problems	The most discriminating symptoms in the analysis, "warm joints", "red joints" and "swollen joints" indicate a difference in inflammatory status.
Wang et al[27]	59/247 [n=148 cold, n=158 hot] Age: 51.3±13.2	Blood sample ESR, CRP, WBC, RBC, Hb, PLT, TP, ALB, GLB, TNF-alfa, IL-1beta DAS28 score ELISA	Cold-damp	Cold and constant pain worsened by cold or rainy weather, and at night, but relieved during warm days; heaviness of the joint. Tongue: fat, pale texture, white greasy coating. Pulse: slow or stagnant.			A highly significant relationship existed between PLT and disease severity, and a negatively correlation between the level of Hb and disease severity.
			Hot-damp	Severe pain; redness, swelling and heaviness of joint or muscle. Fever, thirst, difficulty walking, yellow urine, annoyance and unrest. Tongue: red texture, yellow coating. Pulse: slippery and quick.	DAS28, ESR, WBC, CRP, PLT, GLB, ALB differed significantly between hot-damp and cold-damp		DAS28, ESR, WBC, CRP, PLT, GLB, ALB may serve as criteria for discriminating damp-hot from damp-cold syndrome. ESR; WBC; CRP - were hot risk factors

Wang et al[17]	0/45 33 [RA patients: n=12 cold, n=21 hot, n=18 deficiency, n=15 non-deficiency], [Patients with deficiency pattern: n=8 cold deficiency, n=10 hot-deficiency], [n=12 healthy volunteers]. Age: 18 to 70	Blood sample RNA isolated from CD4+ T cell Microarray; PPI; IPCA BiNGO Databases BIND, BIOGRID, DIP, HPRD, IntAct MINT)	Cold	Cold feeling in joints, pain relieved with warming		Mainly involved in ubiquitination, RNA clipping, and Jak-STAT cascade signaling.	Cold and hot patterns: function of Jak-STAT signaling-related apoptosis
			Hot	Hot feeling, pain relieved with cooling		Function of insulin signaling.	
			Deficiency	Deformity, inhibited bending and stretching in limbs, pain occurring or worsening during moodiness, and numbness. Symptoms clinically occur in the later stage of disease or subsequent to other common articular symptoms.	1. Seven significantly, highly connected regions	1. Mainly involved in protein transcription processes, protein ubiquitination, TLR activated NF-κB regulated gene transcription and apoptosis pathways, RNA clipping, NF-κB signal, nucleotide metabolism-related apoptosis, and immune response processes.	Inhibition of NF-κB pathway is believed to be a potential therapeutic target in RA. TLRs may be on the onset of joint deformity and inhibited bending and stretching in limbs symptoms (deficiency syndrome features)
Sun et al[28]	n=90 [RA patients: n=30 Heat-damp group, n=30 Cold-damp, n=30 Control group], [n=30 healthy patients] Aged from 42 to 56 (51.3 ± 4.3)	Serum pools samples Strong cation exchange Chrotography iTRAQ LC-MS/MS analysis GO DAVID v6.7, UniProtKB/Swiss-Prot, and IPA	Hot	Redness, pain and swelling of the joint, scorching sensation, red tongue with yellow and greasy fur, rapid or slippery pulse	1. Six proteins overexpressed 1.1 FLJ00382, 1.2 Ig lambda chain V-I region WAH, 1.3 Myosin-reactive immunoglobulin light chain variable region, 1.4 C-reactive protein, 1.5 S100A9, 1.6 Cathepsin G	1. Proteins involved in inflammatory responses; five top significant canonical pathways: including Autoimmune Thyroid Disease Signaling, Hematopoiesis from Pluripotent Stem Cells, Primary Immunodeficiency Signaling, IL-17 Signaling, Allograft Rejection Signaling 1.1 Function of regulation of T cell proliferation and immune response 1.2 Involved in the biological process of regulation of immune response and complementary activation 1.3 Play a role in the immune response 1.4 Sensitive but nonspecific marker of inflammation 1.5 Positive regulation of inflammatory processes and immune response, can act as a potent amplifier of autoimmune inflammation 1.6 Significant role in the pathogenesis of RA synovial inflammation as a monocyte chemoattractant.	Hot-damp syndrome of RA has severe inflammatory responses and high RA inflammatory activity. Treatment with anti S100A9 may inhibit amplification of the immune response and help preserve tissue integrity. TNF-α is recognized as a key regulator of inflammatory response.
Jiang et al[29]	n=398 RA patients [TCM therapy n=204: n=115 cold, n=99 non-cold dominant], [Biomedicine therapy n=194: n=87 cold,	RCT ACR20 response after 24 weeks treatment course. Pharmacological Network Building-Up. Molecular Networks of TCM Cold and Hot Patterns.		TCM therapy could target: 1. All three hot-pattern clusters: I-kappa B kinase/ NF-κB, and mRNA splicing) 2. A small part of the 4 cold-pattern clusters: regulation of translation, protein ubiquitination pathway, Jak-STAT cascade, and RNA splicing)		Was better in treating the RA patients with TCM hot pattern. After 24 weeks treatment, the effective rate of the TCM therapy in the patients who showed TCM pattern changes from cold dominant pattern to non-cold dominant pattern were higher ($p<0.05$).	Protein ubiquitin pathway involved in the intersections between the cold and hot. Six months after the treatment, the TCM pattern changed in some patients.

	n=107 non-cold dominant] Age: 18 to 70	Databases: TCMGeneDIT; BIND, BIOGRID, DIP, HPRD, IntAct MINT) IPCA;, BiNGO		Biomedicine therapy targets parts of: 1. All four cold-pattern clusters: regulation of translation, protein ubiquitination pathway, Jak-STAT cascade, and RNA splicing. 2. Two parts of hot-pattern clusters: I-kappa B kinase/ NF-κB and mRNA splicing were targeted by MTX and SSZ 3. Fatty acid metabolism involved in hot pattern RA cannot be targeted by MTX, and SSZ splicing of mRNA in hot-pattern RA was targeted only on 2 nodes.	More effective than TCM therapy in RA cold pattern ($p<0.05$).	The regulation of ubiquitin-protein ligase activity during mitotic cell cycle was the pathway affected by MTX + SSZ combination therapy, and no similar pathway can be affected with the TCM therapy.
Cheng et al.[30]	n=194 [RA patients: cold pattern n=35 Hot pattern n=7; Undefined pattern n=152]	Non-RCT Blood samples ACR20 response at week 12 and 24 Indexes: cytokines, clinical inflammatory, clinical immune			The effective rate of the biomedical combination therapy was higher in the patients with a cold pattern than in the patients with a hot pattern ($p<0.01$).	CRP has potential diagnostics value to hot and cold pattern in RA

ACR (American College of Rheumatology); ALB (albumin); BINGO (Biological NetworkGene Ontology); CAM (Cell adhesion molecules); CCP (Anti-citrullinated protein antibody); CH (Chinese Herbs); CRP (C-reactive protein); DAS28 (Disease Activity score 28); DAVID (Database for Annotation, Visualization and Integrated Discovery); DHEAS (Dehydroepiandrosterone sulfate); ESR (Erythrocyte sedimentation rate); FFA (Free fatty acid); GC-MS (Gas chromatography mass spectrometry); GLB (globulin); Hb (Hemoglobin); HPA (Hypothalamic Pituitary Adrenal); HCM (Hypertrophic Cardiomyopathy); IPA (Ingenuity Pathways Analysis); LC-MS (Liquid chromatography-mass spectrometry); MAPK (mitogen-activated protein kinase); MTX (Methotrexate); NF-κB (Nuclear factor-kappaB); PC (Phosphatidylcholine); PE (Phosphatidylethanolamine); PLT (platelet count); PPAR (proliferator-activated receptors); PPI (protein-protein interactions); RA (Rheumatoid Arthritis); RCT (Randomized Clinical Trial); RBC (red blood cell count); RF (Rheumatoid Factor); RNA (ribonucleic acid); SSZ (sulfasalazine); TCM (Traditional Chinese Medicine); TNF (tumor necrosis factor); TP (total protein); TLR (Toll-like receptor); WBC (white blood cell count).

Figure 2. TCM patterns in Rheumatoid Arthtitis patients. CCP (cyclic citrullinated peptide), DHEAS (dehydroepiandrosterone sulfate), FFA (free fatty acid); HPA (hypothalamic-pituitary-adrenal); MAPK (Mitogen-activated protein kinase); NF-κB (Nuclear factor-kappaB); PC (Phosphatidylcholine); PPAR (proliferator-activated receptors); TLR (Toll-like receptor); TNF (Tumor necrosis factor). ↓ (decrease), ↑ (increase), [] (concentration)

Regarding the common pathways, ubiquitination and apoptosis seem to be shared among cold, hot and deficiency CM patterns in clinical manifestations of RA.[17,29]

Cold and hot pattern patients shared six significantly expressed genes: MMGT1, TDRD7, GTF3C6, BCL2A1, CTLA4, PSMD8),[24] and were related to the following pathways: Cell adhesion molecules (CAMs), T cell receptor signaling, purine metabolism and the proteasome pathways.[24,25,26] Protein ubiquitination, RNA splicing, nuclear factor-kappaB (NF-κB) regulated gene transcription were common biological processes in those affected by cold or hot patterns; however, it seems that they have different signaling pathways.[17,22,24,29]

T cell proliferation, invasion and secretion of pro-inflammatory cytokines might be increased in hot pattern RA patients compared to cold pattern RA patients.[22,23,24] However, a study conducted by the same group research found networks related to immune regulation and cell proliferation in both datasets.[22]

The Jak-STAT cascade signaling pathway was only related to the CM cold pattern by Lu and colleagues[24] however, the same group conducted another study where the Jak-STAT signaling-related apoptosis was a common point between cold and hot pattern groups.[17] Another conflicting result may be reported by Gu and colleagues,[25] the only study that indicates free fatty acids (FFA) prominently up-regulated in those expressing cold patterns compared to RA patients with hot patterns.

The same five pathways (CAMs, T cell receptor signaling pathway, proteasome, CTLA4 and PSMD), were disordered in RA patients with either the cold or hot pattern, compared to healthy persons.[24]

Forty-five discriminating metabolites were identified between RA patients and healthy controls, by using Liquid chromatography-mass spectrometry and gas chromatography mass spectrometry platforms combined with multivariate and univariate statistical analysis, which revealed perturbations of various biological pathways in patients with RA.[25] RA patients presented diverse dysfunctions in inositol phosphate metabolism, lipid metabolism, glucose metabolism, ascorbate metabolism, glyoxylate and dicarboxylate metabolism.[25] Another significant perturbation in RA patients was amino acid metabolism. Alanine, serine, glycine leucine, isoleucine, tyrosine, proline and urea (the end product of amino acid catabolism) were found to be significantly higher in the plasma of RA patients.[25]

Two clinical trials, one randomized[29] and one non-randomized[30] compared the effects of biomedical combination therapy and CM in the context of biomarker discovery.

Jian and colleagues found that biomedical combination therapy targets parts of all four cold-pattern clusters: regulation of translation, protein ubiquitination pathway, Jak-STAT cascade, and RNA splicing.[29] However, CM therapy could target a smaller part of the four cold-pattern clusters: regulation of translation, protein ubiquitination pathway, Jak-STAT cascade, and RNA splicing.[29] It was found that the regulation of ubiquitin-protein ligase activity during the mitotic cell cycle was the pathway affected by Methotrexate (MTX) and sulfasalazine (SSZ) combination therapy, and no similar pathway could be affected with the CM therapy.[29]

CM therapy could target all three hot-pattern clusters: I-kappa B kinase/NF-κB, and mRNA splicing.[29] Biomedicine therapy targets only parts of two hot-pattern clusters: I-kappa B kinase/NF-κB and mRNA splicing were targeted by MTX and SSZ, and fatty acid metabolism involved in hot pattern RA could not be targeted by MTX and SSZ.[29]

Both experimental studies showed that the effective rate of the biomedical combination therapy was higher in the patients with a cold pattern than in the patients with a hot pattern ($p < 0.05$)[30] and, that CM therapy was better in treating the RA patients with a hot pattern.[29,30] However, in both studies it was unclear if patients treated with CM therapy where on any conventional care medication.

CM patterns in RA patients can change during the treatments as found by Jiang and colleagues.[29] Six months after the treatment, the pattern had changed in some patients. After 24 weeks of treatment, the effective rate of the CM therapy in those patients who showed changes from cold dominant pattern to non-cold dominant pattern was higher ($p < 0.05$), while the effective rate of the CM therapy in those patients who showed non-cold dominant pattern to cold dominant pattern was lower ($p < 0.05$). After treatment for 24 weeks, the effective rate of the biomedical combination therapy in those patients who showed CM pattern changes from non-cold dominant pattern to cold dominant pattern was lower ($p < 0.05$), and the effective rate of the biomedical combination therapy in those patients that changed from cold dominant pattern to non-cold dominant pattern was similar to those continuing with cold dominant pattern ($p > 0.05$).[29]

DISCUSSION

This systematic review suggests that stratification of RA patients according to CM functional diagnosis criteria, identifies different subtypes which respond differently to Western medications, and based on CM classification, pattern diagnosis can be determined and used to guide the therapy selection.[17]

The studies included in this review show that a highly diverse range of biomolecules, proteins and genes from RA patients correlated well with cold, hot or deficiency phenotype-based CM patterns, suggesting that they were distinct groupings and that pattern diagnosis in CM has solid foundations in genome and proteome profile. Using metabolomics, proteomics and genomics analytical techniques, better knowledge of the main biological processes involved at a given CM pattern in RA can be determined and might help to choose the most appropriate treatment.[3]

Despite frequently similar levels of rheumatoid factor and CRP between patients experiencing the hot and cold patterns,[26] the difference in the severity of inflammation and disease progression between the CM patterns of RA seems to indicate potential targets to be explored.

Patients with the hot pattern showed higher ACPA levels, many more joint problems (collagen destruction may be more severe), predominance of immune factors, increased expression of genes related to small G protein signaling pathways (TIAM1) and lipid metabolism (ALOX5), severe inflammatory responses and high RA inflammatory activity.[23,28]

The small G protein signaling pathways increase the T cell proliferation, invasion and secretion of pro-inflammatory cytokines and increase the release of lipid inflammatory mediators that lead to augmentation of FFA metabolism in RA patients with the hot pattern. Metabolite disorders, FFA metabolism pathways, presence of oxidative stress and the excess reactive oxygen species production may disturb the redox status, damage macromolecules and exacerbate inflammation in RA patients with CM hot pattern.[22,25]

The differentially overexpressed genes involved in small G protein signaling pathways and lipid metabolism found in RA patients with the hot pattern may provide clues to search for biomarkers and drug targets. For example, TNF-α plays an important role in RA by activating T cells through small G protein signaling pathways[23] and, peroxisome proliferator-activated receptors (PPARs) are activated by FFA and their derivates.[22] These cytokine and nuclear hormone receptors could be potential targets for RA therapy.[22,23,28,31] Regulation of signal transduction mediated by adhesion molecules on T lymphocyte interactions mediated by calcium signaling pathway and cell adhesion molecules, PPAR signaling pathway and FFA metabolism may be a possible effective way for controlling the pathological inflammatory process in RA patients with hot pattern.[22,23]

RA patients with cold pattern, when compared with RA patients with hot pattern, showed that hormones are predominant factors,[23] higher rates of fat and protein mobilization and lower levels of acylcarnitines suggesting less muscle mass and/ or a more pronounced muscle breakdown.[26] Decreased Hypothalamic-pituitary-adrenal-axis function in cold RA patients is associated with a decreased stress response which results in an inadequate response to stress factors that can lead to the persistence of autoimmune and pronouncer inflammatory process.[26] A decreased CTP I activity and a changed carnitine homeostasis in the cold RA group, might explain the higher fatigue levels.[26] Carnitine and acylcarnitine supplementation might be beneficial for cold RA patients and less for hot RA patients.[26]

PRKAA1, HSPA8 and LSM6, genes related to FFA metabolism and the I-kB kinase/ NF-κB cascade in hot RA patients, increase the knowledge of the biological processes involved, can be used as biomarkers for the CM pattern classification and might help to choose the most appropriate treatment.[24] The overexpression of TRPC3, CABLES1, VWOX and IFI27 in hot pattern, with a signature of induction of apoptosis, implied a more brightly prognosis than the cold pattern RA patients.[22]

Owing to the induction of apoptosis of macrophages, synovial fibroblasts or lymphocytes, either through suppression of signaling pathways or inhibition of the expression of anti-apoptotic molecule, could be therapeutically beneficial in RA patients.[22]

EIF4A2, CCNT1 and IL7R, significant gene biomarkers of the RA cold pattern, are related to the up-regulation of cell proliferation and the Jak-STAT cascade.[24] These genes can be candidate markers for a simple, minimally invasive pharmacodynamics assay for RA treatments directed at the NF-κB

pathway. For example, down-regulated IL7R can block apoptosis and promote the proliferation of CD4+ T cells in cold pattern RA patients.[24]

The results also suggested that some pathways were shared in different patterns, which might be the underlying mechanism of shared symptoms in different patterns or intermingled patterns, or an identification of the underlying mechanism of shared symptoms.[17]

TLRs signaling pathways are involved in both the cold and deficiency patterns. They may contribute to the persistent expression of pro-inflammatory cytokines by macrophages and to the joint damage to cartilage and bone.[17,22] TLRs lead to activation of transcription factors such as NF-κB. NF-κB controls a number of genes involved in immune-inflammatory responses, cell cycle progression, inhibition of apoptosis, and cell adhesion, thus promoting chronic inflammatory responses.[22] TLRs receptor activated NF-κB regulated gene transcription and apoptosis pathways are believed to be a potential therapeutic target in RA patients with the cold and deficiency patterns.[17,22]

CTLA4 (up-regulated) and PSMD8 (down-regulated) were found in both cold and hot patterns.[24] CTLA4, a negative regulator in auto-immune diseases, participates in the pathways of CAMs and T cell receptor signaling contributing to autoimmune tissue destruction, and it might exert a down-regulatory effect on TNF-α, TGF-β, IL1-β and IL16 production. On the other hand, PSMD8 proteasome down-regulated in RA patients is involved in the down-regulation of protein ubiquitination in the cell cycle and in the RNA splicing. CTLA4 and PSMD8 could be potential targets for RA patients, independently of the CM pattern.[24]

The clear separation between the patients with RA CM subtypes and healthy controls was achieved by Gu and colleuagues.[25] In particular, RA patients shown up-regulated inositol levels, suggesting that inositol might play a key role in the metabolic disorders and production of inflammatory mediators in RA. FFA were prominently up-regulated in the RA patient plasma and there was a concomitant increase in the pathway of fatty acid catabolism manifested as high levels of carnitine, palmitoylcarnitine and 3-hydroxybutyrate, which may reflect the activation of the immune system in RA patients.[25] Additionally, RA patients had significantly higher levels of saturated and monounsaturated PC, but lower levels of polyunsaturated PC and polyunsaturated PE. Thereby, the altered phospholipids profile reflected the abnormal oxidative status, and suggested that the excess reactive oxygen species production could disturb the redox status, damage macromolecules and exacerbate inflammation in RA patients.[25]

Another significant perturbation of the amino acid metabolism in RA patients suggested that the protein in RA patients may be largely mobilized. For example, levels of proline, an essential component of collagen, were found to be elevated in the plasma of RA patients compared with the healthy controls.[25] It has been demonstrated that inflammation and free radicals can induce collagen degradation and destroy the proper function of joints.[25]

Network analysis and topological comparison points out that hormones are predominant in the cold patterns network,[23] immune factors are predominant in the hot patterns network,[23,28] and these two

networks are connected by neuro-transmitters.[32] Thus, cold and hot patterns reflect two typical conditions of the internal imbalances of neuro-endocrine-immune, and both of which should be taken into consideration during disease diagnosis and treatment.[32]

The effects of biomedicine and CM therapies change according to the patterns of RA patients. However, CM patterns in RA patients might change over time, including during the treatments.[29,30] The results suggested that the efficacy of biomedical intervention was less likely to be influenced by CM pattern changes, while the efficacy of the CM therapy was more likely to be influenced by CM pattern change.[29]

Limitations of the review

Firstly, the stratification of RA patients into cold, hot and deficiency CM patterns is an oversimplification of a complex and sophisticated diagnostic system, where more diagnostic patterns are present and where many patterns are mixed. This may, on the one hand, lead to a potential impact on the conclusions, but on the other hand it simplifies a very complex diagnostic process which often shows poor inter-observer reliability and concordance.[33]

Secondly, some sample studies were relatively small, and might have caused this review to miss significant findings; despite the exploration of distinct pathways of each CM pattern and their correlations.

Thirdly, some of the types of techniques and computational tools, for example the protein-protein interaction network analysis, might miss significant findings regarding the most useful signatures for CM pattern classification.

Fourthly, trials written in Chinese could complement our review by comprising more approaches regarding CM pattern differentiation in patients with RA, and leading to new requirements in the field of traditional and complementary medicine therapies. However, lack of proficiency of Chinese language by the authors compromised the difficulty to access the Chinese literature or Chinese databases.

Implications for practice

Several suggestions for creating diagnostic tools using the presented systems diagnosis approach were discussed in these studies, which are relevant for sub-typing RA patients and can lead to new opportunities to advance personalized medicine for rheumatic diseases. For example, the current nuclear effectiveness of RA biomedical therapies might be improved by targeting it to the right CM RA patterns.

Owing to the induction of apoptosis of macrophages, synovial fibroblasts or lymphocytes, either through suppression of signaling pathways or inhibition of the expression of anti-apoptotic molecule, could be therapeutically beneficial in RA patients.[22]

Finally, the mechanism and effect of specific treatment options used in CM for the different patterns should be studied and might be integrated in standard disease management strategies by using the right CM pattern according to the RA diagnostic profile, so as to bridge the gap between traditional Chinese medicine and Western medicine.[26]

Implications for research

Microarray techniques of gene expression in CD4+T cells were widely used and can provide a better understanding of the underlying molecular mechanisms of phenotype-based CM pattern classifications and provide information on individual disease mediators unique to RA that can show evidence of multiple pathways of tissue destruction and repair.[17,22,23]

With the further development of metabolomics analytical techniques, especially multi-analyzed techniques, metabolomics appears to be a pillar of the bridge between Western and CM, as it promotes research, is beneficial to the modernization of CM and establishes international standards.

The notion of phenotype based CM pattern diagnosis obviously benefits from being macroscopic. The scope of CM symptoms commonly covers multiple organs, organization or functional systems throughout the body, whereas omics explores and recognizes the regularity of vital movement from the perspective of biomarkers. Omics provides integral, systemic, and dynamic technology platforms for the study of CM, the study of which has effectively revealed the essence and connotation of CM phenomena such as Zheng at the molecular level.[25,34]

Future perspectives

Apoptosis induction and T cell interaction, and FFA metabolism, might be directly or indirectly involved in CM pattern RA pathogenesis. Additional work is needed to investigate the mechanism. Literature indicates that sophisticated manipulation of essential fatty acid (EFA) metabolism may have a role in rheumatologic disorders. The exact effects need to be better understood.[22]

Future studies may consider further validation and evaluation of other CM patterns and may include a larger sample size. However, CM diagnostic tools, critical to pattern differentiation (for example, tongue and pulse), may have an objective material basis.

Prospective studies methodologies combining omics and Zheng classification can offer a great enhancement of disease knowledge, not only at the microscopic, but also at the macroscopic level. The omics can introduce new thoughts and give impetus to CM and, the unique theory and perspective of CM offer fresh consideration for the development of omics.[25,31,34]

Knowledge of the differentially over-expressed genes involved in the mechanisms of phenotype-based CM pattern classifications might have a good potential to design highly efficient gene therapy might methods,[35] inducing the overexpression or the suppression of therapeutic factors, involved in joint degeneration.

It was proven that beneficial regulation of genes was developed by different CM techniques.[31] The combination of future omics studies with the symptoms, to explore the synergistic effect of acupoints, Chinese herbs and biofeedback therapies can help allow proper clinical use of CM techniques such as acupuncture, pharmacotherapy, diet and qigong.

CONCLUSION

These findings confirm that CM pattern differentiation based on clinical signs and symptoms show that there are many different gene network-expression profiles in a single disease and these can be useful to stratify subsets of patients with distinct biological bases and might then help to choose the optimally biomedical therapy.

Network analysis can be used as a powerful tool for detecting the characteristic mechanism related to a specific CM pattern, through understanding molecular mechanisms and the correlations between different patterns. The identification of the underlying mechanisms among the CM patterns might contribute to better understanding of pathogenesis of RA and could be used as diagnostic biomarkers for early detection, disease monitoring and therapeutic targets.

Finally, the mechanism and effect of specific treatment options used in CM may have a molecular basis with neuro-endocrine-immune as background,[32] should be studied, and might be integrated in standard disease management strategies, by using a standardized cold RA, hot RA and deficiency RA diagnostic profile.

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Chapter 5

Evaluation of the effect of acupuncture on hand pain, functional deficits and health-related quality of life in patients with Rheumatoid Arthritis

- a study protocol for a multicenter, double-blind, randomized clinical trial

Evaluation of the effect of acupuncture on hand pain, functional deficits and health-related quality of life in patients with rheumatoid arthritis—A study protocol for a multicenter, double-blind, randomized clinical trial

ABSTRACT

Introduction

Rheumatoid Arthritis (RA) is a systemic inflammatory disease characterized by functional disability and pain. Although acupuncture is widely used, until now Western acupuncture studies on RA have not shown conclusive positive results. Acupuncture is regarded as a reflex therapy that has effects on the human autonomic nervous system. By establishing a traditional Chinese medicine (TCM) diagnosis first, the practitioner is able to choose acupoints according to the state of each individual patient.

Methods

We are interested if acupuncture, using a classical diagnostic procedure to allocate acupoints to the patient according to the Shang Han Lun theory, can be effective in relieving pain, improving hand function and increasing health-related quality of life (QoL) in RA.

The authors intend to harmonize TCM diagnosis according to clinical and genetic profiles. Patients with the TCM diagnosis of a so-called Turning Point syndrome will be followed up in a randomized, prospective, double-blind, placebo-controlled, multicenter and three-armed parallel-group study with a standardized treatment in order to optimize potential therapeutic effects of acupuncture on pain, strength and muscle function of patients with RA as also, the influence on inflammation and quality of life.

Discussion

The findings of this study will provide important clinical information about the feasibility and efficacy of acupuncture treatment for RA patients. In addition, it will explore the feasibility of further acupuncture research.

Keywords: acupuncture, rheumatoid arthritis, quality of life, pain, hand strength

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory and multisystemic autoimmune disease characterized by symmetrical, persistent inflammatory synovitis and destructive polyarthritis of the

synovium. According to World Health Organization data, approximately 1% to 2% of all people in the world suffer from RA and its prevalence is about 0.2% to 0.5% in the Portuguese population[1]. More than 90% of patients with RA have hands joints disorders. RA related symptoms lead to activity limitations in 30% of the patients.[2]

The social-economic impact is high on the individuals as well as on the health system.[3] Treatment of RA is dominated by the use of Non-steroidal Anti-inflammatory Drugs (NSAIDs), including second-generation cyclooxygenase-2 inhibitors, disease-modifying antirheumatic drugs and analgesics. Recently, the use of biological agents has began.[3] However, these medications are associated with many unwanted side effects, have limited efficacy and may lead to toxicity.[4,5] Meanwhile, the biological agents have higher costs and the side effects, such as life-threatening infections and increased risk of malignancies, limit their application.[3]

These and other limitations led between 60% and 90% of unsatisfied arthritis patients to use complementary alternative medicines, including acupuncture.[3,5,6] Acupuncture is one of the most popular and most widely used techniques in traditional Chinese medicine (TCM). It is known that acupuncture stimulates the autonomic nervous system, for example, by causing biochemical changes that influence the body's homeostatic mechanisms by releasing neurochemical messenger molecules. It might also positively affect areas of the brain that reduce sensitivity to pain, stress and inflammation by promoting the release of vascular and immunomodulatory factors and by improving biomechanical functions.[7]

Acupuncture in treatment of RA can decrease the levels of pro-inflammatory cytokines, including interleukin-1 (IL-1) and IL-6, increase the levels of inhibitory cytokines (IL-4 and IL-10),[8] induce vasoactive intestinal peptide expression (an anti-inflammatory neuropeptide),[9] inhibit the function of synovial mast cells (which are substantially involved in the initiation of inflammatory arthritis), up-regulate plasma adrenocorticotropic hormone, down-regulate serum cortisol levels and synovial nuclear factor-κB/p65 immune activity and restore the hypothalamus-pituitary-adrenal axis.[10]

It is also known that acupuncture stimulates the nervous system in a way that leads to the release of endorphins, as well as other neurohumoral factors, and thus to changes in the processing of pain in the brain and spinal cord and to an increase in local microcirculation.[11,12]

The choice of the acupuncture treatment, and consequently the efficacy of TCM therapy, depends on the differentiation of the diagnosis. This process is also called syndrome or pattern (Zheng) differentiation, because the pattern guides the choice of treatment. Pattern differentiation considers the physiological, and pathological changes as well as every aspect of a disease phenotype, including the tongue appearance, pulse sensations, body signs and symptoms.[13]

Although RA is classified as a single disease in Western medicine (WM), it can be the result of different patterns in TCM. In classical Chinese medicine, part of the disease is believed to be the result of an invasion of the external pathogens (wind, cold, heat and damp),[14] reactive heat with yin

affection, qi and xue deficiency with stasis and phlegm, as well as the deficiency pattern (liver and kidney yin and yang deficiency).[15–17]

In the general classification of painful obstructions in Chinese medicine, RA is classified as the "Bi" or occlusion syndrome.[18,19] The "Bi" syndrome is characterized by poor or deficient circulation of qi and xue (stasis) as the result of an invasion of muscles and bones by agents that block the energy flow in the conduits.[20]

The HM of CM explains basic body regulation using the regulation of temperature in a water bath as a model. In this regime, the regulation of a system is mathematically explained by a projection of regulatory states of the body or uprising and descending energies (up and down) circular processes with antagonistic parts of the movement (compass rose).[21,22] Therefore, body regions are predominantly stimulated in a certain internal movement and autonomic activation takes place first in the liver region, then in the center of the thorax and the heart and finally progresses via the hypochondria region and lungs to the lower abdomen and the kidney region (Figure 1).[21]
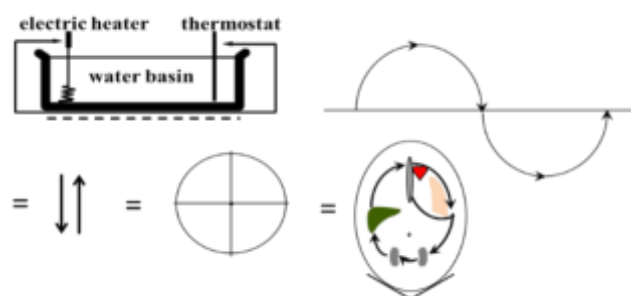
Figure 1. Heidelberg Model of CM concepts. Water basin; Sinus wave; up and downward movements; Compass-rose; projection of up- and downward movements in the body region[21]

The HM uses this mathematical representation to explain the model of the six levels of the Shang Han Lun[21] also known as Treatise on Febrile Disease or, to HM of TCM, as Algor Laedens Theory (ALT). The ALT is viewed as a technical regulative model including a cybernetic sine wave which explains that algor (cold) passes from the extima (outside of the body) to the intima (inside of the body), causing neurological and immunological phenomena on its way, while overcoming the six defense levels (Figure 2).[23]
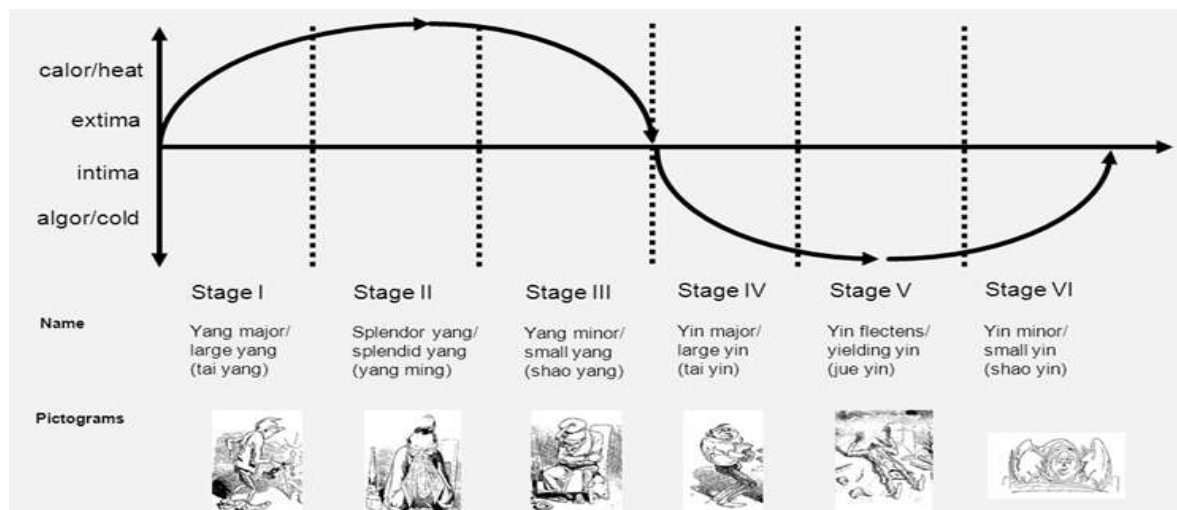
Figure 2. The AlgorLaedens Theory model[21]

ALT combines the language of the orbs, which are signs and clinical symptoms indicating the functional autonomic state of the different body regions, with the language of the system of calor (heat) and algor (cold) that may stand for unspecific defense mechanisms and, in a Western sense, for effects of microcirculation as a part of neuroimmunology. In the HM the six stages are seen as a model of neuro-immunomodulation or clinical neuro- or immunorheumatology.[21,22]

RA autoimmune disease shows an involvement of autonomic mechanisms as well as of the immune system, which can be very well explained by the ALT.

Mathematically it is possible to create a model for qi and xue with two curves, in which both curves create a ball, because both curves proceed vertically to each other. In this case, every human manifestation would be mathematically like a ball in an optimum state of regulation (orthopathic, lineal). In cases of deviations from this regulated state, the ball would look "like an egg" (heteropathic, sloping position). We can also put the ALT model into the classical "compass rose" form (Figure 3).[22]
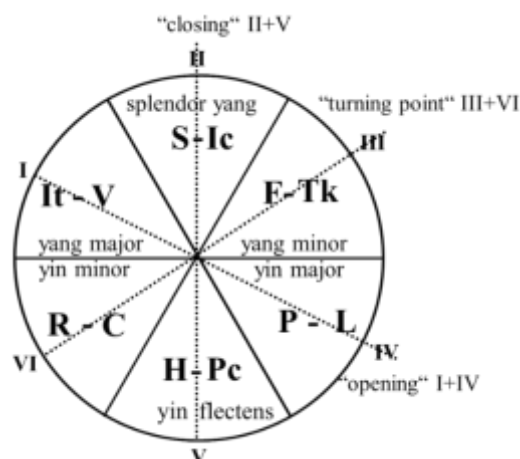
Figure 3. Algor Laedens Theory expressed as "compass rose".[22] It: Tenuintestinal orb; V: Vesical orb; S: Stomachal orb; Ic: Crassintestinal orb; F: Felleal orb; Tk: Tricaloric orb; P: Pulmonal orb; L: Lienal orb; H: Hepatic orb; Pc: Pericardiac orb; R: Renal orb; C: Cardial orb.

This presents a classic version of the ALT, in which we have a connection between the phases that are on opposite sides to each other. Therefore, we can divide the main 6 stages into 3×2 stages:[22]

(1) "Opening Principle" - (stage of the defense of attacks on the outside (Stage I) or defense originating from the inside (Stage IV): the curves mathematically open up to the top.

(2) "Closing Principle" - stage of the maximum of the symptoms (Stages II and V), which means that at the extreme points of the curves we already have included. At all extremes we already have the opposite pole included, the yin together with the yang. Therefore, the curve "closes" and proceeds into the direction of the target value.

(3) "Turning point" - stage of the decision, (Stages III and VI): the curve is on its turning point, the point between inside and outside. Here it will be decided whether the agent algor will proceed into the intima or not (Stage III) or whether recovery will take place or not (Stage VI).

TCM has had success in treating adult patients with RA. The treatment not only can improve the symptoms, but also can obtain the effect of treating both superficial symptoms and the original cause of disease by regulating the balance between yin and yang of the body.

An increasing number of medical researchers are recognizing that the combination of disease diagnosis by both biomedical parameters and the classification of TCM diagnosis is essential for clinical practice because it might target interventions more adequately to patient complaints.[23,24]

The correlations between TCM patterns and biomedical parameters are receiving an increasing amount of attention. If we extend our analysis beyond the physical parameters and characterize RA subtypes (according to TCM diagnosis) using symptom profiles, clinical chemistry, metabolomics measurements and genetic profiles, the differences may lead therapists to better treatment strategies.[14,16]

ALT postulates that the qi and xue are fighting from the inside against the external agent algor (cold). The mobilization of qi and xue leads to internal symptoms like a systemic increase in microcirculation. This "calorization" is at its maximum in Stage II. The agent can only progress further into the intima (Stage IV) after the mobilization of energy (qi and xue) in Stage II and III is exhausted and the intimal heat (increased microcirculation) has become weak (Figure 2).[22]

In our experimental phase, our main diagnostic interest is in the RA patients with a Turning Point affection.

The Turning Point syndrome shows external symptoms of the conduits, as a result of the agent algor remaining in certain extimal conduits (Stage III). The agent algor fights against the remaining levels of qi and xue, which prevent the algor from proceeding to the intima. Because the agent sometimes proceeds to the inside of the body (intima) (Stage VI) and sometimes is repelled again, the symptoms of cold and heat as well as the autonomic signs alternate continuously. The characteristic feature of this syndrome is therefore an inconsistency, or contrariness, of the symptoms: cold and heat sensations, extimal and intimal symptoms according to the affected conduits/ orbs in Stages III and VI.

For the treatment of this pathological picture, we choose points from conduits/orbs that are affected in the Turning Point syndrome: tricaloric conduit (Tk5/TB5, clusa externa/waiguan) and felleal conduit F39/GB39, campana suspensa/xuanzhong) (Stage III) as well as cardiac conduit (C3/HT3, mare minus/shaohai) and renal conduit (R7/KI7, amnis recurrens/fuliu) (Stage VI).

We decided to use the Leopard Spot technique, a bloodletting acupuncture therapy that uses sterile subcutaneous needles (0.30 mm×8 mm) (BD Micro-Fine®) and is clinically applied by pricking certain acupoints.[25]

STUDY DESIGN AND METHODS

Objective

In the current study, our main objective is to investigate the effects of an adjuvant acupuncture treatment on pain, functional deficits and the health-related quality of life of patients with RA.

Eligibility

      Inclusion criteria

Patients will be included who have signed an informed consent and present with active RA, fulfilling the ACR criteria of RA;[26] impairment of hand strength with or without pain in the hands during the grip procedure: chronic pain, either persistent or intermittent over a minimum period of three months prior to recruitment; current pain greater than 30/100 mm on a pain visual analogue scale (VAS) within the last 24 h, despite medication and stable dose treatment for at least 3 weeks.

      Exclusion criteria

Patients will be excluded from this study if they are under the age of 18 years, have previously had acupuncture, have localized skin infections, have severe chronic or uncontrolled co-morbid disease, or have the wish to get a pension.

Design

This pilot study is divided into two parts. In the first part the authors will describe the epidemiological and clinical profile of patients with RA, according to their TCM diagnosis.

The second part will be a randomized, prospective, experimental, three-armed parallel-group, double-blind, placebo-controlled multicenter study to evaluate the acute effects of acupuncture on pain, strength and muscle function of patients with RA and a Turning Point syndrome. The effects of treatment with acupuncture will also be assessed for inflammation and quality of life.

The study will be conducted at the Experimental Pathology and Acupuncture of Faculty of Medicine, University of Coimbra, Portugal. The patients will be recruited from the Hospital of the University of Coimbra, Portugal.

The authors will include patients with RA of the hands according to the inclusion criteria (Figure 4) from January through December 2016.

The protocol for this randomized pilot clinical trial has undergone ethics scrutiny and been approved by the Ethics Review Board of the Faculty of Medicine, University of Coimbra (ref. CE-048/2015). Trial registration number is NCT02553005.

All patients will sign an informed consent at the time of enrollment according to the rules of the Helsinki Declaration.
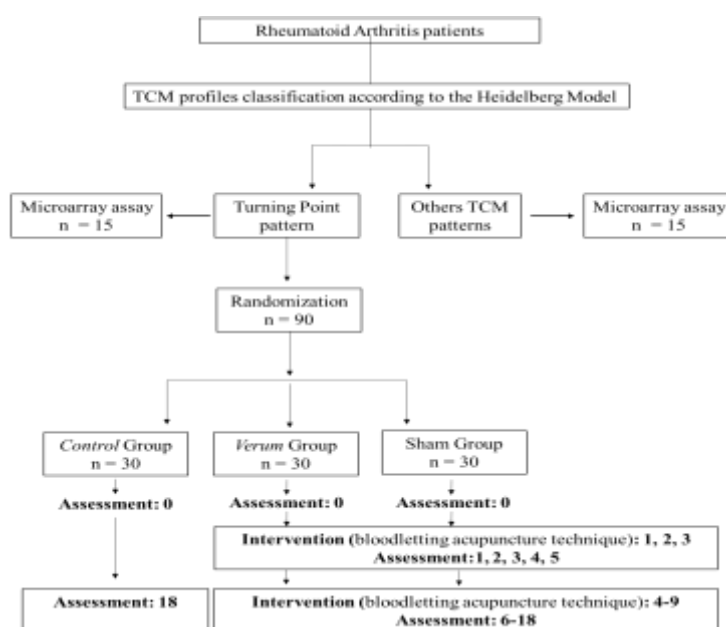
Figure 4. Recruitment flowchart

Task 1

In the first part of the study, the authors will use a non-experimental, exploratory and descriptive approach to describe the epidemiological, clinical and genetic profiles of patients with RA of the hands according to their TCM diagnosis.

We will use a survey specifically designed for the collection of data to characterize the patients socio-demographically and clinically.

The main characteristics, complaints and objective examinations of participants will be determined by a qualified and experienced acupuncturist (first physician), according to the Heidelberg Model of TCM.[21,22] This physician will assess the pain in the hand by using a pressure algometer technique at two different points (Figure 5).[27] The same researcher will also record clinical features based on data from tongue diagnosis that will have been conducted before by an Automatic Tongue Diagnosis System (ATDS) specially constructed for this purpose. The results from this instrument demonstrate that ATDS is very consistent, even in settings with different environmental lighting.[28]

The correlation between TCM pattern classification and genetic biomarkers in RA patients will be explored. Recent studies have indicated that TCM patterns could be regarded as a consequence of biological networks with deviant gene expressions in various affected tissues or cells.[15,16,17]

Due to the absence of previous studies in RA patients that used a treatment specific to the Turning Point, according the HM of TCM diagnosis, we decided to select 15 participants from each study group. Each group will be made of a different TCM pattern that is correlated to gene expression profiles by microarray technology (Figure 4); this number was intermediate relative to previous randomized clinical trials.[16] In this procedure, 8 milliliters of venous blood will be collected in anticoagulation tubes from each participant and then be tested in a microarray assay, using the TRIzol extraction method.[17] These data will be archived safely and anonymously and used exclusively for research, duly approved by the Ethics Committee of the University of Coimbra.

Using the microarray assay we expect to find common genes, biological processes, significantly different gene-based pathways and biological processes that serve as biomarkers of differences among the Turning Point and others TCM patterns of RA.
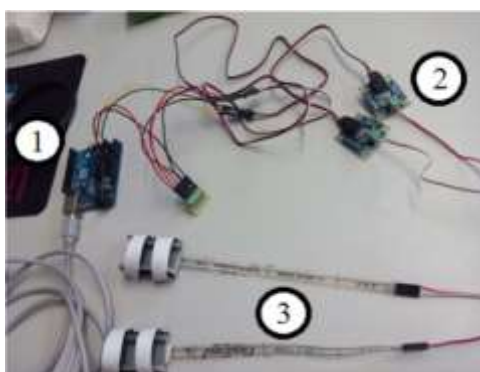
Figure 5. Algometer system

Task 2

We aim to evaluate the effect of acupuncture on pain and strength of the hand, according to the criteria of the Heidelberg Model of TCM for a specific, autonomic nervous system functional state called the Turning Point syndrome.

A sample of 90 patients with clinical features of a Turning Point syndrome, according the diagnostic process of the Heidelberg Model to TCM, will be assigned randomly, in a 1:1:1 ratio to either the control, verum or sham group with the help of a computer-generated randomization program (Figure 4). Due to the absence of previous studies in RA patients using a specific TCM syndrome designated as Turning Point, it was not possible to estimate the sample size and power of the study a priori.

The first physician will mark the points in red or blue color on the patients that had been randomized to the verum intervention group as well as on the patients that had been assigned to the sham intervention group.

Next, the first physician will present these data to a study-coordination program that will assign the color-codes to a sequence of possible treatment modalities by using a computer-generated randomization table. A second physician will be informed, by the program, which of the colored points to needle. The second physician will then perform the standardized bloodletting acupuncture technique on the selected points; this treatment will correspond to either a sham or a verum point. After each acupuncture session, the patients must dress with a light garment to cover any potential marks from needling.

Before and after every treatment, the patients will return to the first physician for an assessment of the outcome. The first physician will not know which acupuncture points have been used.

All patients will receive three sessions of treatment in the first week (first will be directly in the day of assessement 0, the second 24 hours after the first treatment and third treatment 72 hours after the first).

The participants will have six followed up assessments. Assessment 0 will take place after randomization; assessments 1, 3 and 5 will take place five minutes after the intervention; assessment 2 will be done 24 hours after the first intervention and assessment 4 three days after the assessment 1 (Figure 4).

The assessments include an evaluation of the patients' tolerance to pain in the hand by using a pressure algometer (Figure 5), measurement of their grip strength with the help of a dynamometer and an evaluation of the nerve conduction and muscle function in the hand using electromyography.

We also intend to do a longitudinal study to assess the effect of the acupuncture treatment on inflammation and on the quality of life.

After the first week the patients randomized to groups sham and verum will be treated two times per week, over a period of three weeks, with an interval of 72 hours in between treatments. Therefore these participants will be followed up in the assessments 6, 8, 10, 12, 14 and 16, before the

intervention, and assessments 7, 5, 9, 11, 13, 15 and 17, five minutes after intervention (Figure 4). The assessments 0, 5 and 18 will also include another parameter to measure the grade of inflammation: the cortisol and interleukin levels in the saliva.

All the patients randomized to groups sham, verum and control will also be followed up in the assessments 0 and 18–28 days after assessment 0, by measuring the pain with a Visual Analogue Scale and the quality of life with the Health Survey SF-36.

Statistical analysis

The results of the first task will be analyzed using descriptive statistics and parametric or non-parametric tests, as appropriate. The continuous parameters of efficacy will be analyzed by t test or Wilcoxon test. The baseline differences, central effects, or other prognostic or discrepant factors will be analyzed by Pearson Correlation Coefficients and a Multivariate Analysis of Variance. The 95% confidence intervals for the difference between treatments will be considered for each terminal point of the efficacy. Chi-square test will be used for the differences in improvement rates.

DISCUSSION

RA is a progressive disease associated with severe morbidity, permanent disability and increased mortality. In the last decades there has been significant progress in the treatment of RA. However, the medications are associated with multiple unwanted side effects, toxicity and limited efficacy[5,6]. The long-term effects of these therapies are not yet known[29] and the medications do not suppress the progression of clinical disability.[30]

Research has indicated that an estimated 60% to 90% of persons with arthritis, such as RA, are very likely to seek alternative treatments and use CAM, including acupuncture.[3–5] The efficacy of acupuncture treatments in RA has been studied in terms of chronic rheumatic pain, joint destruction, physical function limitation, disability and the impact on health-related quality of life.

Systematic review and analyses of recent studies that were not founded on a well-established TCM diagnosis, but used a form of scientific acupuncture with standardized points, showed contradictory results regarding the effects of acupuncture in the treatment of RA.[4,6]

Chinese clinical trials pointed out that acupuncture was effective in relieving symptoms of RA,[7–9] however the evidence was limited by methodological considerations, such as the type of acupuncture, the site of intervention, the sample size, the long-term benefits which remain unknown, inappropriate randomized control or blind interventions, and scarce use of validated outcome measures.

The acupuncture clinical trials that follow the TCM concept of an individual diagnosis and integrate it as an inclusion criterion are distinguishable by the homogenization of patient samples and give clear evidence about the importance of synergy that must exist between the diagnosis in TCM and the respective selection of acupoints.[15]

The Heidelberg Model of TCM integrates TCM concepts into the language of Western science. It is based on autonomic activity in order to systematize the diagnosis and treatment of TCM by creating a rational, standardized, mathematical and logical model, that can be applied to biological systems,[21,31] because there is a wide dependence on the direction of the following interventions.[21,31,32] It is a logical model of TCM that is not contradictory to the old TCM scripts and fully integrates TCM physiology concepts into the language of Western physiology. It does not challenge TCM but upgrades TCM quality relative to standard medical acupuncture.

In the present study, the acupuncture treatment at variable selected points is not standardized but is based on a specific group of signs and symptoms of RA patients that lead to one specific TCM diagnosis. In our first task the results of this pilot study will focus on the gene expression profile according to different TCM diagnoses of RA patients.

The development of studies describing the epidemiological and clinical profiles of patients with RA, according to their TCM diagnosis, using determinate gene expression profiling, can lead to identification of important genetic biomarkers. It also has the potential to provide opportunities for better treatment outcomes by targeting Western and TCM treatments to specific groups of patients.[16] The studies carried out so far revealed important interesting findings. Lu et al. showed that RA patients with TCM cold pattern and heat pattern have distinct molecular signatures with different biological processes participating.[16]

The biological processes corresponding to the heat pattern in patients with RA mainly include apoptosis induction, T-cell interaction, calcium signaling pathway, cell adhesion molecules, peroxisome proliferator-activated receptors (PPARs) signaling pathway and fatty acid metabolism. The induction of apoptosis of macrophages, synovial fibroblasts or lymphocytes, either through suppression of signaling pathways or inhibition of the expression of anti-apoptotic molecules, could be therapeutically beneficial in RA.[16]

These results suggest that the inflammatory response is stronger in patients with the diagnosis of a cold pattern than in the heat pattern group. This finding correlates well with the fact that the efficacy rate of anti-inflammatory drugs in RA patients with cold pattern is higher than in patients with a heat pattern. On the other side, the heat pattern with a sign of induction of apoptosis was correlated wit better outcomes than the apoptosis resistant cold pattern.[16]

Some practical use from these results was found between cold and heat RA patients. Lu et al.[16] showed that cold RA patients respond much better to a combination therapy with diclofenac, methotrexate and sulfasalazine than heat RA patients.

Multivariate analysis of the urinary metabolic data revealed that the levels of 11 acylcarnitines were lower in the cold RA than in the heat RA patients, suggesting differences in muscle breakdown. Additionally, higher dehydroepiandrosterone sulfate (DHEAS) levels were found in heat patients compared to cold patients suggesting that the cold RA group had a more suppressed hypothalamic-pituitary-adrenal (HPA) axis function. The study suggests differences in the effects of carnitine and

acylcarnitine supplementation in the two groups, as well as differences in the effects of hormone treatments such as with prednisone.[14]

TCM focuses on the role of all symptoms in the classification of diseases and also in the selection of therapy. Therefore, besides the joint pathology-related symptoms, acupoint combinations including the symptoms not related to the joints could be part of diagnostic parameters that improve therapies.

In our experimental task, we expect that acupuncture is a nontoxic, economical intervention with minimal adverse effects, and whose beneficial effects can be detected even for a few months after therapy. We expect to find positive effects on hand pain, hand strength and hand muscle function, in patients with RA and a Turning Point syndrome, using the Leopard spot technique.

In recent years, there has been extensive research on the mechanism of bloodletting therapy. It is known that this technique increases local microcirculation by inducing an autonomic response.[23] It has the ability of alleviating pain. During stimulation, allogenic substances such as prostaglandin E2 (PGE2) will be relieved and pain will be eased. Bloodletting therapy can also accelerate the metabolism and stimulate the medullary hematopoiesis via neurohumoral regulation. This, therefore, improves microcirculation and vascular functions, stimulates blood regeneration and helps to rebuild homeostasis and to recover normal physiological functions. By improving microcirculation, it can inhibit excessive inflammatory reactions and promote recovery. Another recognized bloodletting effect is the improvement of human immunity and activation of the immune defense functions in the body.[25]

We chose distal points for the treatment of the underlying systemic inflammatory disease as well as local points treating the arthritis of the nearby hand joints.

Literature suggested that a combination of at least four distal and local points are required for treating a systemic inflammatory disease, such as RA.[33]

The point TK5 (TB5) is a powerful point against the agent algor (cold). We selected point F39 (GB39) because it is an important yang point and is qualified as the conventus medullae (the spinal meeting). The point C3 (HT3) is characterized by the features of water phase or element in the language of Chinese Medicine It stabilizes the yin of the cardial orb. Stimulation of the point R7 (KI7) stabilizes the renal orb and regulates and harmonizes the metabolism of fluids, especially that of constructive energy and xue, and also regulates calor, especially in combination with dampness.

The outcomes of hand pain, hand strength and the hand muscle functions, evaluated by algometer, dynamometer and electromyography respectively are well suited for evaluating the acute effects of acupuncture treatment.

The longitudinal study will establish if acupuncture is a feasible and adjuvant effective therapy for inflammation, by measuring cortisol and interleukin levels, and the quality of life assessed by the SF-36 scale. It will also give us conclusions about the long-term effects of acupuncture.

Besides the appropriate outcome measures, the proper use of a control group is also a critical issue in designing a high-quality clinical trial. The main aim of this trial is to demonstrate whether

acupuncture is feasible and effective for improving health-related quality of life in patients with RA and a Turning Point syndrome as a clinical manifestation.

In addition, a pragmatic design using acupuncture, sham acupuncture and no treatment should provide evidence on the feasibility and efficacy of acupuncture.

CONCLUSION

In this pilot RCT study, we will evaluate the feasibility and effectiveness of acupuncture for RA patients with one specific TCM diagnosis, a Turning Point syndrome. As recommended, objective measurable parameters were chosen to quantify the effects of acupuncture.

The results of this study will demonstrate whether acupuncture therapy can improve they symptoms of patients suffering from RA and if this specific Chinese diagnosis will be able to enhance clinical therapeutic effectiveness.

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Chapter 6

New Pressure Algometry Device for the Quantification of Acupuncture Induced Pain Relief

New pressure algometry device for the quantification of acupuncture induced pain relief

ABSTRACT

Introduction

Acupuncture is still a controversial topic, as methodologic problems associated to its research impair scientific progress. Besides effective allocation of acupoints and double blinding, quantification of its effects is still a problem that has to be addressed. In particular, the effects of acupuncture need to be quantified more clearly for relieving pain and reducing inflammatory effects associated to Rheumatoid Arthritis (RA).

We aim to study the effects of acupuncture resorting to an algometry device specifically designed to assess the pressure tolerated by RA patients.

Methods/design

A quasi-experimental nature design was developed. Fourteen RA patients with a Traditional Chinese Medicine (TCM) (Heidelberg Model) diagnosis of a so-called pivotal or *Turning Point* syndrome and meeting the criteria of the American College of Rheumatology, received three acupuncture treatments in one week with a standardized treatment.

A newly developed pressure algometry device, designed to assess the tolerance in hand pain in RA, was tested. We compared the outcome of clinical acupuncture, as measured by Pressure Algometry (PA) and Visual Analogue Scale (VAS).

Results

The patients tolerated higher pressure on the hands (p=0.001) as well as improved VAS scores along with the treatment (p=0.005). All 14 patients displayed improvements in PA, while 11 improved their VAS scores. Out of the remaining, two patients had their VAS score unaltered and one (who also displayed the smallest improvement in PA) worsened slightly.

Discussion

The findings of this study suggest that acupuncture effects in hand pain relief can be measured by the PA device. This opens the door to quantify the differences between the tolerated hand pressure before and after the acupuncture treatment to one specific TCM syndrome designed as *Turning Point* in a future double-blinded acupuncture study on pain in RA patients.

Trial registration number: NCT02553005.

Keywords: Acupuncture, Rheumatoid Arthritis, Pressure Algometry, Pain, Turning Point Syndrome

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic inflammatory autoimmune disease. Over 90% of patients with RA have involvement of the wrist and small joints of the hand, including the knuckles and the middle joints of the fingers involving destructive polyarthritis of the synovium. Pain is one of the major symptoms impacting an RA patient's quality of life and leads in around 30% of the patients to limitations in daily life activities.[1,2,3]

About 60 to 90% of patients with RA dissatisfied with conventional treatments side effects, tend to use Complementary and Alternative Medicine, including acupuncture.[3,4,5,6]

Acupuncture in patients with RA can have the following effects: reduction of pro-inflammatory cytokines IL-1 and IL-6 and increase of cytokine inhibitors IL-4 and IL-10;[7] induction of the expression of vasoactive intestinal peptide, an anti-inflammatory neuropeptide;[8] inhibition of the function of synovial mast cells (which are substantially involved in the initiation of inflammatory arthritis) and restoration of the hypothalamic-pituitary-adrenal axis.[9]

Acupuncture generally stimulates the vegetative nervous system, which leads to the release of endorphins and other neuro-humoral factors as well as to changes in the treatment of pain in the brain and spinal cord and to an increase in local microcirculation that helps to reduce edema.[10,11]

Although RA is classified as a single disease in Western medicine, in classical Chinese medicine it is believed to be the result of an invasion of the external pathogens (wind, cold, heat and damp), reactive heat with yin affection, *qi* and *xue* deficiency with stasis and phlegm, as well as of the deficiency patterns (liver and kidney yin or yang deficiency).[12–16]

Neurological and immunological RA phenomena can be explained by the cold (designated algor on the Heidelberg Model of Chinese medicine) aggression passing the skin (biao) to reach the inner tissues of the body, while overcoming the six defense levels explained in detail by the *Shang Han Lun* theory called Algor Leadens Theory (ALT) by the Heidelberg Model (HM) of TCM in our previous paper.[16] RA manifestations can be characterized in different syndromes according to this mathematical regulative model as a deviation from the regulated state.[16]

Pain is inherently subjective, and pain measurement in patients with RA relies primarily on self-reports or by simple palpation of the joints.[2]

Although self-reported pain intensity is important, it is a composition of the physiological and psychological features of the patient and their health problem that is further mediated by social aspects, which can make it difficult to interpret the responses.[17]

Physicians often assume that inflammation is the main determinant factor of RA pain intensity. However more than one in ten RA patients that are shown to be in remission by the Disease Activity Score 28 (DAS28) still report clinically significant pain levels. The fact is that pain persists despite the absence of signs of inflammation.[2]

The magnitude of symptoms may not necessarily correlate with the severity of the underlying disease, and symptoms may persist even when disease exacerbations have apparently settled.

Pain and tenderness associated with the disease are not only present in directly affected joints but also in adjacent, apparently normal, tissues. These symptoms can occur spontaneously, can be evoked by gentle stimulation of the joint when it is moved within its normal working range or can be indicative of changes in their central pain modulation which then becomes a primary cause of pain, possibly outlasting the inflammatory activity.[2,18]

In the classical Chinese medicine language, the occurrence of chronic pain in RA patients is explained as a dysfunctional pattern/sign or symptom of the neurovegetative system and is frequently accompanied by signs of yin deficiency symptoms, reactive heat and emotional imbalances such as anger, sadness or exhaustion.[19]

Thus, objective pain measures are invaluable as they reflect different perspectives of the health condition. Therefore, measuring hand pain is an important component of clinical practice; its importance is evident in the frequency with which it drives healthcare utilization as well as its impact on quality of life.[17]

Pressure Algometry (PA) has been used for the investigation of pain syndromes involving tenderness to assess different aspects of pain and tissue sensitivity to pressure in various rheumatic conditions.[20] This instrument has demonstrated an outcome that physicians are able to use in both clinical as well as research settings to measure and quantify an individual's pain experience by determining the pressure-pain threshold of specific muscle and bone locations – the point at which a subject perceives pain upon the application of a pressure or force stimulus.[21]

The PAs that are currently available rely on either a calibrated spring or an electronic force transducer. They are sensitive and accurate but expensive and fragile.[20] In routine, clinical practice physicians need inexpensive, robust PA as a practical alternative for the assessment of tenderness in a wide range of patients.

To observe quantitatively the differences between the tolerated hand pressure before and after the acupuncture treatment, we need an inexpensive self-assembly device.

In that way, we developed a specific PA, adapted to a computerized system, with the aim to objectify the variability effects of a standardized acupuncture treatment, by a physically measurable parameter. Therefore, we compared the outcome of clinical acupuncture, as measured by VAS and PA, in a sample of 14 RA patients and a specific vegetative functional state called *Turning Point* syndrome, to see whether the methods lead to correlating results.

STUDY DESIGN, MATERIAL AND METHODS
Design
We developed a quasi-experimental nature design study to assess pain severity objectively in RA patients by a developed PA device. The patients were recruited by using media resources distributed

to RA national associations and locally. We have included patients with RA of the hands according to the inclusion criteria.

The protocol for this pilot clinical trial has undergone ethics scrutiny and has been approved by the ethics review boards of the Faculty of Medicine – University of Coimbra (ref. CE-048/ 2015).

The trial registration number is NCT02553005.

Eligibility

Inclusion criteria

The patients were included if they: had previously signed an informed consent; presented with active RA fulfilling the American College of Rheumatology criteria; had impairment of hand strength with or without pain in the hands during the grip test; had chronic pain, either persistent or intermittent over a minimum period of three months prior to recruitment; had current pain greater than 30/100 mm on a VAS within the last 24 hours despite medication and stable dose treatment for at least 3 weeks and the TCM diagnose of *Turning Point* syndrome, determined by a well-trained TCM doctor.

Exclusion criteria

Patients were excluded from this study if they; were under the age of 18 years; previously had acupuncture; had localized skin infections; had severe chronic or uncontrolled co-morbid disease; or had mainly the aim to get benefits.

Pressure algometer device

The PA has been widely used in a variety of studies to measure the pressure-pain stimulus–response, in various rheumatic conditions.[20] However, according to our previous research, it is not from our knowledge the existence of a validated PA device to RA patients, that would allow us to measure the force applied in two different situations: the force applied at two points, considering the hand grip and the thumb resistance force.

In strict cooperation with the Biomedical Engineer department of the Engineer Faculty of the University of Porto, we developed a novel pressure-sensitive sensor device which allows to assess and precisely determine the hand pressure tolerated (in Kgf) until the pain starts during the hand grip (Figure 1).
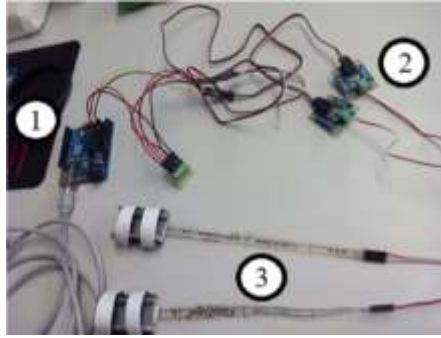
Figure 1. Pressure Algometer.

The PA developed comprise: Number 1 - An Arduino Uno R3 for acquisition and control; Number 2 - two adapters Flexiforce Adapter for signal conditioning from the sensors; Number 3 - two FlexiForce piezoresistive sensors 25 lb / SQI (weight pounds / square inch), or 1,757 kgf /cm2 Tekscan company.

All the software development was carried on LabVIEW 2013 SP1 environment (Figure 1), in order to obtain an application to communicate with the Arduino Uno R3 Board (Number 1) for control and acquire signals between the two adapters Flexiforce Adapter (Number 2) for signal conditioning from the sensors circuits (Number 3). The two FlexiForce piezoresistive sensors (Number 3) are adapted by the physician to the surfaces of the joint between carpal bones (hemato and trapezius) and respective metacarpal bones (fifth and second metacarpal bones). When the sensors are pushed, sensors and time values are paired and stores as a pain event. At the same time in the computer program a text file registers the sensor value and a graphic with force variation through measurement time is automatically create.

The sensors were tested in order to obtain the individual characteristics of each sensor (Figure 2) required to transform the voltage signal of the force applied. For the control interface an application was developed in LabVIEW 2013 to establish communication with the Arduino Uno R3. To this end LIFA library (LabVIEW Interface for Arduino) was implemented on Arduino using analog inputs A0 and A1 of the same. The Arduino and the laptop computer on which the application was installed were connected by USB cable.
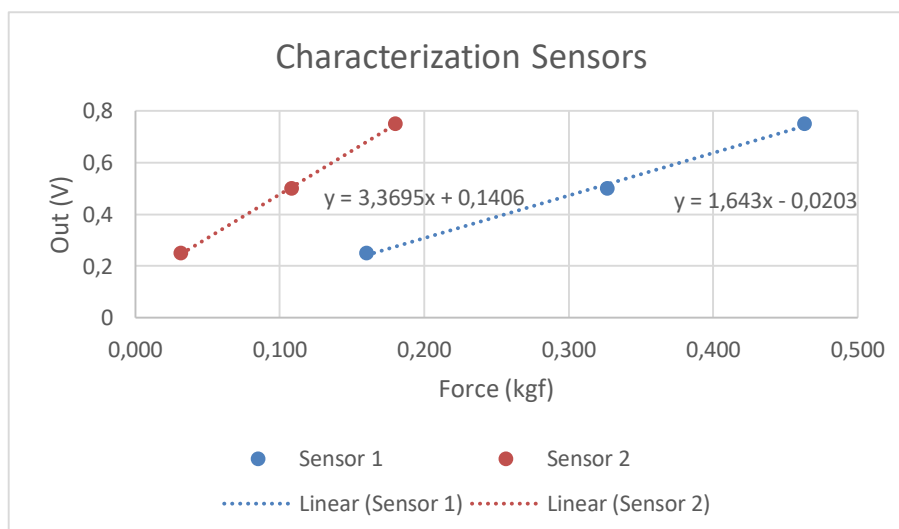
Figure 2. Force sensors characterization

With this equipment, the sensor system controlled and recorded the maximum pressure values by Kgf /cm2 that can be tolerated by each patient before the onset of pain in the hand.

In this work, measuring range was set to a maximum of 1,757kgf/cm2 applied in each sensor. All obtained values and graph plot are stored, respectively, on a .txt file and a .bmp file.

All participants were guided and informed clearly to identify the moment when the stimulus causes the painful sensation. At this time point, the pressure was stopped and maintained until the device recorded its value.

The same process was repeated three times for each patient, with one-minute break between the assessments. This measurement was carried out always before and after the treatment intervention.

The subjects were instructed to give the indication to stop precisely at the moment they felt the sensation was changing from strong pressure to pain. The maximum force pressure values of the sensors system were used for the data analysis. To improve reliability of PA it was recommended that one examiner should carry out all measurements.

Prior to the start of the trial, investigator 1 underwent training sessions in the use of the PA with a healthy volunteer. During these sessions, the investigator practiced keeping the sensors between the base of the second and fifth metacarpal bones. After he positioned the sensors he started the computer program that recorded the data obtained from the plate and applied force at a constant rate until the moment that the patient used a verbal command to stop the pressure.

Protocol

Investigator 1, a qualified and experienced TCM Master, assessed the RA features based on the Heidelberg Model of TCM and the pain in the hand by using the PA device and the VAS scale (T0). The same investigator performed all measurements with the PA.

A second investigator, a physician and experienced acupuncturist, performed the respective standardized bloodletting acupuncture technique to the selected acupoints.

Five minutes after each acupuncture intervention, the first investigator assessed the immediate effects repeating the tests VAS and PA (T1).

To evaluate the short-term effects, all patients were subjected to this process again 24 hours after the first intervention and measurements were taken again before acupuncture and five minutes after (T2 and T3, respectively). The third and final acupuncture intervention was done 72 hours after the first intervention and pain tests were performed and assessments made before and five minutes thereafter (T4 and T5, correspondingly).

For the treatment of this pathological picture we choose points of conduits/orbs that are affected in the *Turning Point* syndrome: Tk5 (TB5/SJ5, *clusa externa, waiguan*), C3 (HT3, *mare minus, shaohai*), R7 (Rn7/ KI7, *amnis recurrens, fuliu*) and F39 (VB39/GB39, *campana suspensa, xuanzhong*).[16]

We used the *Leopard Spot* technique (designation according to HM model of TCM), a bloodletting acupuncture technique that uses sterile subcutaneous needles (0,30mmx8mm) and that is clinically applied by pricking certain acupoints.

An external computer specialist extracted the data from the informatic software and the statistical analysis was performed by the Laboratory of Biostatistics and Medical Informatics.

Statistical analysis

A descriptive analysis of the data was done after checking for normality of the quantitative variables with Shapiro-Wilk tests and visual inspection. Normally distributed quantitative variables were described by their mean and standard deviation or by medians, first quartile and third quartile, ordinal or non-normally distributed variables by their medians, first quartile and third quartile and nominal variables by the number of elements of each category and corresponding percentage.

The associations between qualitative variables were assessed with exact Fisher tests, whereas paired-sample tests (t-Student and Wilcoxon, as appropriate) were used to compare how treatments affected the values of VAS and PA. Finally, the correlations between VAS and PA values were assessed by computing Spearman correlation coefficients. The statistical analysis was performed in IBM SPSS Statistics 21 and the level of significance was 0.05.

RESULTS

Recruitment rate and baseline characteristics

A convenient sample of 14 patients with features of the *Turning Point* syndrome and RA who fulfilled the inclusion and exclusion criteria were recruited between June and December of 2015. Data of the demographics and clinical characteristics of the participants are summarized in table 1.

Table 1: Demographics and clinical characteristics of the patients with RA (n=14)

Sex (Male:Female)			**2 (14.3%) : 12 (85.7%)**
Age, mean ± SD years			56.93 ± 3.23
Disease duration, mean ± SD years			14.36 ± 2.29
Body Mass Index			23.32 ± 0.67
Bone erosions (yes:no)			9 (64.3%) : 5 (35.7%)
Tender joints (0:2:6)			6 (42.9%) :6 (42.9%) :2 (14.3%)
Swollen Joints (0:2:4)			4 (28.6%) : 5 (35.7%) : 5 (35.7%)
Current medication	NSAIDs (yes:no)		6 (42.9%) : 8 (57.1%)
	Biological agents (yes:no)		8 (57.1%) : 6 (42.9%)
	DMARD's (yes:no)		10 (71.4%) : 4 (28.6%)
	Analgesics (yes:no)		10 (71.4%) : 4 (28.6%)
Pain (VAS, 0–10)			5.0 (5.0; 7.0)
Pain sensation	Cold exposure	Relieves	4 (28.6%)
		Worsens	10 (71.4%)
	Heat exposure	Worsens	6 (42.9%)
		Indifferent	2 (14.3%)
	Cold application	Relieves	7 (50.0%)
		Worsens	3 (21.4%)
	Heat application	Relieves	7 (50.0%)
		Worsens	4 (28.6%)

	Indifferent	3 (21.4%)
Hands temperature	Frozen	1 (7.1%)
	Cold	6 (42.9%)
	Heat	7 (50.0%)
Feet temperature	Frozen	1 (7.1%)
	Cold	8 (57.1%)
	Heat	5 (35.7%)

Data are presented as mean ± SD (standard deviation), median (1st quartile; 3rd quartile) or number (frequency). NSAIDs = Nonsteroidal Anti-Inflammatory Drugs; DMARDs = Disease Modifying Anti-Rheumatic Drugs; VAS = visual analog scale.

We compared the pain data assessed by subjective report of VAS and by a physically measurable parameter (using the Pressure Algometer) before and after all the treatments. The variability of the VAS score and PA outcome in patients at baseline as well as 24 hours (second treatment) and 72 hours (third treatment) are presented in Table 2. The improvements induced by the treatment, expressed by the difference between the values obtained after the third treatment and before the first treatment, are shown in the last row of the table.

Table 2: VAS and PA values, before and after treatments (n=14)

MOMENT	VAS	p-value	PA	p-value
T0 (before 1st treatment)	5.0 (5.0; 7.0)	0.011	0.36 (0.32; 0.41)	0.003
T1 (after 1st treatment)	4.5 (3.0; 5.0)		0.52 (0.39; 0.56)	
T2 (before 2nd treatment)	4.5 (3.0; 6.0)	0.015	0.45 (0.30; 0.56)	0.003
T3 (after 2nd treatment)	4.0 (3.0; 6.0)		0.59 (0.41; 0.64)	
T4 (before 3rd treatment)	4.5 (3.0; 6.0)	0.019	0.43 (0.33; 0.45)	0.001
T5 (after 3rd treatment)	3.0 (2.0; 4.0)		0.56 (0.44; 0.68)	
Change during treatment (T0-T5)	1.0 (1.0; 3.0)	0.005	0.17 (0.8; 0.36)	0.001

Data are presented as median (1st quartile; 3rd quartile). The p-values were computed with paired sample t-Student tests or Wilcoxon tests, as applicable.

Figures 3 and 4 summarize the patients' progress through the treatments. The PA values obtained before the first treatment (baseline), immediately after the first treatment and immediately after the third treatment are illustrated in Figure 3. For easier visualisation, the three corresponding PA values for each participant in the study were divided by the baseline values. Each value in the x-axis represents one of the 14 participants, which were placed in increasing order of improvement in PA values between the baseline and the moment after the third treatment. Likewise, the VAS values can be observed in Figure 4. Once again, they were normalised, but this time the y-axis represents the difference for each patient between the VAS value at baseline and each of the other VAS values: in other words, the symmetry of the decrease in VAS. In both plots, higher values can be interpreted as improvements. Note that the order of the patients in the plots do not coincide.
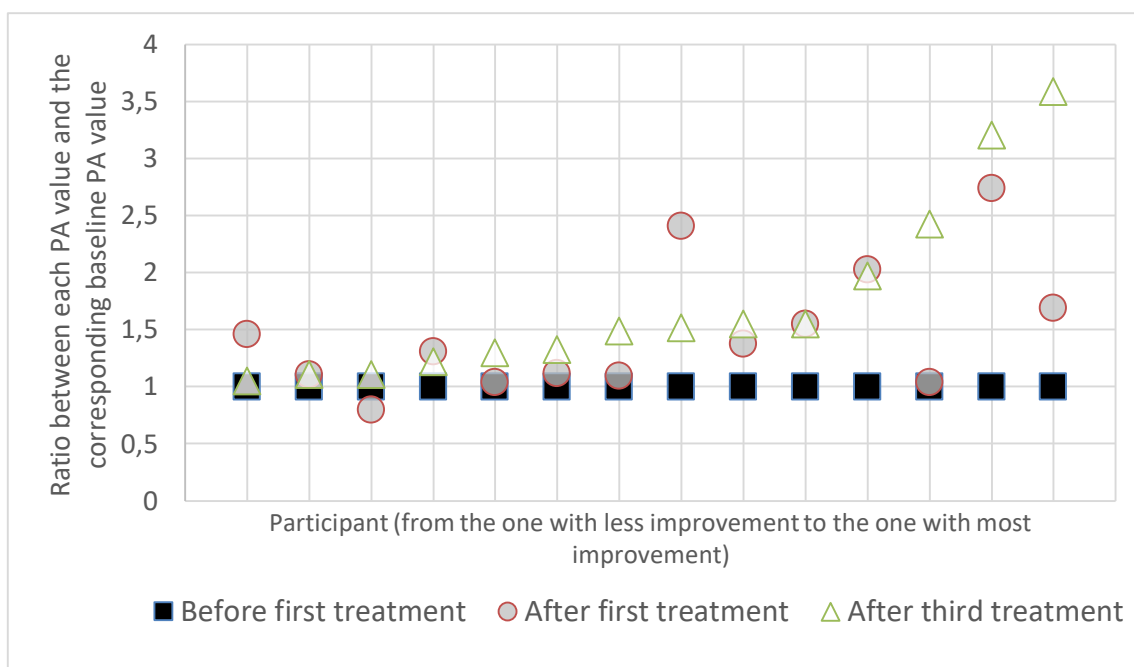
Figure 3. PA values
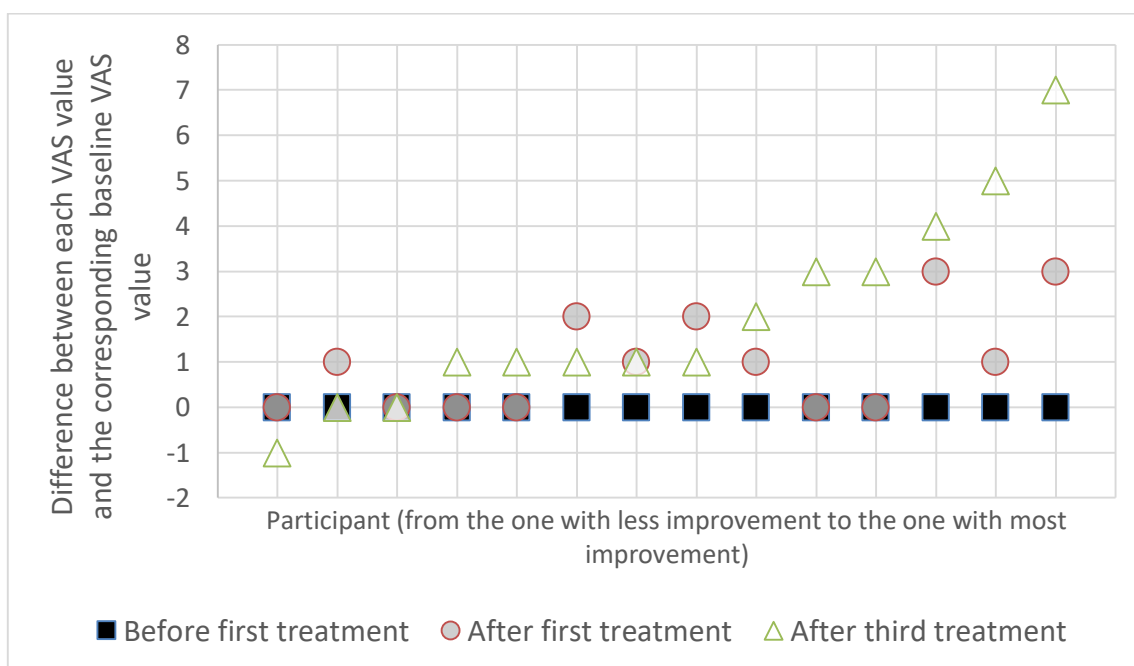
Figure 4. VAS values

As can be seen in the figures 3 and 4, all patients displayed an increase in PA values between the baseline and the end of the third treatment, while 11 improved their VAS scores - out of the remaining, two patients had their VAS score unaltered and one (who also displayed the smallest improvement in PA) worsened slightly.

Table 3: Pain values before and after acupuncture treatment

	VAS	PA

Improve with first treatment (yes:no)	8 (57.1%) : 6 (42.9%)	13 (92.9%) : 1 (7.1%)
Worsen between 1ˢᵗ and 2ⁿᵈ treatment (yes:no)	5 (35.7%) : 9 (64.3%)	8 (57.1%) : 6 (42.9%)
Improve with second treatment (yes:no)	7 (50%) : 7 (50%)	11 (78.6%) : 3 (21.4%)
Worsen between 2ⁿᵈ and 3ʳᵈ treatment (yes:no)	8 (57.1%) : 6 (42.9%)	9 (64.3%) : 5 (35.7%)
Improve with third treatment (yes:no)	10 (71.4%) : 4 (28.6%)	13 (92.9%) : 1 (7.1%)
Improve with treatments (yes:no)	11 (78.6%) : 3 (21.4%)	100 (100%) : 0 (0%)

Data are presented as number (frequency). Throughout the period of acupuncture treatments, no complications were found.

DISCUSSION

This study was performed to evaluate the feasibility of a PA device, which was specifically designed to quantify pressure pain thresholds and possible effects of acupuncture.[16]

PA has been widely used in a variety of studies to measure the pressure-pain stimulus–response of subcutaneous muscles, as an abdominal examination value;[22] for the assessment of muscle hyperalgesia and a few number of studies used pressure algometer to assess the pressure pain thresholds in the temporomandibular joint and masticatory muscles.[23,24,25]

In recent years, expensive and valid electronic pressure algometers have already been introduced on the market.[22,26,27] Additionally, several glove prototypes have been developed to assess the discomfort threshold level at 12 zones on the palmar surface of the hand.[28] These devices were not used to test the pressure pain threshold by the hand grip in RA patients. We have no knowledge of existing PA devices that have been tested and validated to assess and precisely determine the process of determining the hand pressure that can be tolerated, as well as identify when the pain starts, all while being gripped by the RA patients themselves. Creating such a device was one of the objectives of the future RCT that we intend to develop.[16]

The PA device that we developed was created specifically to assess the pain tolerance threshold of RA patients with hand pain whose features are related with a specific TCM diagnosis.

We tested the new PA device in a small group of 14 RA patients that fulfilled the research criteria's. To reduce possible risks of mistakes, the examiner had intensive training to use the device and the same examiner assessed all of the participants.

The patients showed an increase in PA values and a decrease in VAS values (Table 2) during the progression of the treatment. The VAS values decreased significantly in most patients by the end of the third treatment. The change post treatment, shown in the last row of the table 2, is promising and we can see that each treatment resulted in an improvement of the clinical parameters (Table 3). The only patient that presented an increase in the VAS value was an older patient and only two male patients remained with the same VAS scores.

The increase of PA toleration can be correlated with the effect of the *Leopard spot* technique at the chosen acupuncture points on the central vegetative nervous system and the induced mechanisms and is further supported by the decrease of the VAS-score. It is known that this technique increases local microcirculation by inducing a vegetative response[29] and that it has the ability of alleviating pain.

Acupuncture positively influences areas of the brain that reduce sensitivity to pain, stress and inflammation, by promoting the release of vascular and immunomodulatory factors and by improving biomechanical functions.[30]

Our results showed that exist a statistically significant association between the presence of nodules and an improvement in VAS, $p=0.003$ (Fisher). Notably, all patients with nodules (11) improved and those without nodules (3) did not report any improvement. Recovering anormal physiological functions induced by the nodules presence, bloodletting therapy can also accelerate the metabolism and stimulate the medullary hematopoiesis via neurohumoral regulation. This, therefore, improves microcirculation and vascular functions, stimulates blood regeneration and helps to rebuild homeostasis. By improving microcirculation, it can inhibit excessive inflammatory reactions and promote recovery.[31]

We observed an increase in the pressure tolerated by the hand (objectively measurement) and a decrease of the self-reported pain, assessed by VAS score (subjectively measurement). Our pilot study suggests that using the PA developed we can observe and measure objectively the individual hand pressure toleration variability of patients, before and after the acupuncture treatment.

The data obtained with PA can be often quite variable. We recognize that such an instrument will have certain limitations as the non-applicability to other syndromes, not comparability with devices already created, we have no data enough to validated the specific device and also, the fact that it doesn't have a patient controlled 'stop' button. Thus, we recognize that caution is required in the interpretation and reporting of clinical findings when using such device.

However, in the future, we intend to use the device to support and quantify the effects of the acupuncture in the treatment of RA patients with one specific TCM syndrome, and the use of subjective instruments can limit the interpretation of the results. Unfortunately, the devices existing in the market are not adjusted to assess the force tolerated by the hand grip of RA patients with a specific *Turning Point* syndrome.

On the basis of our methodology we keep the traditional Chinese acupuncture practice-characterized by a holistic approach to the management of the disease.[32,19] Based on the main characteristics, complaints and objective examinations of participants, a qualified and experienced TCM doctor established the functional diagnosis.[19] In the present study, the clinical results show that the principle of point selection based on a specific TCM diagnosis including specific groups of signs and symptoms increases the effects of pain reduction and the toleration of hand pressure in RA patients.

A main purpose of our PA is to develop basic evidence that this device can be used as step towards objective research on acupuncture and, by objectifying pressure tolerance, as a measure of pain reduction, thus validating the effects of acupuncture.

In terms of sensory assessment, the detection of pressure pain thresholds may allow the development of mechanism-based therapeutic interventions that would specifically target the underlying

pathophysiology.[33] By using one objective assessment we can help to clarify and direct appropriate interventions in the treatment of RA patients.

Translation of these and other sensory findings into clear clinical benefits and improved outcomes for injured people is an area for future research. Future studies using pressure algometry are required to determine whether the PA is reliable when used on RA patients and also whether the algometry displays adequate inter-investigator reliability.

CONCLUSION

The findings of this study suggest that acupuncture effects in pain relief can be objectively assessed by the PA device developed. This opens the door to quantitative measurement of the pain improvement in future double-blinded acupuncture studies on pain in RA patients.

Conventional pressure algometry is unsuitable for assessing the clinical therapeutic effectiveness on pain of RA patients with a *Turning Point* syndrome. We had need to create a new PA device that could meet our future goals. The PA device tested has proven to be correctly adjusted to quantify the pressure pain threshold by the hand grip.

Based on the present data we are looking forward to using this instrument to do further investigation on the role of acupuncture in managing the symptoms of RA patients who are not willing to accept or react adversely to conventional pharmacological treatment, or who are seeking additional benefits from unconventional therapeutic combinations.

Concomitantly this was a preliminary test study preceding a longitudinal pragmatic design using acupuncture, sham acupuncture and no acupuncture treatment to assess the long-term effects of acupuncture on hand pain, functional deficits and health related quality of life in patients with RA.

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Chinese Medicine functional diagnosis: an integrative insight to understand Rheumatoid Arthritis of the hand

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ABSTRACT

Introduction

Chinese medicine (CM), may provide insights into understanding the neuro-immunological mechanisms involved in Rheumatoid Arthritis (RA).

Objective

We were interested to ascertain if objective assessment strategies may help to determine the CM functional diagnosis and if the complicated issues surrounding the symptoms of RA of the hand can be easier understood by using the Shang Han Lun.

Methods

First, 190 RA patients were stratified into two groups: (1) "hand pain worsened by handgrip" or (2) "hand pain worsened by thumb resistance". Second, a CM diagnosis of patients with "hand pain worsened by handgrip" was performed, obtained through inspection, auscultation, interrogation and palpation. Third, clinical features based on data from tongue-diagnosis were assessed by two CM doctors.

Results

(1) 79.5% of the participants showed worsening hand pain by handgrip; (2) all these patients showed concomitant presence of imbalances and intermingled symptoms; (3) clinical findings of the invasion of the pathogen agent algor/"cold": cold hands (62.9%), tearing and localized pain with gradual onset (82.9%), worse pain upon cold exposure (82.9%), pain relief by applying warmth to the affected area (62.9%), tongue exhibiting a hyaline (85.7%) and white coating (52.4%).

Conclusions

This study provides new options for assessing the CM diagnosis, which may improve RA treatment strategies. Identification of joint non-related symptoms and pathogenic external factors such as algor/"cold" may help understanding activation of specific immunological mechanisms, changes of capillary endothelium and the microcirculation disturbances. Overactivation of the functional defence mechanisms by algor/"cold" seem to be of utmost importance for RA symptoms.

Key Words: Rheumatology, hand pain, Heidelberg model, functional diagnosis

INTRODUCTION

Rheumatoid Arthritis (RA) pathogenesis is a multistep process between the dysregulated neuro-immune system, abnormal neuro-endocrine-immune and individual genetic (HLA-DRB1 gene) that may predispose some individuals to excessive cytokine responses.[1,2,3,4]

An increase of anti-citrullinated protein antibodies (ACPAs) or rheumatoid factor (RF) levels and inflammatory markers may be detected in RA serum more than 10 years before the onset of the disease, suggesting that the autoimmune response begins outside the joint.[5,6] However, it is known that 20–30% of patients may be negative for these autoantibodies and be designated as 'seronegative' RA.[7]

While the joints are the predominant organs targeted by immune and inflammatory responses, other extra-articular tissues, including the lung, can be affected as well.[7]

Risk factors or pathogen agents (such as viruses, bacteria, smoking, toxic substances or vulnerable environments as cold, wind or humidity) may change the surface of the connective tissue resulting in immune-activation and microcirculation disturbance.[4]

Western biomedical advances offer a variety of biomarkers and have contributed to the progress of RA treatment in the last decades. However, patients usually require long-term therapy, mostly for pain and inflammation, using medications such as nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, or disease-modifying anti-rheumatic drugs (DMARD). [8,9,10] These are not free of adverse drug reactions (ADRs) and have high variability in treatment responses.[8,9,10,11,12]

Holistic approaches, such as Chinese medicine (CM), may help in understanding RA physiopathology, improve biomedical therapies and increase the quality of life.[13]

In the point of view of CM, RA is not just a rheumatologic disease with joint related symptoms. The joint non-related symptoms, the neurological vegetative defence mechanisms as well as emotional, psychosocial and external factors are also part of the CM diagnosis. These clinical parameters might help finding specific indications for therapies.[14]

CM has its own specific diagnostic methodology under which patients with the same Western diagnosis, but other subsets of symptoms, can be divided into different groups (also known as *zhèng*/"patterns" or syndromes). As a simple example, a patient with a runny nose may need different acupoints than a patient with a dry nose, although the Western diagnosis may be rhinitis in both cases. CM syndromes as *Bi-zhèng*, cold, hot, or deficiency have already been described in RA patients.[15,16,17,18,19]

The *Bi-zhèng* is characterized by obstruction of *qi* (vegetative functional capacity) and *xue* (microcirculation) in the conduits/"meridians" and collaterals.[15] The cold pattern is described as an attack from the external pathogen agent *algor*/"cold", showing symptoms such as cold feeling in the limbs and joints; joint or muscle stiffness relieved by applying warmth and increasing upon cold exposure; local signs of lack of microcirculation; thin and white tongue coating; wiry and tight pulse; facial pallor; loose stools; clear profuse urine and absence of thirst.[17,18] The heat pattern is correlated

with hot, red, swollen and inflamed joints; severe pain generally relieved by applying cold to the joints; red tongue with a yellow coating; the pulse may be rapid; flushed face; constipation and deep-coloured urine; thirst and irritability.[19] The deficiency pattern normally occurs in the later stages of the disease and is characterized by deformity and inhibited flexion and extension of the limbs.[16]

In our experience, classic CM syndromes as hot, cold or deficiency,[16,17,18,19] are rarely found as isolated patterns singularly attributed to RA patients, because RA patients often show mixed signs.

A more recent recompilation generated in cooperation with Chinese scientists is the so-called Heidelberg Model (HM), which combines the essential classical schools of CM and also includes ancient sources such as the *I Ging*.[20] This contemporary-understanding model offers rational access to CM by systematically grouping clinical findings and signs as four components of the diagnosis: (1) constitution (vegetative reaction type of the patient), (2) agent (pathological factor), (3) orb/functional cycle (current symptomatic orb or localization of the symptom) and (4) the eight guiding criteria (GC) (overall evaluation of the regulatory status).[4,20]

The HM of CM develops a sophisticated individualized approach to understanding immunological control involving neuronal mechanisms, which is of particular importance for RA, especially in inflammation and pain management.[4,20]

According to this teaching, six functional defence mechanisms are overcome by the invasion of the external agent *algor*/"cold" attack, from the outside (*extima*) (skin and conduits/"meridians") to the body islands (organs) of the inside (*intima*).[4] This six layers of defence concept, also known as the algor laedens theory (ALT) according to the teaching of the HM of CM, or Shang Han Lun (SHL) (theory on cold damage), seems to be of utmost importance for symptoms such as RA and can only briefly be mentioned here.

In Western terms, the invasion of the agent *algor*/"cold", evokes a generalized inflammation[4]. If the pathological factor *algor* invades further into the "interior"/*intima*, the GC *algor*/"cold" results in markedly diminished microcirculation and reduced vigilance and unspecific defence reactions.[20,21]

When the agent *algor*/"cold" persists and becomes chronic, it develops distinct constellations.[4,22] They are of particular importance for the treatment of infections and immunological residual states, for example, for the treatment of chronic inflammations and collagenoses. The conduits affected are the same as in acute infections so that the dysfunctional patterns seen correspond to the orbs ("organ patterns" or "functional circles" or "circles" for short) affected.[4,20]

For some years we have observed in our department that CM functional diagnosis of RA patients with invasion of the agent *algor*/"cold" and hand pain can be assessed by using a quick physical exam: the differences in the level of pain induced by either handgrip or by thumb resistance. Clinical experience has shown that when the hand pain becomes worsened by handgrip, the SHL *shaoyang* pattern seems to be the ALT stage present. Hand pain worsened by thumb resistance seems to be related with the Lung-channel pattern.

We were interested to ascertain if objective assessment strategies may help to determine the CM functional diagnosis and to understand if the complicated issues surrounding the symptoms of RA of the hand can be easier understood by using the ALT.

STUDY DESIGN AND METHODS

Patient selection

The study was conducted at the Experimental Pathology and Acupuncture department of the Faculty of Medicine, University of Coimbra, Portugal. Patients were enrolled from June 2015 to December 2017, by using media resources distributed to rheumatology departments in Coimbra and RA national associations.

We included patients with RA of the hands if they had (1) previously signed an informed consent, (2) active RA fulfilling the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) 2010 criteria[23] as assessed by an independent rheumatologist not involved in the study, (3) chronic pain over a minimum period of three months prior to recruitment, (4) had current pain greater than 30/100 mm on a VAS despite medication and stable dose treatment for at least 3 weeks, (5) impairment of hand strength, (6) pain worsened by grip in the fingers, (7) pain worsened by grip in the knuckles or in the thumb, (7) exhibited signs and symptoms of invasion of the agent algor/"cold".

Patients were excluded from this study if they (1) were under the age of 18 years, (2) previously had acupuncture (3) suffered from local skin infections, (4) had severe chronic or uncontrolled comorbidities, (5) or if they sought economic benefits i.e. by applying for a pension during the study.

Design, methods and outcomes

We developed a non-experimental, exploratory study considering both Western Medicine and CM principles.

First, a patient stratification took place using a quick physical exam (the differences in the level of pain induced by handgrip or by thumb resistance). The patients were distributed into two different groups: "hand pain worsened by handgrip" or "hand pain worsened by thumb resistance".

Second, a CM functional diagnosis of the largest group of RA patients was performed by a "diagnosing acupuncturist" (referred to in this paper as SS). A full case history was taken by the "diagnosing acupuncturist", obtained through auscultation, interrogation, palpation and inspection, including the tongue movement and appearance, pulse, body signs and symptoms, in accordance to the principles of the HM. SS is a qualified acupuncturist with over 9 years of CM experience and high intensive training of CM diagnostic techniques according to the HM.

Images of tongue and sublingual vessels were taken in a standardized environment by using a digital camera (Canon EOS400D) with an auxiliary light source (Brite Vision® LED ring light) under a uniform temperature (25℃) and humidity (60%). The images were simultaneously assessed by two

experienced CM doctors with five years or more of clinical experience and well trained in CM on the basis of the HM. CM doctors inspected every image of the tongue and sublingual vessels, and tongue features were recorded, namely: colour, size and form, motion, substance, coating, geometric shape, changes in the tongue body, such as thickness, cracks, and teeth marks. Any disagreements between the CM doctors were resolved through discussion, or by a third doctor.

Statistical analysis

Each categorical variable was described by its absolute and relative frequencies while each quantitative variable was described by its median, 25th percentile and 75th percentile. Chi-square and Fisher tests were used to assess the association between categorical variables. Shapiro-Wilk tests were performed to assess the normality of quantitative variables. The analyses were performed on IBM SPSS Statistics 24 and on R 3.3.2. The significance level adopted was $p<0.05$.

RESULTS

Of the 284 RA patients enrolled, 94 were excluded because they did not meet the inclusion criteria. 151 (79.5%) RA patients showed worsening hand pain induced by handgrip and 39 showed worsening hand pain induced by thumb resistance (figure 1). All patients were under stable doses of biomedical combination therapy including use of NSAID, DMARD, biologics and analgesic drugs.
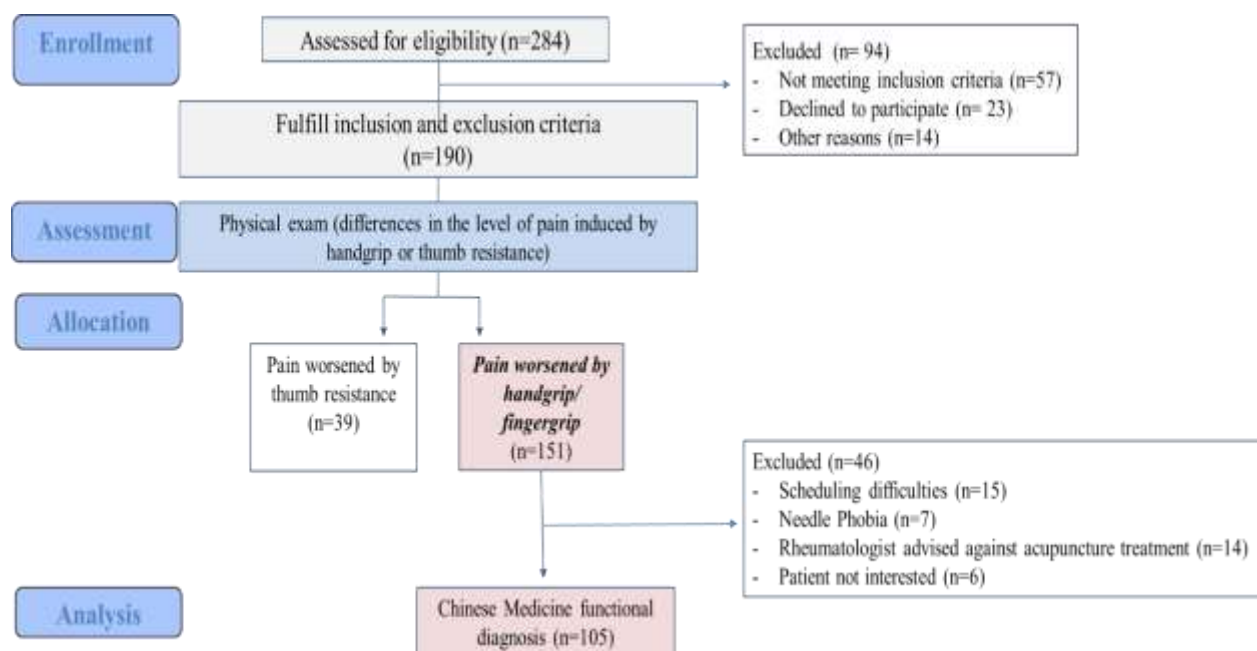
Figure 1. Flow chart

Of the eligible patients, we further assessed 105 patients with "hand pain worsened by handgrip", according to the principles of the HM (figure 1).[4]

Demographic, clinical features and CM functional vegetative state assessment, according to the

symptoms and signs manifested by RA patients with "hand pain worsened by handgrip", are described in Table 1 and 2.

Table 1. Demographic and clinical features of the RA patients assessed (n=105)

Demographic and clinical characteristics	Total sample (n=105)
Gender (F: M)	94 (89.5%): 11 (10.5%)
Age (years)	57.14±13.05
Duration of disease (years)	12 (6, 19.25)
Physical exercise practice (yes: no)	40 (38.1%): 65 (61.9%)
Positive serum test for rheumatoid factor, n (%)	67 (68.4%)
High blood cholesterol (yes: no)	49 (46.7%): 56 (53.3%)
BMI score	25.61 (24.045, 28)
History of joint surgeries (yes: no)	48 (45.7%): 57 (54.3%)
Erosive Disease (yes: no)	64 (64%): 36 (36%)
Early morning stiffness (minutes)	15 (5, 25)
Swollen Joints	1 (0, 2)
Tender Joints	2 (0, 4)
Deformity or inhibited bending and stretching in limbs (yes: no)	67 (63.8%): 38 (36.2%)
ESR (mm/hr)	7.50 (2.50; 15.00)
CRP (mg/dl)	0.21 (0.07; 0.38)
VAS (score 0–10)	5 (4, 6)
Pharm. Treat. — NSAID (yes: no)	91 (86.7%): 14 (13.3%)
Pharm. Treat. — BIOLOGICAL (yes: no)	54 (51.4%): 51 (48.6%)
Pharm. Treat. — DMARD (yes: no)	93 (88.6%): 12 (11.4%)
Pharm. Treat. — ANALGESICS (yes: no)	66 (62.9%): 39 (37.1%)
Use of non-pharmacological treatments (yes: no)	72 (68,6%): 33 (31.4%)

BMI (Body Mass Index); ESR (erythrocyte sedimentation rate); CRP (c-reactive protein); VAS (Visual Analogue Scale); NSAID (nonsteroidal anti-inflammatory drug); DMARD (disease-modifying antirheumatic drug). Data are presented as mean ± SD (standard deviation), median (1st quartile; 3rd quartile)

Table 2. TCM clinical signs and symptoms of the RA patients assessed (n=105)

		TCM clinical signs and symptoms	Total sample (n=105)
Temp.		Body feeling (cold: hot: facial flushing: cold/hot alternation)	38 (36.2%): 41 (39%): 2 (1.9%): 24 (22.9%)
		Hands (cold: hot and red)	67 (63.8%): 38 (36.2%)
Pain	General	Tearing and localised pain with gradual onset (yes: no)	87 (82.9): 18 (17.2)
		By cold exposure (better: worse: indifferent)	9 (8.6%): 87 (82.9%): 9 (8.6%)
		By warm exposure (better: worse: indifferent)	63 (60%): 30 (28.6%): 12 (11.4%)
	Hand	Stiffness (yes: no)	66 (62.9%): 39 (37.1%)
		By applying cold (better: worse: indifferent)	27 (25.7%): 66 (62.9%): 12 (11.4%)
		By applying warm (better: worse: indifferent)	66 (62.9%): 15 (14.3%): 24 (22.9%)
Tongue features		Size (small: normal: large)	83 (79%): 20 (19%): 2 (1.9%)
		Colour (pale: normal: excessively red: livid)	25 (23.8%): 6 (5.7%): 36 (34.3%): 38 (36.2%)
		Structural signs (cracks: fissures: wadi: vileda: Tigger ducks)	23 (22.1%): 25 (24%): 9 (8.7%) 2 (1.9%): 45 (43.3%)
		Coating color (normal: white: yellow)	43 (41%): 55 (52.4%): 7 (6.7%)
		Coating (dry: normal: sticky: hyaline)	7 (6.7%): 1 (1%): 7 (6.7%): 90 (85.7%)
		Movement (normal: shooting out: cannot be held: trembling)	8 (7.6%): 51 (48.6%): 40 (38.1%) : 6 (5.7%)
		Body tongue (Cardio-Renal line: dysbalance between the sides: Spoon form: asymmetry of the sides)	35 (33.3%): 43 (41%): 6 (5.7%): 21 (20%)
		White gums (yes: no)	70 (66.7%): 35 (33.3%)

Other signs	**Sweat (fetid: abundant: sticky: frequent at night: hot: cold)**	2 (2.5%): 24 (29.6%): 15 (18.5%): 23 (28.4%): 10 (12.3%): 7 (8.6%)
	Urine amount (clear and abundant: dark and reduced: frequent at night)	34 (41%): 16 (19.3%): 33 (39.8%)
	Thirst (absence: intense: dry throat)	46 (45.5%): 15 (14.9%): 40 (39.6%)
	Emotions (irritability: agitation: depression: dizziness: bitter taste in the mouth)	29 (29.9%): 18 (18.6%): 7 (7.2%): 19 (19.6%): 24 (24.7%)

Data are presented as mean ± SD (standard deviation), median (1st quartile; 3rd quartile)

Algor/"cold" was shown mainly in the coating of the tongue (hyaline and white), manifested by tearing and localized pain with gradual onset (82.9% of the patients), pain relieved by applying warmth to the affected area and worsening by cold application (see table 2). For 87 patients with "hand pain worsened by handgrip" (82.9%) the pain was worsened by cold exposure and 63 patients (60%) felt better in a warm environment. Self-description of the body temperature sensation may be too subjective but examination of the temperature by the "diagnosing acupuncturist" showed that 62.9% of the patients had cold hands with a feeling of stiffness (see table 2).

Detailed analysis shows that clinical features of all patients with "hand pain worsened by handgrip" concomitantly and constantly alternated. For example, deficiency and calor/"hot" signs and symptoms. A small tongue, cracks, fissures and "tiger duck" signs (transverse cracks on the sides of the tongue) or even dry throat (a symptom for lack of fluids), were yin deficiency signs. Redness of the tongue, shooting the tongue out quickly, hot and red hands or intensive sweating during the night, and red spots on the surface of the tongue, were calor/"hot" manifestations (as listed in Table 2).

Emotional trauma and psychosomatic symptoms such as irritability, dizziness and agitation of patients with "hand pain worsened by handgrip", can have an additional importance in the increase of the immune-neuro-vegetative signs.

DISCUSSION

As we have observed in our department, the differences in the level of pain induced by thumb resistance or by handgrip express different CM diagnoses.

RA patients with hand pain worsened by thumb resistance may have structural dysbalances related with the respective channel that crosses the thumb muscle i.e., the Lung-channel. RA patients with hand pain worsened by handgrip seem to express a set of signs and symptoms of the SHL *shaoyang* pattern.

A group of symptomatic distinctions or a certain pattern of symptoms define the individual vegetative functional state of the patient and suggest that the correlations between CM syndromes and biomedical diseases are not necessarily "one to one". [4,24,25] In clinical practice, this means that a set of acupoints may be effective in one individual with a certain pattern of symptoms, whereas others with the same Western diagnosis but other subsets of symptoms may not benefit.

CM functional diagnosis based on signs and symptoms, especially using objective strategies, may give researchers the chance to establish various predictors of response to therapy in RA, which will in turn improve patients' therapeutic selection and outcomes.[17,19]

Western medications are used worldwide by RA patients and for the purposes of this study, we determined the CM functional diagnosis of patients whose setting is closest to the typical RA patient. This was not considered in further studies.[16,17,18,19] Throughout the period in which the study took place, the participants remained on stable doses of conventional Western medicine treatments such as NSAIDs, glucocorticoids, or DMARD. These medications can show a high variability in treatment responses, induce immune-neurovegetative changes and have side effects described by the HM as pathogenic agents (such as toxic *algor*/"cold", toxic *calor*/"heat" or *humor*/"phlegm").

Signs of the invasion of the pathogen agent *algor*/"cold" were identified in all the patients. By using the ALT, the complicated issues surrounding RA can be more easily understood. As this technical regulative model explains, invasion of muscles and bones by *algor*/"cold" blocks the energy flow in the conduits, causing neurological and immunological phenomena, lack of microcirculation and affecting metabolic pathways on its way.[4,26]

The invasion of the pathogenic agent *algor*/"cold" results in areas of low blood flow on the tongue surface shown by paleness and tendency to damp lining. Hyaline pads are formed, the tongue surface looks less reddened and milky-glass-like, "as if egg whites had been dripped onto the tongue".[27]

Identification of joint non-related symptoms and pathogenic external factors as *algor*/"cold" may help to understand the RA patients with hand pain worsened by handgrip. Our data has shown that tearing and localized pain with gradual onset that is worsened by cold exposure is extremely frequent (82.9%) and analysis of the CM diagnosis of these RA patients showed, that also other signs and symptoms of the GC algor such as cold susceptibility, cold body temperature, pain alleviated by warmth and increased by applying cold to the joints were present with a higher frequency. However, all the patients also expressed in some way signs of central nervous system excitation, GC *calor*/"heat" (increase of microcirculation), *xue* stasis or deficiency, as expected in an inflammatory disease such as RA.

Agent *algor*/"cold" aggression evokes a generalized activation of specific immunological mechanisms such as formation of antibodies, adhesion molecules and the coupling of complement and coagulation system, referred to as the GC *calor*/"heat", with increased microcirculation and increased central nervous excitation in order to eliminate the agent *algor*/"cold"[4]. The organism tends to react with irritability, agitation, and inner unrest through *calor*/"heat" development, as a reaction to psychosomatic excitation/stress and to external agents.

The defence mechanisms against the invasion of the agent *algor*/"cold" evoke a generalized increase of the microcirculation in the peripheral vessels assessed by signs including reddish tongue and/or shooting out of the tongue, intensive sweats, night sweats, and a relative deficient volume of the

central blood vessels with water retention mechanisms, which appears as concentrated urine, dry stool or dry mucous membranes.

A majority of the patients showed a small tongue body which corresponds to an innate yin deficiency. However, persistent aggression of the agent *algor*/"cold", in the course of life and in such inflammatory chronic disease, damage the *yin* (structure)[23]. This is revealed by signs such as transverse cracks on the sides of the tongue ("tiger duck"), deep cracks in the body of the tongue, white gums (*xue* deficiency), difficulty to hold the tongue outside of the mouth, deformity and inhibited flexion, thin bone structure or tiredness.

These signs express the exhaustion of the body mechanisms and/or loss of physical functions, classified in the language of CM by poor or deficient *xue*, *qi* and *yin*/"structure".

Our sample of RA patients with hand pain increased by handgrip showed not only a *shaoyang* dysfunction but also a mixture of contrary/inconsistent autonomic signs and apparently opposite clinical manifestations resulting from the interaction between the body's defence levels and the pathogenic agents (for example, environmental cold, or toxic substances) under certain conditions, for example, structural deficits.

The Pivot syndrome (*shaoyang* pivot and *shaoyin* pivot, firstly described by Huang Di Nei Jing, the earliest extant canon of CM), also called Turning Point Syndrome (TPS) in the HM, seems to be the ALT stage that best characterizes our patients with hand pain worsened by handgrip and their RA symptoms, including the *Zang-Fu* dysfunctions and the complications between cold and heat, and deficiency and excess.[4,21]

Based on the ALT, the TPS summarizes a set of physiological imbalances and/or disordered metabolic processes that alternate continuously and are an underlying mechanism of shared symptoms or intermingled patterns. Basically, the signs and symptoms of the agent *algor*/"cold" fighting against the remaining levels of *qi* and *xue* in the *extima*/"exterior" alternated with exhaustion of the body mechanisms and consequently *algor*/"cold" proceeds to the *intima*/"interior". However, sometimes it is repelled again. Concomitantly, an increase of microcirculation (*calor*/"heat" GC) related with the *shaoyang* (Felleal/"Gallbladder" and Tricaloric/"Sanjiao" conduits and respective body islands), and lack of microcirculation (*algor*/"cold" GC) related with the *shaoyin* (Cardial/"Heart" and Renal/"Kidney" conduits and respective body islands) are present.[4,21]

The TPS helps to understand the signs and symptoms surrounding RA patients with hand pain worsened by handgrip: pathologically the Kidney naturally becomes deficient and results in a Kidney deficiency body constitution, the *Zang-Fu* functions become weaker leading to a deficiency of *qi* in the Ren meridian and a deficiency of *xue* in the Chong meridian resulting in an imbalance. This imbalance leads to an exhaustion of Tian Gui resulting in a sudden change in *qi* movement and *yin-yang* balance, making it difficult for the body to adjust. When Tian Gui is exhausted, *algor*/"cold" can easily invade the bones leading to a Pivot dysfunction and the irregular movement of *qi*. The Heart and Kidney cannot communicate and Yin-Wei cannot consolidate. This causes the *Zang-Fu*,

qi-xue and Yin-Wei to become imbalanced, the declining Kidney *qi* leads to stagnation resulting in Pivot dysfunction or increasing TPS symptoms.

The main strategies in the treatment of RA patients with hand pain worsened by handgrip should be to first regulate and harmonize the Pivot to expel the cold, remove the blood stasis and dampness and promote the blood circulation, and secondly to treat deficiency signs and tonify the Kidneys. This can be achieved by supplementation of *qi* and tonification of the *yin* and *yang*, for instance, by the use of acupuncture, anti-rheumatism herbs, diet and biofeedback exercises like qigong.

Several potential limitations in our study should not be neglected. Firstly, we stratified the sample using a basic physical exam that seems to be effective in differentiating RA hand pain patients. Nevertheless, clinical evidence of this exam must to be better explored. Secondly, the reliability and credibility of the Tongue diagnosis could be increased if the assessment had been repeated a second time, some days after the first assessment was carried out, involving the same clinicians and the images presented in a changed order. The comparison of the 2 assessments would have allowed us to analyze the intra- and interrater reliability and credibility of tongue diagnosis. Thirdly, only the patients with hand pain worsened by handgrip were discussed, due to its highly representative features of a CM pattern in RA. However, although the RA patients with hand pain worsened by thumb resistance were a small group, further research analysing the CM syndromes of these kind of patients could improve the understanding of risk factors for RA- interstitial lung disease (ILD) and its most appropriate therapies, by optimizing the cohort selection in clinical trials with the combined use of CM.

The hand pain worsened by thumb resistance may be a sign of a disorders of the Lung meridian related to CM lung dysfunction. CM considers that an orb/"organ" disharmony which can lead to pain along the conduit/meridian position . According to CM, the lung are the first to be attacked by the external agents, as for example the agent algor/"cold". Data suggested that the lung may play a role in the initiation of RA, perhaps due to gene and environmental interactions at the mucosal surface of the lung[7]. This theory is supported by a subgroup of patients who are ACCP positive with lung disease but have no articular manifestations. Smoking may also play a specific role in RA-ILD by promoting citrullination of lung proteins, thus leading to the development of ACPAs. This especially seems to be the case for individuals who have the shared epitope human leukocyte antigen HLA-DRB1.[5,6]

In a future study, we intend to explore if the CM pattern influences the clinical effectiveness of interventions in RA patients in a controlled biomedicine program. The TPS pharmacological molecular networks analysis and system biology of RA patients may represent characteristics and subtypes of the disease, and it is our goal to explore them. Further studies about diet, environment and epigenetic factors may be necessary to understand how these aspects can interfere with RA, so that possible necessary recommendations can be made.

CONCLUSION

Data collection by the evaluation of RA patients with invasion of the agent *algor*/"cold" and hand pain increased by handgrip, based on objective strategies used for many years in our department, supports our theory about how the invasion of the pathogen *algor*/"cold" of the conduits might cause physiological imbalances and/or disordered metabolic processes that alternate continuously and show an underlying mechanism of shared symptoms, so well understood by the pivot theory or TPS, interpreted by the ALT as the stage in which the agent *algor*/"cold" can proceed into the *intima*/"interior" or not (*shaoyang*) and whether recovery will take place or not (*shaoyin*).

More research in this area is necessary. However, these findings provide new options for objectively and specifically assessing the CM diagnosis, which may improve RA treatment strategies.

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Chapter 8

Effectiveness of acupuncture on pain, functional disability and quality of life on rheumatoid arthritis of the hand
- Results of a double-blind randomized clinical trial

Effectiveness of acupuncture on pain, functional disability and quality of life on rheumatoid arthritis of the hand - Results of a double-blind randomized clinical trial

ABSTRACT

Background

Rheumatoid Arthritis (RA) is characterized by pain, functional disability, poor quality of life (QoL), high socio-economic impact and annual costs of over $56 billion in the United States. Acupuncture (AC) is widely in use, however, studies show severe methodological shortcomings, did not consider the functional diagnosis for the allocation of acupoints and their results shown no differences between verum and control groups.

Objective

We aimed to objectively assess the safety and efficacy of AC treatments for RA.

Methods

105 RA patients with a functional diagnosis of a "Pivot syndrome" or "Turning Point syndrome" were randomly assigned to (1) verum-AC (verum acupoints), (2) control-AC (sham acupoints - points outside of the conduits/ meridians and of the extra-conduits), or (3) waiting list (each group n = 35). AC groups experienced the exact same number, depth and stimulation of needles. Assessments took place before and 5 min after AC with follow-ups over 4 weeks.

Results

(1) Verum-AC significantly improved self-reported pain (Z=-5.099, p<0.001) and pressure algometry (Z=-5.086, p < 0.001); hand grip strength (Z=-5.086, p<0.001), and arm strength (Z=-5.086, p<0.001); health status improved significantly (p<0.001, Z=-4.895); Quality of Life improved significantly in 7/8 survey domains; number of swollen joints (Z=-2.862, p=0.004) and tender joints (Z=-3.986, p<0.001) significantly decreased. **(2) control-AC** showed no significant changes, except in self-reported pain improvement. **(3) Waiting list group** showed an overall worsening.

Conclusion

This is the first double-blind controlled study on AC in RA of the hand that objectively and specifically assesses positive effects supporting its integration in rheumatology. Acupoint allocation according to Chinese Medicine functional diagnoses is extremely relevant to assess acupuncture effectiveness in a patient group primarily defined by a "western" medicine diagnosis. Based on clear allocation criteria for acupoints, we minimized the possible bias of unspecific and suggestive effects on the control group, showed the specific effects of the points chosen, improved efficacy and identified an evidence base for AC.

Key Words: Rheumatoid Arthritis, Acupuncture, Hand pain, Chinese Medicine diagnosis, Double-blind, Quality of Life

Trial registration: clinicaltrials.gov **Identifier:** NCT02553005

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease, characterized by pain, loss of physical function and a reduced health-related quality of life (HRQoL).[1,2] The worldwide prevalence is estimated at 1% with at least twice as many women affected as men.[2,3] Over 90% of patients with RA have involvement of the wrist and small joints of the hand, including the knuckles and the middle joints of the fingers involving destructive polyarthritis of the synovium.[2,4] RA annual costs have been estimated at over $56 billion in the United States in 2016.[5] Thus, the social-economic impact is high on the individuals, on work-related problems like absenteeism or on inability to work as well as additional impacts on the health care system.[1,5]

In recent decades, the treatment of RA has largely improved. However, patients frequently require therapy with analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), or glucocorticoids over a long time. These are not free of adverse drug reactions (ADRs), and show a high variability in treatment responses.[6] ADRs include NSAID-induced enteropathy with gastrointestinal ulcers, renal failure and cardiovascular events.[7,8] Glucocorticoid use is limited for the development of serious ADRs such as loss of bone mass, infections, diabetes, hypertension, and others.[9] So-called disease-modifying anti-rheumatic drugs (DMARD) like methotrexate (MTX) may even limit family planning,[10] as women with RA are often of childbearing age.

Recently, efforts have been focused on using the class of drugs called biologics.[11,12] Although these agents reduce inflammation and joint destruction, their use is limited by their higher costs and severe side effects such as life-threatening infections and increased risk of malignancies.[11,12,13]

It seems understandable, that an estimated 30 to 60% of RA patients use some form of complementary medicine, like Chinese medicine (CM), and its most widespread methodology acupuncture (AC).[14]

AC-effects on RA are contradictory, the studies show methodological shortcomings, or are inconclusive. For example, standardized AC protocol results have not shown any differences between verum and control groups.[15,16] The type of intervention and stimulation, the number of sessions, unsuitability of the protocol for treating RA and the small sample sizes might have influenced the lack of efficacy of AC. Individualized AC protocols showed better results but, have methodological limitations due to inappropriate controls, inadequate quantification of AC-effects or lack of double blinding.[17,18,19,20]

A contemporary understanding of CM explains AC as a reflex therapy with both peripheral and central nervous system effects, thereby causing the release of neurochemical messenger molecules and biochemical, affective and cognitive changes that influence the body's homeostatic mechanisms.[21,22,23] It may promote the release of vascular and immunomodulatory factors, improve

biomechanical functions, and can positively affect areas of the brain that reduce sensitivity to pain, stress and inflammation.[24,25] These complex patterns of effects must match with the patient and his/her complaints.

One of the central problems of AC studies is how to systematically and effectively allocate acupoints to an individual. A set of acupoints may be effective in one individual with a certain pattern of symptoms, whereas others with the same Western diagnosis but other subsets of symptoms may not profit. These symptomatic distinctions are part of the CM diagnosis and may be due to the individual vegetative functional state of the patient that this functional diagnosis of CM may define, as described in detail previously.[23] In order to overcome this allocation problem, we decided to functionally homogenize the groups of our study by adding the underlying functional diagnosis of CM to the inclusion criteria. By this we tried to avoid mixing potential responders and non-responders by not considering the functional basis for the allocation of acupoints, which may have resulted in showing no differences between verum and control groups and potentially impaired outcomes of previous AC studies.[15,16,26] By setting this inclusion criterion, we avoided individualizing to AC protocols which had shown better results but may have intensified patients relation to the therapist, thereby possibly inducing more suggestive effects, and have limited proper blinding and double blinding.[17,18,19,20] The diagnostic process was described in detail previously,[23,26,27] as well as the principle of targeting subgroups of patients most likely to respond.[26]

We have observed in our department that RA patients with affection of the hand and pain worsened by grip in the fingers worse than in the knuckles or in the thumb, changeable temperature sensations and wandering complaints, present a clinical picture defined as Pivot syndrome (shaoyang pivot and shaoyin pivot, firstly described by Huang Di Nei Jing, the earliest existant canon of CM), also called Turning Point Syndrome (TPS) in the Heidelberg Model to CM.[23,26,27]

Basically, the pathogen agent algor/"cold" is fighting against the remaining levels of qi and xue in the extima/"exterior" alternated with exhaustion of the body mechanisms and consequently algor/"cold" proceeds to the intima/"interior". However, sometimes it is repelled again. This imbalance elicits a set of autonomic signs that alternate continuously and are an underlying mechanism of shared symptoms or intermingled patterns, resulting in Pivot dysfunction or TPS symptoms to arise. Concomitantly, an increase of microcirculation signs related to the shaoyang (Felleal/"Gallbladder" and Tricaloric/"Sanjiao" conduits and respective body islands), and lack of microcirculation signs related to the shaoyin (Cardial/"Heart" and Renal/"Kidney" conduits and respective body islands) are present.[23,26,27]

The neuro-immunological pathways involved in RA, especially inflammation and pain, may be understood by the Shang Han Lun (SHL) (theory on cold damage) or algor leadens theory (ALT) and it can only briefly be mentioned here.[23,27,28]

In order to truly objectify the outcome of the treatment, we assessed both patient reported outcomes (PRO) and objectively measurable physical parameters in a double-blind, prospective randomized

clinical trial. We were aiming to objectify specific AC-effects based on clear allocation criteria for acupoints by objectively assessing outcomes utilizing valid scientifically recognized benchmarks for assessing the safety and efficacy of RA treatments, which by nature cannot fully be captured by clinical laboratory markers.

METHODS

Patient's selection

The study was conducted at the Experimental Pathology and Acupuncture Department of the Faculty of Medicine, University of Coimbra, Portugal. Patients were enrolled from September 2015 to December 2017, after approval of the respective committee according to the Helsinki declaration, by using media resources distributed to rheumatology departments in Coimbra and RA national associations.

We included patients with RA of the hands if they had (1) previously signed an informed consent, (2) active RA fulfilling the American College of Rheumatology (ACR) criteria as assessed by an independent rheumatologist not involved in the study, (3) chronic pain over a minimum period of three months prior to recruitment, (4) had current pain greater than 30/100 mm on a VAS despite medication and stable dose treatment for at least 3 weeks, (5) impairment of hand strength, (6) pain worsened by grip in the fingers worse than in the knuckles or in the thumb, (7) showed the clinical picture of a pivotal or TPS according to the criteria defined previously[23,26,27,29] and diagnosed by a CM practitioner with a master degree in CM.

Patients were excluded from this study if they (1) were under the age of 18 years, (2) were pregnant, (3) previously had acupuncture (4) suffered from local skin infections, (5) had severe chronic or uncontrolled comorbidities, (6) hand pain worsened by grip in the knuckles or in the thumb, (7) or seemed to be seeking for economic benefits i.e. by applying for a pension during the study.

All patients were under stable doses of biomedical combination therapies including NSAIDs, DMARDs, biologics and analgesic drugs, and were instructed not to change their usual therapies during the study.

Design of the study and double blinding

After checking the inclusion and exclusion criteria during a first visit by the "diagnosing acupuncturist" (referred to in this paper as SS), patients were randomly assigned in a 1:1:1 ratio by a computer-generated randomization program to either verum, control or waiting list group during a second visit. Outcome measures were assessed for the first time (baseline) after randomization. Patients randomized to the verum and control AC groups received three treatment sessions in the first week. After the first week, they were treated twice per week over a period of three weeks, with a minimum interval of 72 hours in between treatments and continued conventional treatment as before. Waiting list patients did not receive AC treatments but continued their usual treatments.

Double blinding was achieved as described previously by our group.[30,31] In brief, this four-step procedure included**:**

(1) Assessment of baseline values and acupoint allocation by a physician unaware of the allocation of the groups.

(2) All the patients received the same approach: measurement and marking the verum acupoints and sham acupoints by dots in different colors by a physician unaware of the allocation of groups or acupoints and their colors, leaving the patients unaware of the meaning of the colors (blinding of the patient). The allocation of colors and patients was randomly changed by a randomization computer program.

(3) The "therapists" were western medical doctors and at the same time novices to AC, unaware of the meaning of the points or the symptoms of the patients. These "therapists" were informed by the randomization computer program about the color of the points that were supposed to be needled, and instructed to maintain a standardized method as to needle insertion or needle stimulation throughout all the sessions (blinding of the "therapist").

(4) After each acupuncture session, the patients were dressed with a light garment to cover any potential marks from needling, to hide the treatment received, and post-treatment assessments were performed by a person unaware of the allocation of groups or acupoints and their colors (blinding of the observer).

Weeks after the final assessment, the participants treated with acupuncture were contacted and specifically asked to state their group by selecting one option: "real acupuncture" or "false acupuncture".

Outcome Measures

Primary clinical outcomes

Pain in general was measured with a Visual Analogue Scale (VAS) ranging from 0 (no pain) to 10 (maximum pain). Pain pressure threshold in the hand of RA patients was measured with a Pressure Algometer (PA) device, specifically designed by us to objectively assess the hand pressure tolerated by RA patients.[32] Measures of Arm Strength (AS) and Hand Grip Strength (HGS) were assessed with a Jamar® Hydraulic Hand Dynamometer (Patterson Medical®).

All the primary outcomes were assessed before the AC treatments at specific times (T): T0, T2, T4, T6, T8, T10, T12, T14, and T16, and 5 minutes after the AC treatments at: T1, T3, T5, T7, T9, T11, T13, T15, and T17. Primary clinical outcomes were assessed at baseline (T0) and four weeks after the first visit (T17) in the waiting list group.

Secondary clinical outcomes

Functional ability and health status were assessed with the Disability Index of the Health Assessment Questionnaire (HAQ), a PRO that assesses eight subscales: arising, common daily activities, dressing

and grooming, eating, grip, hygiene, reach and walking. The HAQ subscales ranged from 0 (no difficulty) to 3 (unable to do).

HRQoL was assessed using the Medical Outcome Short Form-36 health survey (SF-36). SF-36 consists of a self-assessment tool that measures personal and individual functional health and wellbeing parameters. The scores ranged from 0 (worst) to 100 (best) for each of the eight domains (bodily pain, general health, physical functioning, role-physical, mental health, role-emotional, social functioning and vitality). We established the minimum clinically important difference for assessing improvement or deterioration as a 2.5 to 5 points difference from baseline.

Other secondary outcomes included disease activity score-28 for RA, which includes the number of tender and swollen joints, and the grade of inflammation by the ESR and CRP blood levels.

Secondary clinical outcomes assessments were assessed at baseline (T0) and four weeks after the first visit (T17).

Intervention

The patients allocated to the verum AC (VAC) group were treated with a specific choice of points of the affected conduits/"meridians": San Jiao 5 (Tricaloric 5, TC5 /triple burner, TB5), (*clusa externa/ Waiguan*); Felleal 39 (F39)/ Gallbladder 39 (GB39), (*campana suspensa, Xuanzhong)*; Cardial 3 (C3)/ Heart 3 (HT3), (*mare minus, Shaohai*); Renal 7 (R7)/ Kidney 7 (KI7), (*amnis recurrens, Fuliu*)[23].

The patients allocated to the control AC (CAC) group were treated with the exact same number, depth and stimulation of needles, but not according to the CM diagnosis and, on points allocated in areas close to the real acupoints but at non-acupoints.

The acupoints and the non-acupoints were stimulated using sterile subcutaneous needles (0.30 mm × 8 mm) (BD Micro-Fine®)[29] using the *Leopard Spot* technique (bloodletting or *fang xue* acupuncture), a way of dispelling "blood" (*xue*) stasis described in the third century.[33]

The "therapists" were trained to execute the Leopard Spot technique by pricking quickly the points (5 times per point, 3-5 blood drops per point) with the color indicated by the randomization computer program.

Statistical analysis

Each categorical variable was described by its absolute and relative frequencies while each quantitative variable was described by its median, 25th percentile and 75th percentile. Chi-square and Fisher tests were used to assess the association between categorical variables. Shapiro-Wilk tests were performed to assess the normality of quantitative variables. When they were normally distributed, ANOVA was used to verify whether statistically significant differences exist between the verum, control and waiting list groups. When the normality requirements did not hold, Kruskal-Wallis tests were used instead. When the comparisons were performed between only two of the groups, t-Student

tests or Mann-Whitney tests were used, as applicable. Within each of the three groups, Wilcoxon tests were used to assess whether quantitative outcomes were altered with statistical significant differences between the baseline and after the last treatment. The analyses were performed on IBM SPSS Statistics 24 and on R 3.3.2. The significance level adopted was 0.05.

RESULTS

Recruitment rate and baseline characteristics

Of the 284 RA patients enrolled, 151 (79.5%) RA participants showed pain worse by grip in the fingers more than in the knuckles or thumb, and 147 of these patients were diagnosed, according to the CM diagnose process, with the TPS (figure 1).

Of those 147 eligible patients, 105 patients were randomized. The study flow chart and the reasons for discontinuation are shown in figure 1.

Figure 1: CONSORT 2010—Flow Diagram.
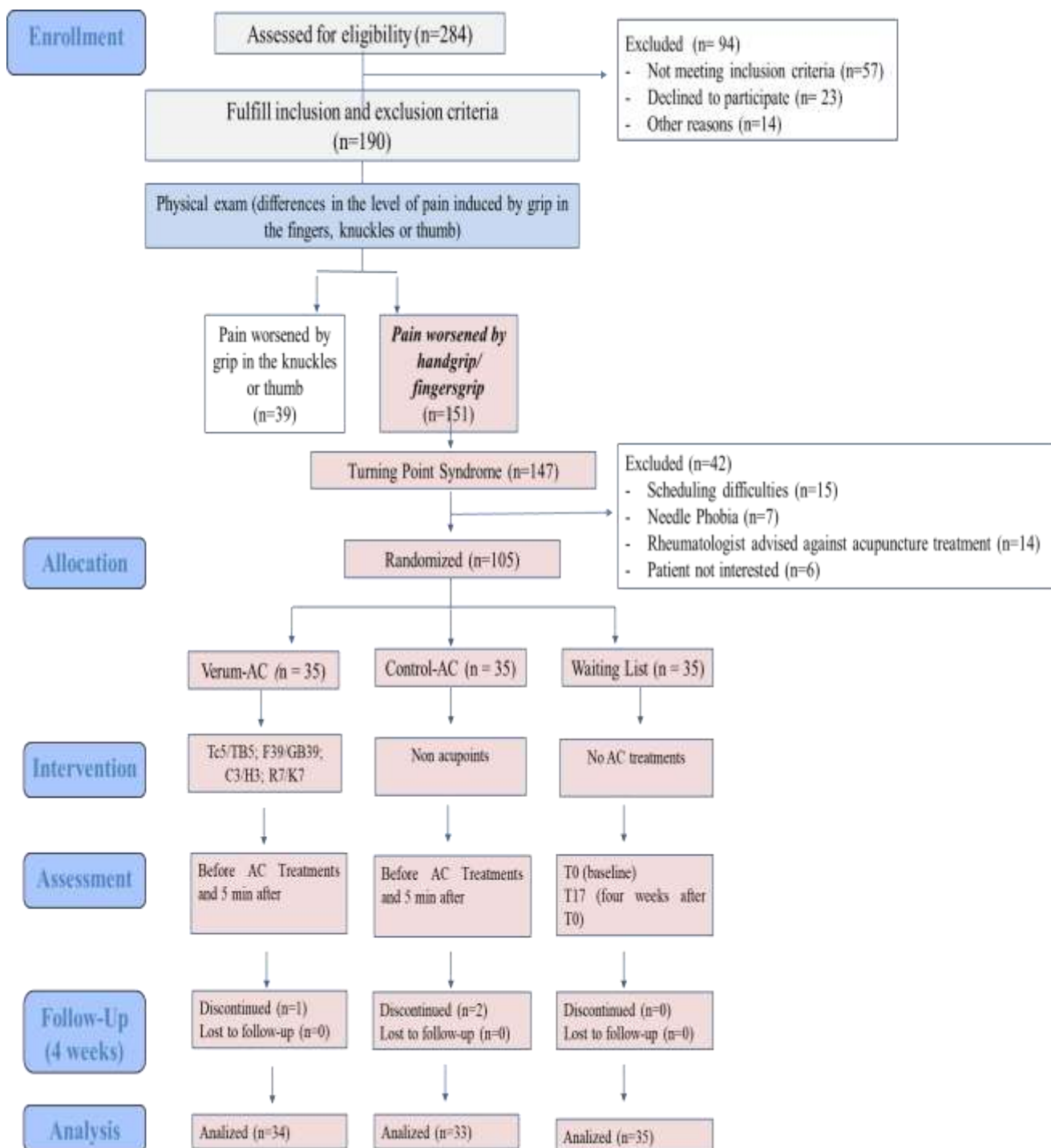
Study flow diagram and patients' progress through the trial.

Demographic, clinical features and CM functional vegetative state assessments, according to the symptoms and signs manifested by RA patients, with hand pain worsening by handgrip (n=105), at baseline are described in Table 1. There were no significant differences in baseline characteristics between the three groups.

Table 1: Demographic and clinical characteristics (baseline)

		Total sample (n=105)	Verum AC (n=35)	Control AC (n=35)	Waiting list Group (n=35)
Gender (F:M)		94 (89.5%): 11 (10.5%)	31 (88.6%): 4 (11.4%)	30 (85.7%): 5 (14.3%)	33 (94.3%): 2 (5.7%)
Age (years)		57.14±13.05	57.31±11.3	56.46±16.43	57.66±11.07
Duration of disease (years)		12 (6, 19.25)	10.5 (5.25, 16.75)	15 (7.5, 21.5)	12 (7, 19)
Positive serum test for rheumatoid factor, n (%)		67 (68.4%)	23 (74.2%)	24 (72.7%)	20 (58.8%)
High blood cholesterol (yes: no)		49 (46.7%): 56 (53.3%)	18 (51.4%): 17 (48.6%)	16 (45.7%): 19 (54.3%)	15 (42.9%): 20 (57.1%)
BMI score		25.61 (24.045, 28)	26.34 (25, 28)	25.54 (24, 28.384)	25 (24.045, 27.15)
History of joint surgeries (yes: no)		48 (45.7%): 57 (54.3%)	16 (45.7%): 19 (54.3%)	17 (48.6%): 18 (51.4%)	15 (42.9%): 20 (57.1%)
Erosive Disease (yes: no)		64 (64%) : 36 (36%)	21 (61.8%) : 13 (38.2%)	20 (64.5%) : 11 (35.5%)	23 (65.7%) : 12 (34.3%)
Early morning stiffness (minute)		15 (5, 25)	15 (10, 25)	10 (0, 27.5)	15 (7.5, 20)
Pharm.Treat.	**NSAID (yes: no)**	91 (86.7%): 14 (13.3%)	27 (77.1%) : 8 (22.9%)	31 (88.6%): 4 (11.4%)	33 (94.3%): 2 (5.7%)
	BIOLOGICAL (yes: no)	54 (51.4%): 51 (48.6%)	17 (48.6%): 18 (51.4%)	15 (42.9%): 20 (57.1%)	22 (62.9%): 13 (37.1%)
	DMARD (yes: no)	93 (88.6%): 12 (11.4%)	29 (82.9%): 6 (17.1%)	32 (91.4%): 3 (8.6%)	32 (91.4%): 3 (8.6%)
	ANALGESICS (yes: no)	66 (62.9%): 39 (37.1%)	22 (62.9%): 13 (37.1%)	22 (62.9%): 13 (37.1%)	22 (62.9%): 13 (37.1%)
Use of non-pharmacological treatments (yes: no)		72 (68,6%): 33 (31.4%)	22 (62,9%): 13 (37.1%)	21 (60.0%): 14 (40.0%)	29 (82.9%): 6 (17.1%)

F (Female); M (Male); BMI (Body Mass Index); NSAID (Nonsteroidal anti-inflammatory drugs); DMARD (Disease-Modifying Drugs). Data are presented as number (frequency); mean ± SD (standard deviation) or median (1st quartile, 3rd quartile). There was no significant difference in any of the characteristics between the three groups.

Clinical Efficacy

At baseline, there were no significant differences in the primary outcomes between the three groups. At the end of the treatment, all VAC patients significantly improved in HGS (p= <0.001), AS (p= <0.001), VAS (p= <0.001) and PA (p= <0.001). The CAC patients showed only self-reported pain improvement, VAS (p= <0.001). In the waiting list group, there was no change from baseline in AS and VAS, while there was a significant worsening in HGS (p= <0.029) and PA (p= <0.001) (Table 2) (Figure 2). At the last assessment, the differences in all the primary outcomes between groups were significant (p < 0.001) (Table 2).

Table 2 – Clinical outcome changes for the three groups of patients

	Verum AC	Control AC	Waiting list Group	*p-value*
PRIMARY OUTCOMES				
Hands Grasp Strength (Kgf)				
Baseline	13.45 (8.6, 18.28)	12.45 (8.66, 19.48)	11.47 (7.72, 16.95)	0.488
28 days after first treatment/assessment	21.83 (15.53, 24.83)	11.5 (9.1, 20.2)	11.126 (7.94, 15.25)	<0.001
Changes from baseline to post last treatment/assessment	6.2 (4.65, 8.8)	-0.05 (-1.55, 1.95)	-0.295 (-1.67, 0.63)	<0.001
Statistical value (Wilcoxon Z)	-5.086	-0.243	-2.179	
p value	<0.001*	0.808	0.029*	
Arm Strength (Kgf)				
Baseline	9.34 (7.873, 14.24)	10.06 (7.14, 16.65)	8.47 (8.41, 9.79)	0.872

28 days after first treatment/assessment	19.74 (14.36, 23.77)	10.04 (5.79, 16.13)	7.64 (7.09, 8.44)	<0.001
Changes from baseline to post last treatment/assessment	7.13 (5.19, 10.65)	0.27 (-2.14, 0.91)	-1.82 (-2.64, -0.52)	<0.001
Statistical value (Wilcoxon Z)	-5.086	-0.027	-1.069	
p value	<0.001*	0.979	0.285	
VAS (0–10, 10 worst health)				
Baseline	6 (4, 7)	5 (4, 7)	5 (4, 6)	0.304
28 days after first treatment/assessment	1 (0, 2)	4 (3, 6)	5 (4, 7)	<0.001
Changes from baseline to post last treatment/assessment	-4 (-6, -3)	-1 (-2, -1)	0 (0, 2)	<0.001
Statistical value (Wilcoxon Z)	-5.099	-3.674		
p value	<0.001*	<0.001*		
Pressure Algometry (Kgf)				
Baseline	0.315 (0.20, 0.42)	0.37 (0.26, 0.52)	0.38 (0.30, 0.50)	0.074
28 days after first treatment/assessment	0.64 (0.53, 0.80)	0.37 (0.31, 0.52)	0.35 (0.25, 0.42)	<0.001
Changes from baseline to post last treatment/assessment	0.34 (0.24, 0.41)	-0.02 (-0.08, 0.06)	-0.07 (-0.10, -0.02)	<0.001
Statistical value (Wilcoxon Z)	-5.086	0.545	-3.227	
p value	<0.001*	0.586	0.001*	
SECONDARY OUTCOMES				
Health Related Quality of Life (SF-36 ITEMS) (0–100, 0 worst health)				
Physical function				
Baseline	40 (25, 52.5)	40 (12.5, 62.5)	35 (27.5, 50)	0.966
28 days after first treatment/assessment	50 (40, 58.75)	45 (25, 65)	35 (20, 45)	0.021
Changes from baseline to post last treatment/assessment	10 (0, 15)	5 (0, 10)	-5 (-15, 2.5)	<0.001
Statistical value (Wilcoxon z)	-3.994	-3.029	-2.469	
p value	<0.001*	0.002*	0.014*	
Role- physical				
Baseline	25 (0, 25)	25 (0, 62.5)	25 (12.5, 50)	0.135
28 days after first treatment/assessment	50 (50, 75)	50 (25, 75)	25 (0, 25)	<0.001
Changes from baseline to post last treatment/assessment	25 (25, 50)	25 (0, 25)	0 (-25, 0)	<0.001
Statistical value (Wilcoxon z)	-4.533	-3.084	-2.277	
p value	<0.001*	0.002*	0.023*	
Bodily pain				
Baseline	31 (22, 41)	36.5 (22, 51)	41 (32, 46.5)	0.012
28 days after last treatment	51.5 (41, 61.75)	41 (31, 52)	32 (22, 41)	0.001
Changes from baseline to post last treatment/assessment	19 (10, 21)	10 (0, 21)	-9 (-10.5, 0)	<0.001
Statistical value (Wilcoxon z)	-4.711	-2.89	-3.555	
p value	<0.001*	0.004*	<0.001*	
General health				
Baseline	35 (27.5, 43.5)	35 (22.5, 42.5)	40 (30, 43.5)	0.642
28 days after first treatment/assessment	35 (25.5, 48.75)	40 (30, 45)	35 (25, 40)	0.517
Changes from baseline to post last treatment/assessment	5 (-5, 10)	5 (0, 10)	0 (-5, 0)	0.009
Statistical value (Wilcoxon z)	-1.289	-2.264	-1.711	
p value	0.198	0.024*	0.087	
Vitality				
Baseline	30 (20, 47.5)	40 (22.5, 55)	40 (37.5, 50)	0.161
28 days after first treatment/assessment	47.5 (40, 68.75)	50 (25, 60)	30 (17.5, 45)	<0.001
Changes from baseline to post last treatment/assessment	20 (5, 25)	5 (0, 10)	-10 (-17.5, -5)	<0.001

Statistical value (Wilcoxon z)	-4.572	-2.508	-3.968	
p value	<0.001*	0.012*	<0.001*	
Social Function				
Baseline	50 (37.5, 75)	62.5 (50, 81.25)	50 (37.5, 62.5)	0.189
28 days after first treatment/assessment	75 (50, 87.5)	62.5 (50, 87.5)	50 (31.25, 62.5)	0.001
Changes from baseline to post last treatment/assessment	12.5 (3.125, 25)	0 (0, 12.5)	0 (-12.5, 0)	<0.001
Statistical value (Wilcoxon z)	-4.288	-0.923	-1.841	
p value	<0.001*	0.356	0.066	
Role-Emotional				
Baseline	33.3 (33.3, 66.67)	33.33 (0, 66.67)	33.33 (16.5, 83.335)	0.575
28 days after first treatment/assessment	66.7 (66.67, 100)	33.33 (33.3, 100)	33.33 (30.15, 66.67)	<0.001
Changes from baseline to post last treatment/assessment	33.34 (0, 66.7)	0 (0, 33.33)	0 (-3.015, 0)	<0.001
Statistical value (Wilcoxon z)	-3.862	-2.621	-1.296	
p value	<0.001*	0.009*	0.195	
Mental Health				
Baseline	56 (40, 68)	56 (42, 84)	52 (42, 64)	0.427
28 days after first treatment/assessment	72 (57, 80)	56 (48, 80)	48 (38, 56)	<0.001
Changes from baseline to post last treatment/assessment	14 (0, 24)	0 (0, 12)	-4 (-10, 0)	<0.001
Statistical value (Wilcoxon z)	-3.576	-1.222	-2.714	
p value	<0.001*	0.222	0.007*	
HAQ (1–4, 4 worst health)				
Baseline	1.375 (1, 1.8125)	1.25 (0.4375, 1.625)	1.125 (0.875, 1.375)	0.062
28 days after first treatment/assessment	1 (0.75, 1.25)	1.25 (0.5, 1.5)	1.25 (1, 1.625)	0.057
Changes from baseline to post last treatment/assessment	-0.25 (-0.5, -0.125)	0 (-0.125, 0.125)	0.125 (0, 0.25)	<0.001
Statistical value (Wilcoxon z)	-4.895	-0.529	-2.506	
p value	<0.001*	0.597	0.012*	
SWOLLEN JOINTS				
Baseline	2 (0, 2.5)	1 (0, 2)	1 (0, 2.5)	0.257
28 days after first treatment/assessment	0.5 (0, 2)	0 (0, 2)	1 (0, 2.5)	0.372
Changes from baseline to post last treatment/assessment	0 (-1.75, 0)	0 (0, 0)	0 (0, 0.5)	0.002
Statistical value (Wilcoxon z)	-2.862	-0.289	-1.004	
p value	0.004*	0.773	0.315	
TENDER JOINTS				
Baseline	2 (1, 4)	1 (0, 3)	1 (0, 2)	0.033
28 days after first treatment/assessment	1 (0, 2)	2 (0, 2)	1 (0, 3.5)	0.661
Changes from baseline to post last treatment/assessment	-1 (-2, 0)	0 (0, 0)	0 (-1, 1)	0.001
Statistical value (Wilcoxon z)	-3.986	-0.036	-0.647	
p value	<0.001*	0.971	0.518	
ESR				
Baseline	8 (2.25, 17.5)	8 (3, 14)	5 (2, 15)	0.710
28 days after first treatment/assessment	7 (2.5, 14.5)	5.5 (2.75, 12.5)	6 (2, 12)	0.826
Changes from baseline to post last treatment/assessment	0 (-2.5, 1)	0 (-2.25, 3)	0 (-4, 0)	0.568
Statistical value (Wilcoxon z)	-1.212	-0.112	-1.249	
p value	0.226	0.911	0.212	
CRP (mg/l)				
Baseline	0.28 (0.07, 1.05)	0.22 (0.1, 0.33)	0.17 (0.05, 0.28)	0.360

28 days after first treatment/assessment	0.23 (0.055, 1.01)	0.17 (0.0575, 0.305)	0.13 (0.07, 0.37)	0.654
Changes from baseline to post last treatment/assessment	-0.01 (-0.08, 0.105)	0 (-0.0525, 0.02)	0.01 (-0.1, 0.09)	0.846
Statistical value (Wilcoxon z)	-0.267	-0.664	-0.147	
p value	0.789	0.506	0.883	

Kgf (kilogram force)VAS (**visual analogue scale**); SF-36 (**Short Form 36**); HAQ (**Health assessment Questionnaire**); ESR (**erythrocyte sedimentation rate**); CRP (**C-reactive protein**).
Data are presented as median (1st quartile; 3rd quartile). ***p-value*** (probability value) adopted was 0.05, *p<0.05 comparing before and after treatment.

Figure 2: Primary outcome changes for the three groups of patients. A radar plot is displayed for each group (verum AC, control AC, waiting list), in which the different SF components are shown. To enable an easy visualization, the normalized medians are shown for each group and for each variable. The normalization procedure consisted of dividing, for each group and each variable, the corresponding median with the maximum of the 6 medians obtained, over all the groups, for that variable.

Patients in the VAC group showed significantly better outcomes compared to CAC group for all outcomes measures, in particular after T3 for VAS, after T5 for PA, after T7 for AS, and after T11 for HGS. Figure 3 summarizes strength (AS and HGS) and pain (VAS and PA) changes during acupuncture treatment in VAC and CAC groups (Figure 3) (Table 2).

Pressure Algometry

Visual Analogue Scale - Self-reported Pain
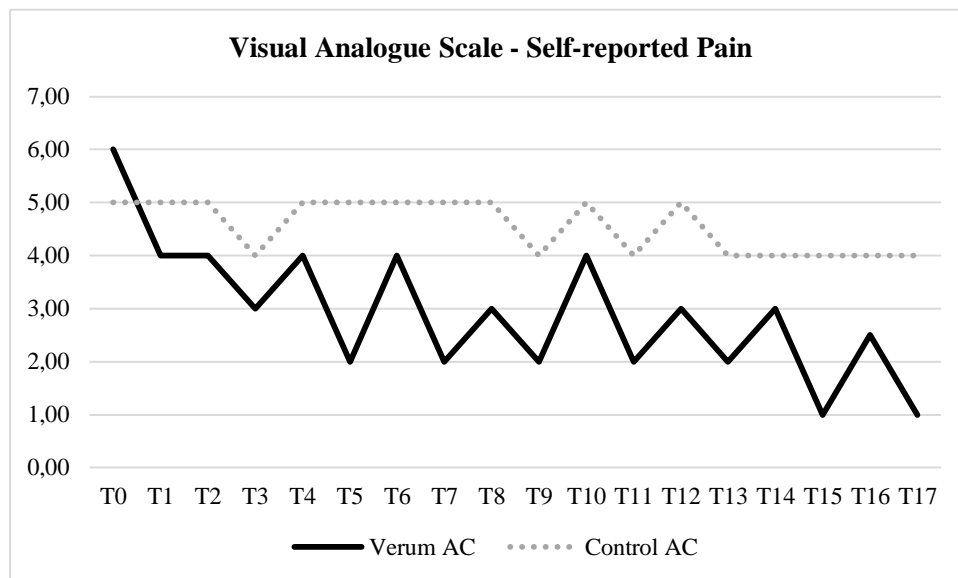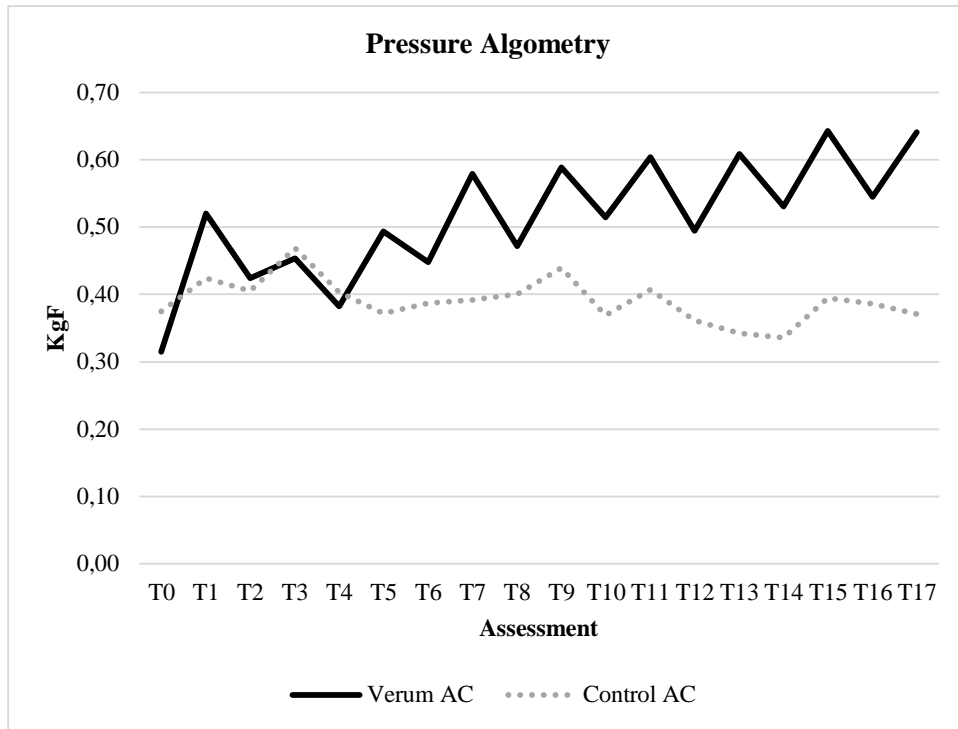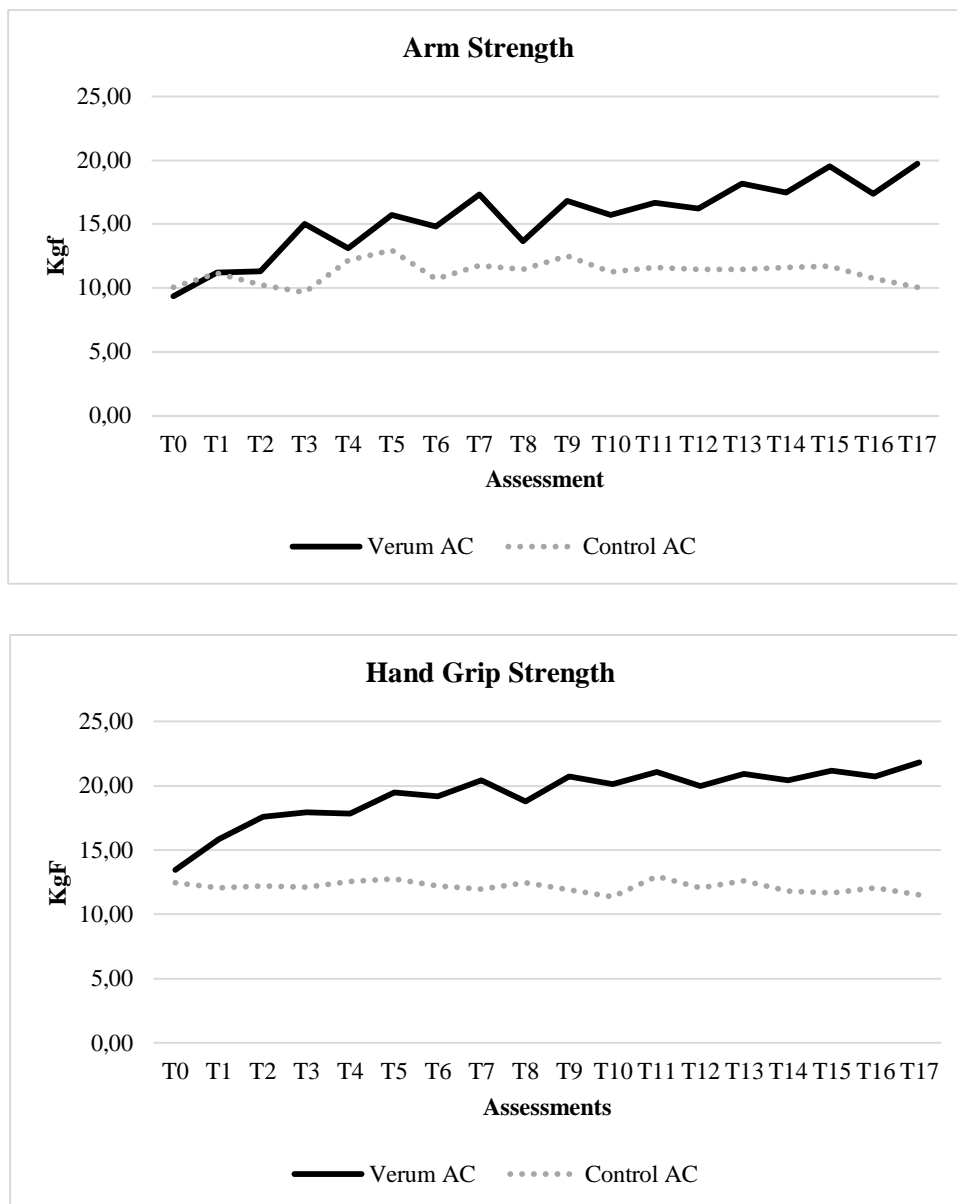
Figure 3: Primary outcomes changes for the groups treated with acupuncture

With respect to secondary outcomes, at baseline the SF-36 bodily pain domain was significantly worse in the VAC group and the number of tender joints was significantly higher in the CAC group compared to the other groups (Table 2). Also at baseline, the median scores of the SF-36 assessments showed that physical function was the most compromised domain and mental health the least.

Secondary outcomes analyzed after four weeks showed that HAQ scores significantly decreased in the VAC group, while there was no change in the CAC group and an increase in the waiting list group; verum acupuncture improved significantly 7/8 SF-36 domains, while sham acupuncture improved significantly only 5/8 SF-36 domains and the waiting list group showed a statistically significant worsening of 5/8 SF-36 domains (Table 2) (Figure 4). The number of swollen and tender joints

significantly decreased in the VAC group, while there was no change in the CAC and waiting list groups (Table 2) (Figure 4). There were no changes within groups and between groups for ESR and CRP (Table 2) (Figure 4).

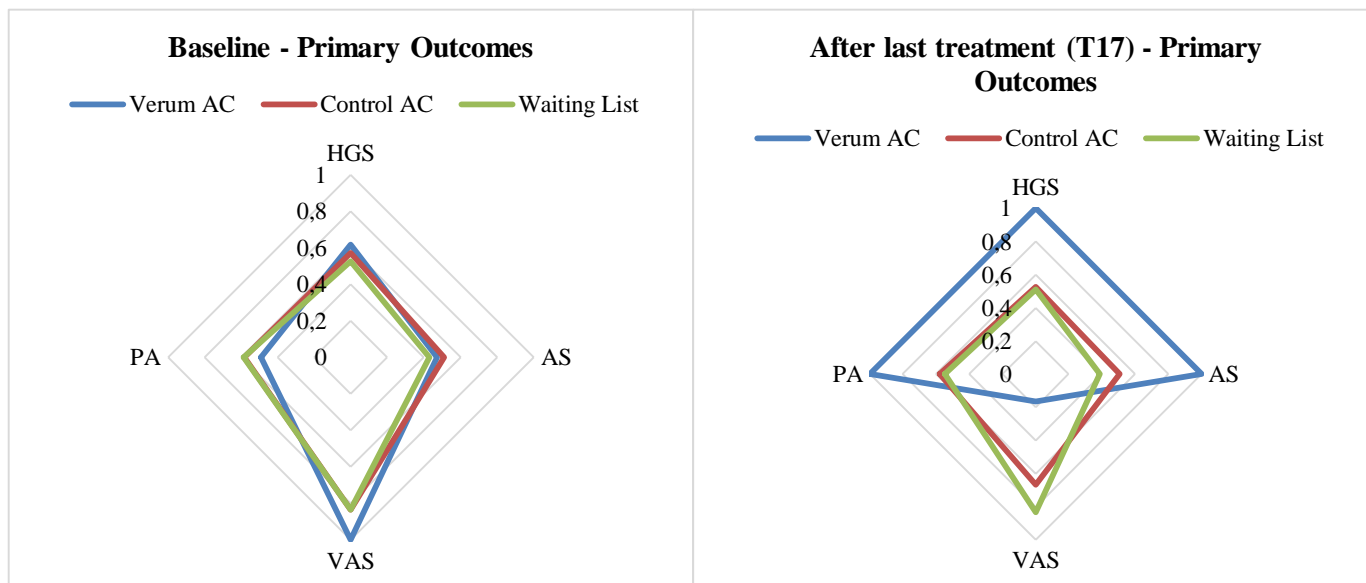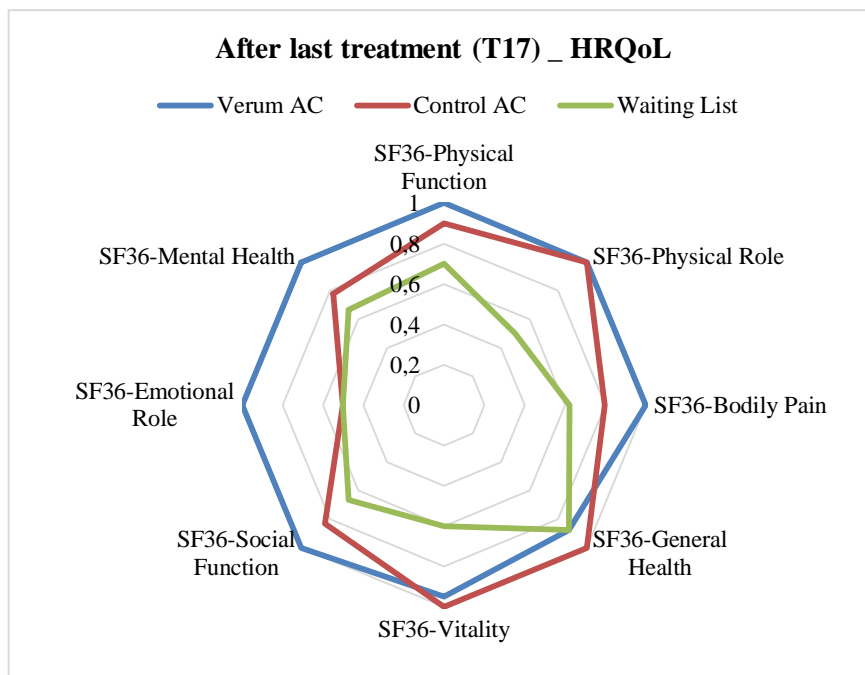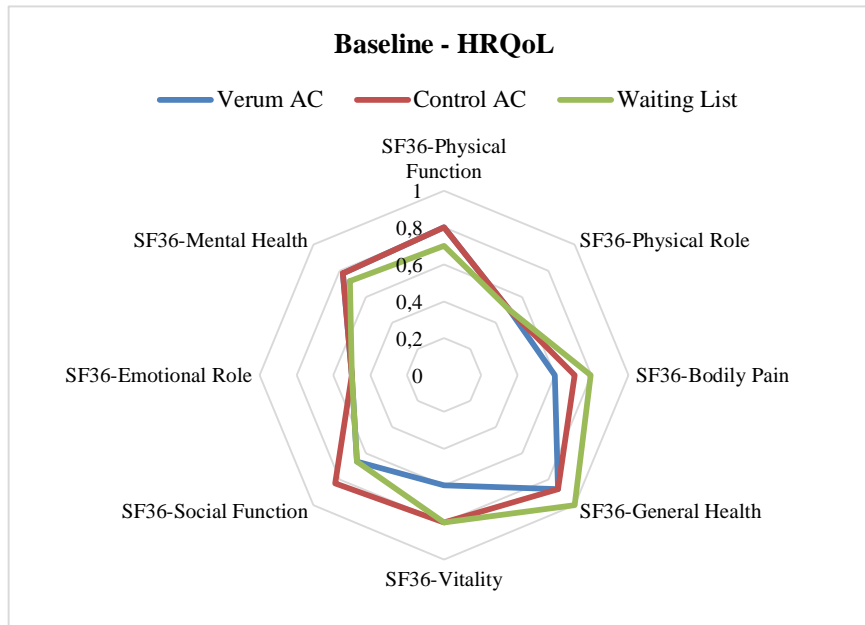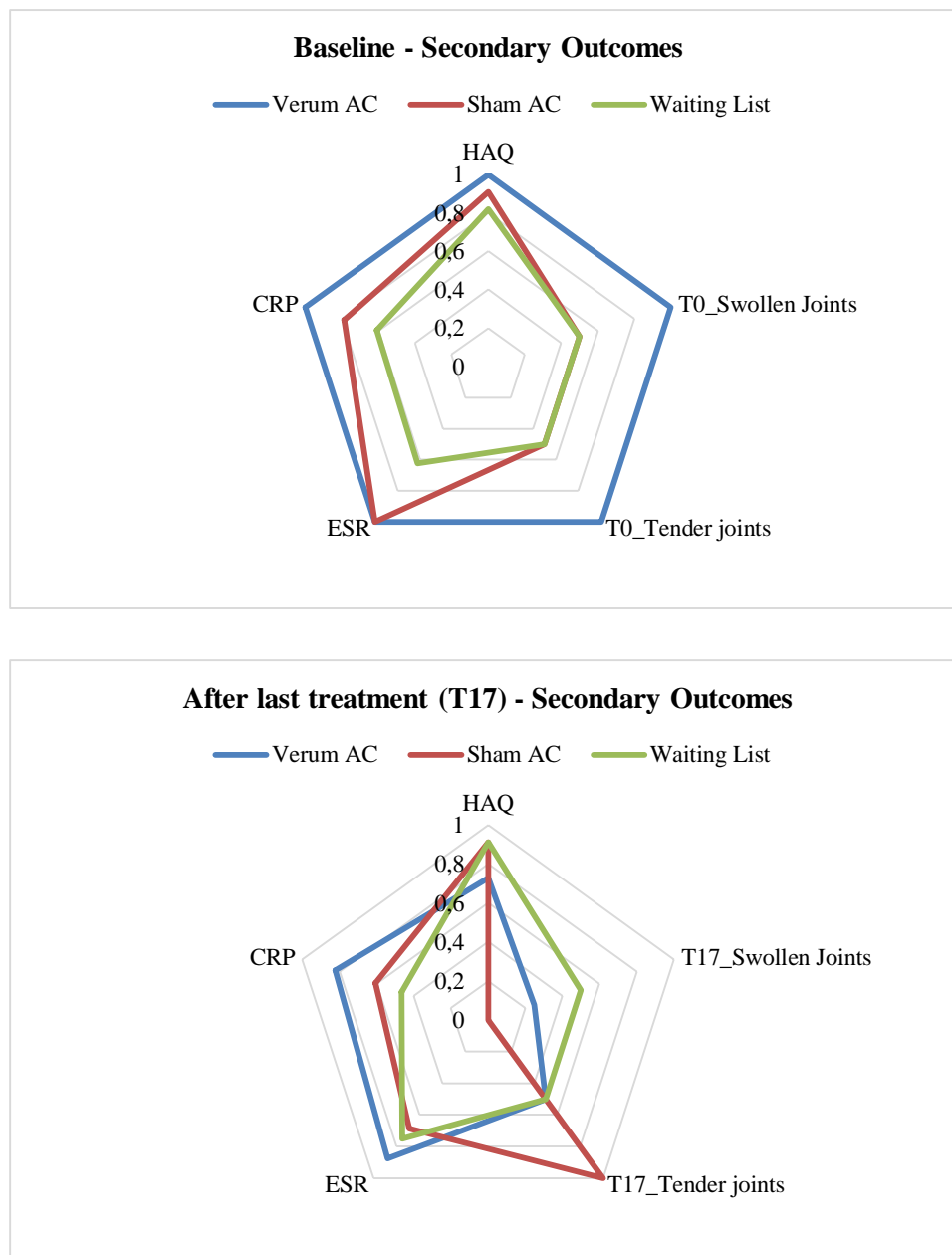**Figure 4:** Secondary outcome changes for the three groups of patients. A radar plot is displayed for each group (verum AC, control AC, waiting list), in which the different SF components are shown. To enable an easy visualization, the normalized medians are shown for each group and for each variable. The normalization procedure consisted of dividing, for each group and each variable, the corresponding median with the maximum of the 6 medians obtained, over all groups, for that variable.

All the participants remained on stable doses of existing medications. Therefore, medications are unlikely to represent a confounding factor in the analyses presented.

Throughout the period in which the study took place, AC treatments were well tolerated. No side effects were reported except for minor bleeding at the site of needle insertion.

The patients treated with acupuncture gave an opinion of their treatment group after the study had been completed. Eighty-one percent of the acupuncture group and 82% of the sham group replied. Of the replies 14 of the VAC (41%) and 15 of the CAC (44%) correctly named their treatment allocation. These were not significantly different (Chi-square test, p= 0.39). Twenty-three percent of those that had acupuncture and 15% of the CAC group wrongly guessed their treatment allocation.

DISCUSSION

Our results clearly indicate a relevant clinical effect of AC on RA of the hand in patients suffering from TPS. We used the exact same number, depth and stimulation of needles in the VAC and CAC groups so that we could identify if one group of points works better than the other. It is not like the usual 'explanatory' placebo trial where the verum acupuncture technique is compared to one placebo strategy. As the effects were shown in a double-blind manner, a mere placebo or suggestive AC effects can be excluded and the differences between the AC groups can therefore be considered to be specifically induced by the acupoints used.

The rigorous design of this randomized controlled clinical trial also avoids major other problems of AC studies such as non-specific effects, weak allocation of acupoints or lack of objective assessment of effects.

Non-specific AC effects may depend on the depth of penetration, which has consequences for study designs or control interventions to be chosen. We decided not to use streitberger placebos, shallow 2mm needlings or pyonex controls, because the depth of penetration is zero or low. Therefore, we would compare high depth of needling in the verum versus low depth of penetration in controls. This is the reason why we chose the same number of needlings and mode of stimulation techniques in verum and control interventions to minimize the influence of unspecific effects. Specific effects of acupoints can only be shown if the verum intervention is maximally effective in comparison to unspecific and suggestive effects of the control intervention. Therefore, we included the CM diagnosis according the Heidelberg Model of CM.

It is interesting to note that in our study sham AC only improved significantly the self-reported pain (VAS scores), a subjective outcome and tendentially (but not significantly) improved 5/8 SF-36 domains, but in objectively measurable parameters (AS and HGS) as well as the functional status assessed by the HAQ no change or even worsening was observed. This shows how important double blinding, randomization and objective assessment of AC-effects are, as they help to discriminate and

quantify suggestive and placebo effects of sham and verum acupoints. In our case, sham points showed no significant changes, indicating that acupoints truly make a difference over unspecific skin points in clinical efficacy, which was frequently doubted in the past.[34] We could repeatedly show this in a double-blind manner and by objective assessment methods for indications like gait disorders in the elderly[30] or pain in the knee.[31]

To carry out this study, we needed to develop a specific PA to assess the pain tolerance threshold of RA patients with hand pain whose features are related to the TPS.[32] The device was tested in a small group of 14 RA patients with the TPS before we performed this double-blind randomized controlled trial.[32] We acknowledge that such a device may have certain limitations such as the non-applicability to other syndromes, a not comparability with devices already created, and that we may have not enough data to validate this specific device for other studies, and finally, the fact that it doesn't have a patient controlled 'stop' button. Thus, we recognize that caution is required in the interpretation of clinical findings when using such a device.[32]

Although we can clearly state the objectivity and specifity of the effects shown, the study also raises a couple of questions like the mechanisms behind, and sustainability of effects, and the options of combinations with given conventional therapies. Also the blinding of "therapist" novices to AC can be regarded as a weakness.

Bloodletting AC is considered a technique that removes "blood" (xue) stasis. It has been shown that the bleeding of acupoints induces cell proliferation and migration, particularly of fibroblasts, modulates cytokines, growth factors and inflammatory mediators as well as improves tissue oxygenation, and decreases oxidative stress and edema.[35,36] In addition, it can also relieve pain, stimulate the medullary hematopoiesis via neuro-humoral regulation and promote tissue regeneration.[37] Given the benefit seen in the VAC group, the bloodletting of the verum acupoints must have activated sensory receptors in the conduits affected by the TPS and helped to rebuild homeostasis regarding edema.[35,38] This potential mechanism would also be supported by the lack of changes in serum ESR and CRP, which point to an effect of AC on the microcirculation rather than on inflammation.

However, the fact that bloodletting AC changed pain, function, strength, and HRQoL but not inflammatory parameters like CRP in our study suggests that vegetative and nervous mechanisms may be more involved in our setting than anti-inflammatory effects.

Also, we saw a quick onset of symptomatic relief within five minutes, that continued to improve throughout the period of four weeks, as shown by the VAC. We speculate that the velocity of the effects can hardly be explained by primary induction of complicated anti-inflammatory biochemical pathways, which is also compatible with the reflex and central nervous system mechanisms behind the effects seen. One of the potential changes of vegetative functions may include an increase of microcirculation as shown earlier,[39] which may contribute to pain relief and reduction of functional disability.[40,41,42]

After four weeks treatment, patients treated with verum AC improved across all clinical symptoms except inflammation measured by CRP, which resulted in less pain, better functional ability and improved HRQoL. AC, a non-pharmacologic and nontoxic technique, was an effective and well-tolerated treatment. Further research is needed to explore whether long-term effects can be obtained and if treatment variations may be necessary to achieve this.

The treatment underlying our study was developed in the Heidelberg School of CM, where treatments of RA have frequently been performed for two decades in a similar manner as standard intervention. After the intensive treatment of four weeks, frequency is gradually reduced to one session every three weeks and symptoms remain on a comparable level. However, this should be examined and objectified by follow-up studies.

Based on the observations of this study, we can now estimate that a sample size of 37 patients in each group, to an expected effect size of 0,2 (f=0,2), with an alpha value of 0,05 (α=0,05), would be required for a 95% power.

Combination of this therapy with conventional treatments is not only an option, but will remain a necessity according to our clinical experience. There is no cure for RA, and the goals of treatment are considered to minimize symptoms, to prevent deformity of joints and control inflammation, and to maintain day to day function.[43] Clinical experience and common sense may support the thesis that some reduction of RA-medication may in the future be achieved by follow-up studies, but this remains speculation until data on that are systematically acquired.

In this context, the role of AC in rheumatology should be reconsidered as complementation but not replacement of conventional therapies, with the allocation of individual acupoints following the scientific rules quoted.[23,26,29]

Follow-ups concerning sustainability and potential reduction of RA- associated medications are necessary, as well as towards the question of extending these positive results to other joints and possible extra-articular manifestations of RA.

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How can acupuncture serve nurses in their job?

How can Acupuncture serve nurses in their job?

Nursing is a profession within the health care sector focused on the care of individuals, families, and communities. In the constant pursuit for a better professional performance the nurse, in the late 20th century, has gained autonomy, increased knowledge based on critical thinking and an upgraded ability to set up priorities.[1]

Nurses are trained to prescribe, implement and evaluate interventions to improve the health and functional capacity of individuals.[2] In their work, they can use all valid techniques to improve the quality of care and nursing services including complementary and alternative medicine, as acupuncture, since these are based on scientific and technical knowledge.[3]

Nursing care can be supplemented, extended and enriched by knowledge of acupuncture.[3] In the last few years, acupuncture studies using appropriate control measures and adequate methodologies have increased the scientific evidence of its efficacy and safety.[4] Both sciences have a holistic view of the person as a human being in constant interaction with everything that surrounds it, including environment, lifestyles, social relationships, emotional state and diet, requiring a personalized care according to each individual clinical state.

We suggest the contemporary understanding of Chinese Medicine (CM), according to the Heidelberg Model (HM), as a basis for the nurses to develop their knowledge of CM diagnosis, principles of CM treatments, acupuncture or other CM techniques.

As explained on Chapter 2 of this work, the HM to CM is based on one system of sensations and discoveries to establish a functional vegetative state, describing functional abnormalities through its signs and symptoms resulting from disorders of body tissues.[5,6] The HM to CM centers on the fact that the main technical terms of CM, such as yin and yang, phases or elements may be understood as being terms of vegetative regulation.[7]

According to this Model, the functional diagnosis is established attending four components: the constitution (internal nature of the patient), pathogenic factors (what factors affect the patient), affected orbs (manifest signs and symptoms) and respective Guiding Criteria, also understood as indicators of the current functional status (neurovegetative signs, neuroimmunological, humoro-vegetative and the presence of a structural or regulatory deficiency).[4,5]

One particularity in the use of CM is, for example, the selection of points, herbs or exercises in individual cases. The treatment is directly dependent on the data. A basic principle is to treat people, not diseases. The diagnosis is its fundamental principle and before the application of any technique, a correct assessment of the individual must to be taken because what works in one case may fail in another.[8]

The group leaded by the Professor Greten have been implementing randomized clinical studies in several areas, using methodologies that included objective outcomes and both Western and CM

diagnoses, proving the effectiveness of the CM tecnhiques and finding a strong analogy between the classics Chinese writings on cybernetics and the systems of biology of Western medicine.[9-16]

How acupuncture can assist nursing care

The World Health Organization recomends the inclusion of acupuncture in health care systems. It provides strategies for health promotion and illness prevention, health recovering, decrease of pain and signs and symptoms of diseases, which can have an unquantifiable importance for people with acute and chronic illness.[17]

Acupuncture has low cost, minimal side effects and can be used in several diseases with Western forms of treatment have limited sucess. It has a vast range of effects namely, immune system regulation, increased pain threshold and improved microcirculation. It may assume great importance in the control or relief of signs and symptoms, for example, anxiety, pain (including phantom pain), nausea and vomiting, may have an anesthetic effect in minor surgical procedures, and decrease pharmacological side effects and drug interactions, either by reducing the need for some medications, or acting in the affected organ or system in order to protect it.[8]

When the nurses choose to consider acupuncture as a complementary treatment strategy, they should take into account several factors to assess the cost-effectiveness including the side effects, the long-term outcomes, the comparative studies between acupuncture treatments and biomedicine, the economic drug impact and the overall economic impact on the individual's health and quality of life.[18]

Currently acupuncture is widely used in hospitals in several countries. In China 95% of the hospitals have units of Chinese medicine. In the United Kingdom, as in the Unites States of America, acupuncture is practised in state hospitals and taught in state universities.[19] In Germany it is still mostly used in private establishments but with a significant contribution from social security and insurance.

The inclusion of acupuncture in health care systems derives from several advantages:[20] the necessary resources, specially the instruments, have low cost; the rooms and units in health care institutions can be easily adapted to CM queries; almost total independence from hospital medical technology; applicability in the field of preventative and curative medicine could contribute to reduce the waiting lists in public health systems, and the costs associated with expensive drugs, invasive techniques and hospital admissions.

In the context of nursing care, procedures to use complementary and alternative medicines may prove to be an asset in; reducing the medication consumption, pain and fatigue relief, improvement of functional status, clinical and laboratory signs, and increasing the quality of life with repercussions on the physical, mental and social health.

CONCLUSION

The nurses, as a key element of the health teams, have a responsibility to participate in the decisions about the individual's health promotion, treatment and recovery, by assuming the duty of updating

continuous knowledge, incorporating the research findings and evidence in their practice and the use of the best and most individually adequate treatment strategies, developing the quality of the health care procedures and services.

In their practice, nurses can use complementary and alternative therapies, since these are based on scientific and technical knowledge, taking all measures to improve the quality of nursing care that can be supplemented, extended and enriched by knowledge of acupuncture.

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Chapter 10

Discussion of critical points

Discussion of critical points

The Chapters presented in this work mainly include published papers. The intention of this last Chapter is to contribute to the coherence and therefore a better understanding of the thesis by synthetizing the strengths and limitations of the research findings, their potential implications in an integrated perspective and by identifying potential areas for further work.

The work presented in this thesis was developed within the context of the doctoral program in Health Sciences, branch in Nursing. We aimed to assess the effects of acupuncture, a non-pharmacological intervention. We wanted to find out its potential in the management of rheumatoid arthritis (RA) symptoms and if it could possibly be a future treatment option for the nurses. A special focus was on the outcomes pain, physical function and quality of life (QoL).

Besides the advances in medical science that lead to more effective treatments and better long-term outcomes, a large proportion of RA patients with tight control of inflammation still live with chronic pain, severe functional decline, negative consequences in almost all domains of well-being, both physical and emotional,[1] and the disease impact cannot be improved by further disease control.

The fact is that in more than one in ten RA patients, pain and disability persists despite the absence of laboratory signs of inflammation. It is therefore understandable that unsatisfied RA patients are using complementary alternative therapies (CAMs), and acupuncture has been heavily advertised with broad, attractive claims.

Interest in acupuncture is growing not only among RA patients but also in the general public and in all therapeutic fields, like nursing. Nurses are moving away from the prevailing orthodox medical model that has dominated their practice for the last century and are making a transition into a practice which encompasses more holistic principles. Acupuncture treatment principles and concepts go along with the principles of nursing practice, and thus it is an attractive area for them to include.

Some studies are demonstrating that acupuncture is effective in pain relief, physical function and health related quality of life (HRQoL) in RA patients. However, after an analysis of the most scientific, evidence-based, worldwide published studies we found out that due to the heterogeneity and methodologic limitations of these studies, the evidence was not strong enough to produce a best practice guideline.[2]

It is apparent that there is still limited evidence for the effectiveness of acupuncture. However, based on over two decades of clinical experience of the Heidelberg School of Chinese Medicine, where acupuncture treatments of RA have frequently been performed and patients' symptoms usually improve, we should not dismiss acupuncture effects as unscientific. We rather should investigate further the benefits achieved.

Patients' use of evidence-based therapies is imperative to support safe therapeutic decisions. Nurses, using acupuncture or advising patients on its use must follow evidence-based principles and ensure

that informed consent is given. Also, as in other areas of practice, adequate training and supervision are required.

With the help of multidisciplinary collaborations among different professionals and researchers of western and Chinese medicine this multi-task scientific work was developed to assess the effects of acupuncture in the pain and function of the hands of selected patients with RA. Our results intend to provide a better scientific base for the use of acupuncture by nurses and RA patients.

Contrary to what is stated, the CONSORT criteria were not strictly followed. Please comment and address the potential consequences regarding validity of the results and conclusions.

The CONSORT guidelines were strictly followed to strengthen the evidence base on acupuncture treatment and to understand its effects (please see table 1).

The Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) recommendations were also followed emphasizing the need to provide rationed detailed protocol information, such as needling, treatment regimen, co-interventions, practitioners background, and control interventions (please see table 2).[3]

Trial registration and implementation of CONSORT guidelines were strictly followed but we understand that this work still has problems. Weakness and limitations of this research were consistently addressed in each of the papers and these were considered by co-authors, peer reviewers and journal editors.

We believe that the problem of this work is not the randomization because it gives us causal identification and individual sampling variation. Unfortunately, from a design point of view, acupuncture research involves complex processes that require many decisions and steps at different levels that bring their own assumptions and degrees of bias to the results (e.g. the diagnosis based on Chinese medicine) and the control choice, the non-acupuncture points, are not completely inert.

Randomized control trials (RCTs) are restricted in answering questions about how to achieve the desired outcomes, but they cannot always be conducted easily in cases of multiple and complex treatments or simultaneous outcomes that often reflect the reality of acupuncture treatments or for example surgical treatments as well.

Thus, in order to increase the understanding of acupuncture effects and not to neglect other important issues, other methods could be used in future studies (e.g. longitudinal observational studies).

Table 1: CONSORT 2010 checklist of information to include when reporting a randomised trial

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	Chapter 5 (p.128), Chapter 8 (p.174)
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	p.175
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	Chapters 2, 3, 4, 5 and 8
	2b	Specific objectives or hypotheses	Chapter 5 (p.134-138), Chapter 8 (p.178-180)
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	Chapter 8 (p.178-179)
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	Chapter 8 (p.178)
Participants	4a	Eligibility criteria for participants	Chapter 8 (p.178)
	4b	Settings and locations where the data were collected	Chapter 8 (p.178)
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	Chapter 8 (p.180)
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	Chapter 5 (p.135-138), Chapter 7, Chapter 8 (p. 179-180)
	6b	Any changes to trial outcomes after the trial commenced, with reasons	-
Sample size	7a	How sample size was determined	Chapter 5 (p.137)
	7b	When applicable, explanation of any interim analyses and stopping guidelines	-
Randomisation:			

Sequence generation	8a	Method used to generate the random allocation sequence	Chapter 5 (p.137), Chapter 8 (p.178)
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	p.178
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	p.178
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Chapter 5, Chapter 7 and Chapter 8 (p.178)
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	p.178-179
	11b	If relevant, description of the similarity of interventions	p.180
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	p.180
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	p. 180
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	p.182-183
	13b	For each group, losses and exclusions after randomisation, together with reasons	p.181
Recruitment	14a	Dates defining the periods of recruitment and follow-up	p.181
	14b	Why the trial ended or was stopped	-
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	p.182
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	p.181-182
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	p.183-185
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	p. 183-185

Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	p. 183-185
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	p. 182- 190
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	p.191-192
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	p.192
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	p.190-192
Other information			
Registration	23	Registration number and name of trial registry	p.176
Protocol	24	Where the full trial protocol can be accessed, if available	Chapter 5
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	Not applicable

Table 2: Checklist for items in STRICTA 2010

Item	Detail	Page number
1. Acupuncture rationale	1a) Style of acupuncture (Traditional Chinese Medicine)	Chapters 2, 5, 7 and 8
	1b) Reasoning for treatment provided, based on historical context, literature sources, and/or consensus methods, with references where appropriate	Chapters 2, 3, 5, 7 and 8
	1c) Extent to which treatment was varied	Chapter 5 (p. 136) Chapter 7 Chapter 8 (p. 177, 178 and 180)
2. Details of needling	2a) Number of needle insertions per subject per session (mean and range where relevant)	Chapter 8 (p. 180)
	2b) Names (or location if no standard name) of points used (uni/bilateral)	Chapter 5 (p.140) Chapter 8 (p.180)
	2c) Depth of insertion, based on a specified unit of measurement, or on a particular tissue level	Chapter 8 (p.180)
	2d) Response sought	Chapter 8 (p.180)
	2e) Needle stimulation (manual)	Chapter 8 (p.180)
	2f) Needle retention time	Chapter 8 (p.180)
	2g) Needle type (diameter, length, and manufacturer or material)	Chapter 8 (p.180)
3. Treatment regimen	3a) Number of treatment sessions	Chapter 5 (p. 137) Chapter 8 (p.179-180)
	3b) Frequency and duration of treatment sessions	Chapter 8 (p.178)
4. Other components of treatment	4a) Details of other interventions administered to the acupuncture group (e.g. moxibustion, cupping, herbs, exercises, lifestyle advice)	Not applicable
	4b) Setting and context of treatment, including instructions to practitioners, and information and explanations to patients	Chapter 8 (p.178-180)
5. Practitioner background	5) Description of participating acupuncturists (qualification or professional affiliation, years in acupuncture practice, other relevant experience)	Chapter 8 (p.178-179)
6. Control or comparator interventions	6a) Rationale for the control or comparator in the context of the research question, with sources that justify this choice	
	6b) Precise description of the control or comparator. If sham acupuncture or any other type of acupuncture-like control is used, provide details as for Items 1 to 3 above.	Chapter 8 (p.180)

Primary and secondary endpoints should have been more clearly defined and definitions of "success" should have been explicitly made: e.g. did all primary outcomes need to be achieved?

Our aim was to assess the endpoints relevant to RA patients after the acupuncture interventions, such as pain and functional capacity, that may improve RA patients' autonomy in daily living activities and might have an impact on their quality of life.

Primary and secondary endpoints were designated on the protocol of this study, approved by the ethical committee of the Faculty of Medicine, University of Coimbra (ref. CE-048/2015) and assessed in the randomized clinical trial.[4,5]

Outcome Measures[4,5]

Primary clinical outcomes

(1) Pain (assessed with a Visual Analogue Scale (VAS) ranging from 0 (no pain) to 10 (maximum pain)),

    (2) Pain pressure threshold in the hand (assessed with a Pressure Algometer),[6]

    (3) Arm Strength (AS) and Hand Grip Strength (HGS) (assessed with a Jamar® Hydraulic Hand Dynamometer (Patterson Medical®)).

Secondary clinical outcomes

    (1) Functional ability and health status (assessed with the Disability Index of the Health Assessment Questionnaire),

    (2) Health Realted Quality of Life (HRQoL) (assessed using the Medical Outcome Short Form-36 health survey),

    (3) Disease activity score-28 for RA,

    (4) Erythrocyte sedimentation rate (ESR) and c-reactiv protein (CRP) blood levels.

The definitions of the primary and secondary endpoints assessed can be found in the Chapters 1, 3, 5 and 6. To assess the clinical efficacy and safety of a health intervention, medical or not, the outcomes recommended by the European Medication Agency, pain as well as physical and emotional function, need to be assessed with validated instruments and in well-designed randomized controlled parallel group studies.[7] However, the definition of "success" of endpoints can be very questionable. For example, clinicians may be content with the lack of synovitis and low blood inflammatory parameters while RA patients suffer due to depression or fatigue. Thus, a new field of nursing interventions with positive impact on patients' symptoms need to be explored, and the definition of "success" needs to be adjusted to patients.

Nearly 85% of patients have trouble doing household chores, and often women require more assistance than men. Patients report that their disease makes them less independent and interferes with their activities like working, participating in hobbies and having support, thereby reducing their quality of life.[8]

The nurses are part of multidisciplinary care team and can play a key role in the field of chronic disease areas such as RA. This includes the recognization of the various ways in which RA can cause pain, physical disability and poor quality of life, and to provide advice on RA management using non-pharmacological treatments characterized by evidence-based practice. Acupuncture, an intervention that may provide analgesia by creating up-regulation of endogenous opioids and serotonin, regulate inflammation and increase function, seems to be a promissory choice.

Pain management is a critical issue in the management of RA, and in this study it was one of the most important outcome measures, because inflammation is not the only cause of pain in RA and, when left untreated, non-inflammatory pain can have tremendous impact on patients' quality of life and mobility.[8]

As pain is always subjective, patient self-reported measures such as Visual Analog Scale (VAS) provide the most valid measure of the experience but none self-assessment pain instrument is completely free of limitations.[7] According to the European Meadication Agency, 30 or 50 percent reduction in pain intensity compared to baseline might be appropriate for chronic pain conditions.[7]

As chronic pain interferes with multiple aspects of function, additional patient reported outcome (PRO) measures of physical function and health-related quality of life are recommended as secondary endpoints, if supportive independent validation is provided.

To assess acupuncture effects, RCTs with objective outcomes are necessary to support differentiation between real and false acupuncture. To measure pain severity objectively is difficult and at present no validated objective measures are available that would be feasible in clinical trials.[7] To address the aforementioned challenge of this study, the pain pressure threshold in the hand of RA patients was measured with a Pressure Algometer (PA) device, specifically designed by us to objectively assess the hand pressure tolerated by RA patients. Limitations of this advice and its validity were reported.[6] This was an instrument specifically built for this RCT. No evidence-base was done before to establish the minimum clinically important difference for assessing improvement or deterioration from baseline.[5] However, it is clear that even a minimal increase on the pressure threshold tolerate will mean for the RA patients an increase in them daily activities and social lives.

The negative consequences of RA on the physical function of patients are multidimensional, involving decrease of strength and restricted range of joint movement. Functional disability causes psychosocial stress affecting the perception of pain. Disability also causes a loss of income to the individual and to society at large. It is estimated that there is a total annual societal loss of approximately $40 billion dollars when taking intangible and indirect costs into account.[8] If we offer RA patients an intervention that improves patients' strength and still decreases pain, it might make the difference necessary for a RA patient to be able to open a water bottle on his own.

We assessed HRQoL using the Medical Outcome Short Form-36 health survey (SF-36). SF-36 consists of a self-assessment tool that measures personal and individual functional health and wellbeing parameters. The scores ranged from 0 (worst) to 100 (best) for each of the eight domains (bodily pain, general health, physical functioning, role-physical, mental health, role-emotional, social functioning and vitality). We established the minimum clinically important difference for assessing improvement or deterioration as a 2.5 to 5 points difference from baseline.[5]

For the remaining endpoints, no minimum clinical values of improvement or deterioration were established. Clinical success was assessed by statistical analysis of the outcomes measurements and statistical significant differences between the baseline and after the last treatment. The significance level adopted was 0.05. Analyses before and after all the treatments were also done to assess patients progress during the treatments.

To sum up in our protocol we did not define how many primary and secondary outcomes needed to be achieved, but our results have shown that the pain in the intervention group decreased and the pressure threshold as well as the strength increased. In our opinion every outcome parameter that improved statistically significant was a success.

A variety of outcomes that encompass the relevant scope of disease manifestations were used to assess evidence-based of acupuncture effects, in one context that incorporate acupuncture as part of contemporary Chinese medicine as a model of system biology.

Nevertheless, there is a growing trend amongst nurses and the general public, to seek systems of health care that take a holistic approach. Again this statement refers to the rising popularity of acupuncture.[9]

Through the implementation of acupuncture into their practice, nurses are given an ideal opportunity to reinstate the concept of holistic care which orthodox nursing practices have not yet, and may never achieve.[9]

Further research is needed to explore whether acupuncture long-term effects can be obtained and if treatment variations may be necessary to achieve this.[5] Future follow-up studies may include a couple of new outcomes necessary to determine the therapeutic success in a nurse-led patient care model and patient viewpoints.

The reader needs to be made sure that the patients included effectively had Rheumatoid Arthritis: what, exactly, were the criteria? who applied them? Were these confirmed by a third party? Can this be verified now?

We included adult (≥18 years) RA patients with involvement of the hands and disease classification according the American College of Rheumatology (ACR) (10) criteria. The RA and ACR criteria were applied by independent rheumatologists and internal medicine doctors that had not been involved in the study.[5]

Patients whose diagnosis for RA was not clearly defined were excluded.[5] Questions regarding the diagnosis of RA, that conditioned the inclusion or exclusion of participants, were discussed with a third element, a physician specialist in internal medicine, that had also not been involved in the study project.

All included patients were subscribed in the national digital platform for the register of rheumatic patients (reuma.pt).

We used an anonymized sample, so at the moment it cannot be verified if the patients included effectively had RA. However, if the doctors conducted a proper diagnose we believe that will continue to be verified.

The reader needs to understand what percentage of patients with Rheumatoid Arthritis met the inclusion/exclusion criteria. How many patients were examined before this number was reached? Percentage seropositive? What was the state of their disease at the time of intervention: disease activity, structural damage, functional status, medication? Otherwise it is not possible to understand to whom the results can apply.
In case this information is not available the candidate is invited to discuss the potential implications in terms of validity and interpretation of the results.

To answer these questions, it is important to remember the inclusion criteria of this study:[5]

      (1) previously signed an informed consent,

(2) active RA fulfilling the ACR criteria as assessed by an independent rheumatologist not involved in the study,

(3) chronic pain over a minimum period of three months prior to recruitment,

(4) had current pain greater than 30/100 mm on a VAS despite medication and stable dose treatment for at least 3 weeks,

(5) impairment of hand strength,

(6) pain worsened by grip in the fingers worse than in the knuckles or in the thumb,

(7) showed the clinical picture of a pivotal or TPS according to the criteria defined previously and diagnosed by a Chinese medicine (CM) practitioner with a master degree in CM.

The study flow chart and the reasons for discontinuation are shown in figure 1.[5] As described in our protocol (Chapter 5), our first task aimed to ascertain if objective assessment strategies could help to determine the Chinese medicine functional diagnosis in a non-experimental, exploratory study. In this first task, of the 284 RA patients enrolled, 100 were excluded, of which, 57 participants did not meet one or more of the inclusion criteria mentioned above with the numbers 1, 2, 3, 4 or 5; 39 patients have been excluded for not meeting the inclusion criteria number 6 and more four participants have been excluded for not meeting the inclusion criteria identified with the number 7.
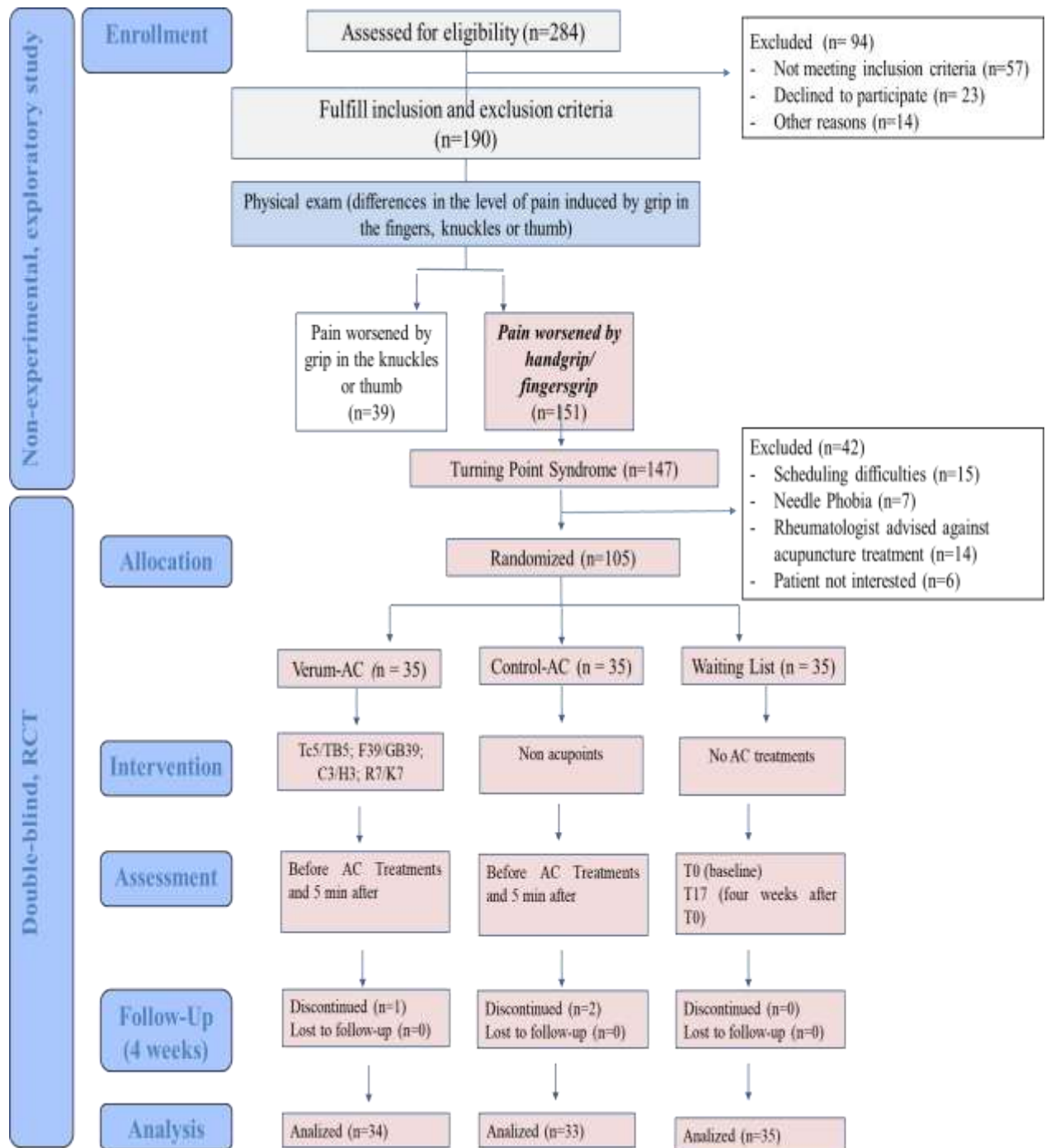
Figure 1: Study flow diagram and patients' progress through the trial (adapted from Seca et al 2018)[5].

AC (acupuncture); non acupoints = sham acupuncture points; no AC treatments = without acupuncture treatments.

Our second task aimed to objectively assess the safety and efficacy of acupuncture on pain, functional disability and HRQoL in RA patients of the hand. 151 (79.5%) RA participants showed pain worsened by grip in the fingers more than in the knuckles or thumb, and 147 of these patients were diagnosed, according to the CM diagnose process, with the TPS (figure 1). Of those 147 eligible patients, 105 patients were randomized (figure 1).

Demographic, clinical features and CM functional vegetative state assessments, according to the symptoms and signs manifested by RA patients, with hand pain worsening by handgrip (n=105) were described in two of our published papers.[5,11]

Summary information concerning percentage of seropositive patients and the state of their disease at the time of intervention (disease activity, structural damage, functional status and medication) can be found in tables 3 and 4 below. There were no significant differences in baseline characteristics between the three groups.

Table 3: Clinical characteristics of RA patients assessed to the RCT (baseline) (adapted from Seca et al 2018)[5]

		Total sample (n=105)	Verum AC (n=35)	Control AC (n=35)	Waiting list Group (n=35)
Positive serum test for rheumatoid factor, n (%)		67 (68.4%)	23 (74.2%)	24 (72.7%)	20 (58.8%)
DAS28-CRP (remission: low disease activity: moderate disease)		72 (68.6%): 25 (23.8%): 8 (7.6%)	21 (60%): 11 (31.4%): 3 (8.6%)	26 (74.3%): 7 (20%): 2 (5.7%)	25 (74.4%): 7 (20%): 3 (8.6%)
Erosive Disease (yes: no)		64 (64%) : 36 (36%)	21 (61.8%) : 13 (38.2%)	20 (64.5%) : 11 (35.5%)	23 (65.7%) : 12 (34.3%)
Early morning stiffness (minute)		15 (5, 25)	15 (10, 25)	10 (0, 27.5)	15 (7.5, 20)
Pharm.Treat.	**NSAID (yes: no)**	91 (86.7%): 14 (13.3%)	27 (77.1%) : 8 (22.9%)	31 (88.6%): 4 (11.4%)	33 (94.3%): 2 (5.7%)
	BIOLOGICAL (yes: no)	54 (51.4%): 51 (48.6%)	17 (48.6%): 18 (51.4%)	15 (42.9%): 20 (57.1%)	22 (62.9%): 13 (37.1%)
	DMARD (yes: no)	93 (88.6%): 12 (11.4%)	29 (82.9%): 6 (17.1%)	32 (91.4%): 3 (8.6%)	32 (91.4%): 3 (8.6%)
	ANALGESICS (yes: no)	66 (62.9%): 39 (37.1%)	22 (62.9%): 13 (37.1%)	22 (62.9%): 13 (37.1%)	22 (62.9%): 13 (37.1%)

NSAID (Nonsteroidal anti-inflammatory drugs); DMARD (Disease-Modifying antirheumatic drugs).
Data are presented as number (frequency); mean ± SD (standard deviation) or median (1st quartile, 3rd quartile). There was no significant difference in any of the characteristics between the three groups.

Table 4 – Functional status of RA patients assessed to the RCT (baseline) (adapted from Seca et al 2018)[5]

	Verum AC	Control AC	Waiting list Group	*p-value*
SECUNDARY OUTCOMES				
HAQ (1–4, 4 worst health)				
Baseline	1.375 (1, 1.8125)	1.25 (0.4375, 1.625)	1.125 (0.875, 1.375)	0.062

HAQ (Health assessment Questionnaire). Data are presented as median (1st quartile; 3rd quartile). *p-value* (probability value) adopted was 0.05, *p<0.05 comparing before and after treatment.

Therapies used by patients prior and during the RCT must be accounted for in detail to ensure comparability.

Summary information concerning RA patients' medication are described in table 5. There were no significant differences in baseline characteristics between the three groups.

Table 5: Therapies used by RA patients prior and during the RCT (adapted from Seca et al 2018)[5]

			Total sample (n=105)	Verum AC (n=35)	Control AC (n=35)	Waiting list Group (n=35)	p-value
Pharm.Treat.	**NSAID (yes: no)**		91 (86.7%): 14 (13.3%)	27 (77.1%) : 8 (22.9%)	31 (88.6%): 4 (11.4%)	33 (94.3%): 2 (5.7%)	0.144
	BIOLOGICAL (yes: no)		54 (51.4%): 51 (48.6%)	17 (48.6%): 18 (51.4%)	15 (42.9%): 20 (57.1%)	22 (62.9%): 13 (37.1%)	0.226
	BIOLOGIC.	**Infliximab**	25 (23.8%)	8 (22.9%)	8 (22.9%)	9 (25.7%)	
		Etarnercept	23 (21.9%)	6 (17.1%)	8 (22.9%)	9 (25.7%)	
		Adalimumab	6 (5.7%)	2 (5.7%)	2 (5.7%)	2 (5.7%)	
		Abatacept	2 (1.9%)	1 (2.9%)	0	1 (2.9%)	
	DMARD (yes: no)		93 (88.6%): 12 (11.4%)	29 (82.9%): 6 (17.1%)	32 (91.4%): 3 (8.6%)	32 (91.4%): 3 (8.6%)	0.577
	DMARD	**Methotrexate**	38 (36.2%)	13 (37.1%)	12 (34.3%)	13 (37.1%)	
		Hydroxychloroquine	20 (19.1%)	8 (22.9%)	6 (17.1%)	6 (17.1%)	
		Leflunomide	11 (10.5%)	3 (8.6%)	5 (14.3%)	3 (8.6%)	
		Sulphasalazine	50 (47.6%)	17 (48.6%)	18 (51.4%)	15 (42.9%)	
	ANALGESICS (yes: no)		66 (62.9%): 39 (37.1%)	22 (62.9%): 13 (37.1%)	22 (62.9%): 13 (37.1%)	22 (62.9%): 13 (37.1%)	1.000
Use of non-pharmacological treatments (yes: no)			72 (68,6%): 33 (31.4%)	22 (62,9%): 13 (37.1%)	21 (60.0%): 14 (40.0%)	29 (82.9%): 6 (17.1%)	0.081
Non-pharmacological treatments		**Thermotherapy**	8 (7.6%)	1 (2.9%)	0	7 (20%)	
		Pilates/ Yoga	5 (4.8%)	2 (5.7%)	1 (2.9%)	2 (5.7%)	
		Physiotherapy	35 (33.3%)	10 (28.6%)	12 (34.3%)	13 (37.1%)	
		Massage	6 (5.7%)	2 (5.7%)	2 (5.7%)	2 (5.7%)	
		Others	18 (17.1%)	7 (20%)	6 (17.1%)	5 (14.3%)	

NSAID (Nonsteroidal anti-inflammatory drugs); DMARD (disease-modifying antirheumatic drug). Data are presented as number (frequency); mean ± SD (standard deviation) or median (1st quartile, 3rd quartile). There was no significant difference in any of the characteristics between the three groups.

All patients were under stable doses of biomedical combination therapies including nonsteroidal anti-inflammatory drugs, disease-modifying anti-rheumatic drug, biologics and analgesic drugs, and were instructed not to change their usual therapies including their doctors' recommendations to rescue medication during the study.

Assessment of rescue medication was not done. Future studies can be improved by doing a daily report of the rescue medication and the impact on the trial results should be explored as appropriate

in the analyses of efficacy and safety. For example, the need for rescue medication as an indicator of treatment failure may be defined as a trial endpoint (e.g. dose requirement, time to rescue or time to non-trial analgesia as appropriate).

Please discuss the appropriateness of the duration of the RCT, namely in view of the European Medicines Agency regarding acute or chronic treatment of pain.

The European Medicines Agency (EMA) is an agency of the European Union in charge of the evaluation and supervision of medicinal products for human and veterinary use including biologics and advanced therapies and herbal medicinal products.

Although this is a RCT where the effects of a non-pharmacological intervention (acupuncture) have been assessed, a critical analysis regarding the duration of this study was done as shown below.

The old ortodox current model of research into a pharmacological agent it is a challenge in clinical practice. This is especially critical when it is used to pain treatment research and, particularly in the case of acupuncture treatments, can underestimate its value.

According to the International Association for the Study of Pain, pain is a complex interplay between pathophysiological, psychological, genetic, environmental, socioeconomic and emotional factors, involving various neurobiological mechanisms and interactions between peripheral and central nervous system pathways. Persistent or recurrent pain lasting longer than 3 months and beyond various complex mechanisms (e.g. persistent inflammation, peripheral or central sensitization, neuroplastic events, catastrophizing, avoidance behaviour) may lead to a transition into chronic pain, a condition that often is difficult to treat and the response to currently available pain treatments is highly variable.[7]

EMA guidelines for the treatment of the pain indicate that all efforts should be made to obtain a robust double-blind setting following a clearly pre-specified algorithm in line with the expected clinical use of the product and, the sustained therapeutic effect in chronic pain should in general be demonstrated in pivotal efficacy randomized controlled trials with a treatment period of at least 12 weeks.[7]

While this approach contains some practical advantages, it also contains some risks. It is recognized that there are a number of substantial challenges in chronic pain trials that can ultimately lead to study failure. This happened in drug trials in conditions such as chronic low back pain whose results have often been inconclusive.[7] So, EMA guidelines, under realistic conditions, are not always possible to follow.

The treatment underlying our study was developed in the Heidelberg School of CM, where treatments of RA have frequently been performed for two decades in a similar manner as designed in this work. According to clinical observations in the Heidelberg School of CM, after the intensive treatment of four weeks, patients' symptoms improved. Consequently, the frequency is then gradually reduced to one session every three weeks and symptoms remain on a comparable level.[5]

We developed a RCT that all acupuncturists can accept as truly reflecting the practice experience and, after four weeks' treatment, we have shown that patients treated with verum acupuncture improved

in all clinical symptoms except inflammation measured by CRP and ESR, which resulted in less pain, better functional ability and improved HRQoL.[5] However, and as we mentioned in our published paper, further research is needed to explore whether long-term effects can be obtained and if treatment variations may be necessary.[5]

Please discuss the adequacy of the sites used as "sham" in the context of published literature on the topic.

Acupuncture points or acupoints are used ubiquitously in research protocols and they are collectively different from "non-acupuncture points" or "sham" or "false" acupoints.[12]

The term acupoint is used in two different ways. One is to describe a general area based on anatomical landmarks found in acupuncture textbooks, the other is to describe a discrete "point" in the general vinicity of the designated anatomical area, yet with an exact location with varies, contigent on local tissue qualities (texture, stiffness, moisture, or temperature are different compared with surrounding tissues) that elicit specific neurovegetative alterations and may change over time within a person.[12]

Acupuncture experiments attempting to test whether the "verum" acupuncture points have specific effects compared to "sham" acupuncture points typically confound the following anatomical levels: body region (e.g., head, arm and abdomen), anatomical location (e.g., anatomical description of an acupoint) and "point" (e.g., small depression palpable on the skin in the vicinity of an acupuncture point location) (please see figure 2).
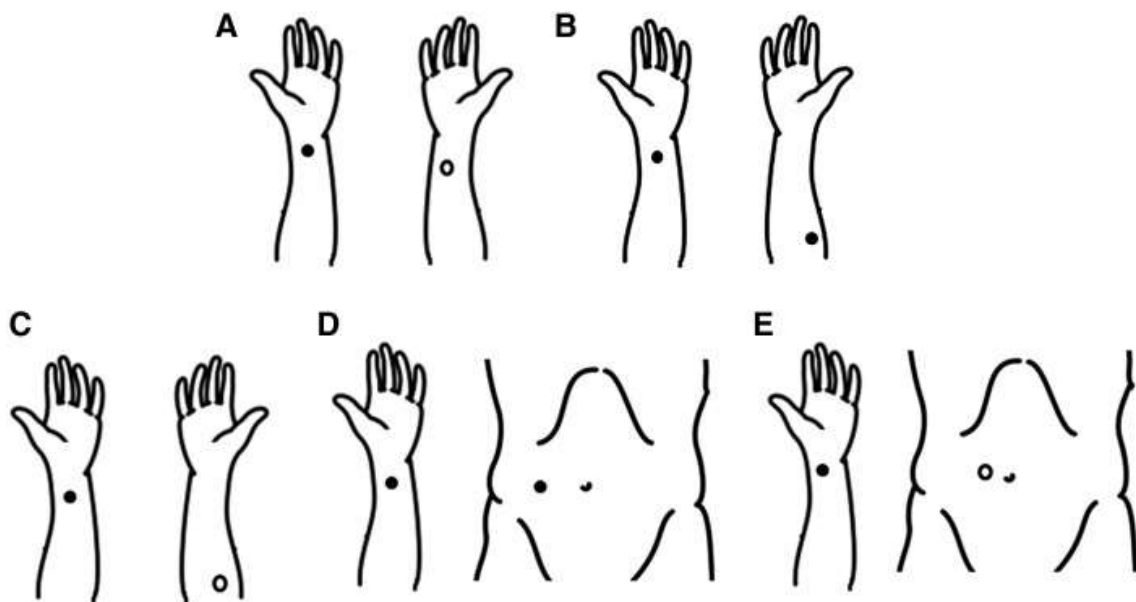
Figure 2. Examples illustrating nonconfounded (**A, B**) and confounded (**C–E**) experimental designs. (**A**) Nonconfounded design comparing point type (acupuncture point vs. non-acupuncture point) within the same anatomical location. (**B**) Nonconfounded design comparing anatomical locations within same body region. (**C**) Design confounding point type and anatomical location. (**D**) Design confounding anatomical location and body region. (**E**) Design confounding point type, anatomical

location, and body region. *Closed* and *open circles*, respectively, denote "acupuncture" and "non-acupuncture" point locations.[12]

If one wants to test whether needling of a small palpable "point" differs from a "non-point", one must compare the two conditions within the same anatomical location (Fig. 2A). Comparing an acupuncture point on the arm with another acupuncture point on the abdomen confounds anatomical location with body region (in this case, body regions would systematically differ with respect to subcutaneous tissue thickness, fascia and muscle depth).[12]

In our study we chose distal acupuncture points for the treatment of the underlying systemic inflammatory disease as well as local acupoints treating the arthritis of the nearby hand joints. The non-acupuncture points or "sham" acupoints chosen were located on the same anatomical location but in points located outside of the meridian points and of the extra-meridians (see figure 3) (for example the acupuncture point C3/H3 and non-acupoint were both located on the arm). The needling location of non-acupoints was marked a certain constant distance away (1 or 2 cm medial or lateral) from the palpable acupoint.

(A) ● Real acupuncture points
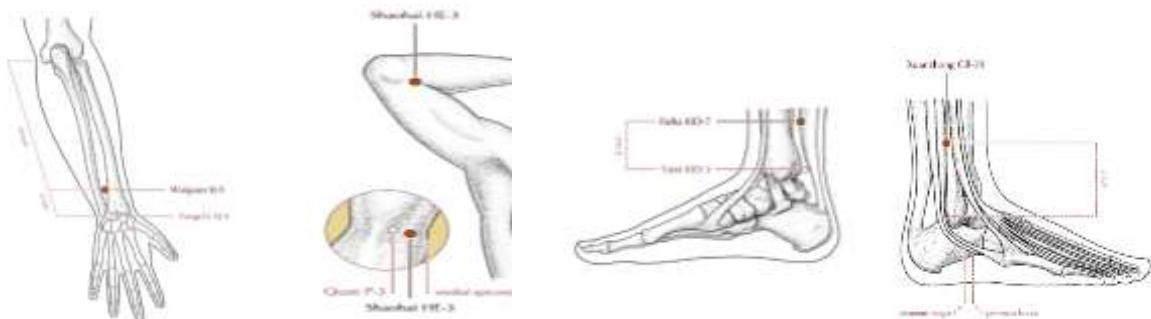
(B) ● Sham acupuncture points (points outside of the meridian points and of the extra-meridians)

Figure 3. Intervention points: (A), red circles denote real or verum acupuncture points; (B) blue circles denote sham or false acupuncture points. (Adapted from Susana Seca, Research Project presented to the ethical committee of the University of Coimbra and approved in May 2015)

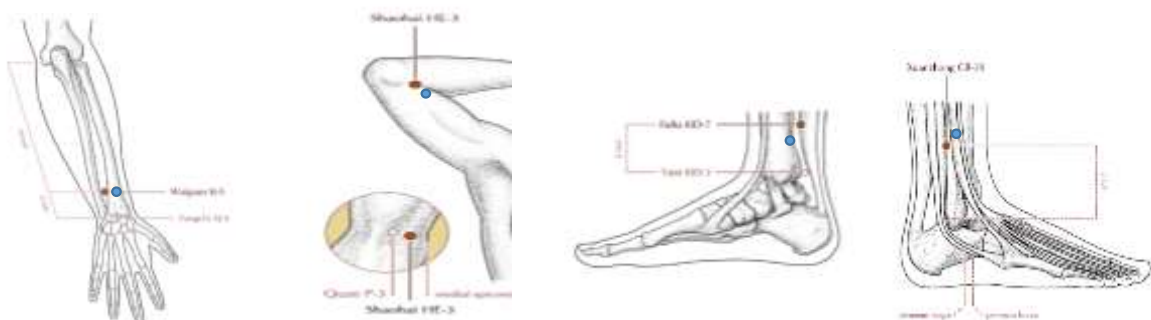The key point to remember when performing sham acupuncture is that it is absolutely critical that the patient be unaware of whether or not they are receiving sham or true acupuncture. The method and time of puncture, number of needles must to be the same on all study groups, as well as same depth of insertion, but point selection is based on using areas that are external to the meridian courses to avoid the puncture in acupoints.[2]

The use of placebo or sham is essential for differentiating non-specific from specific treatment effects.[2] Five main types of sham control have been employed in acupuncture research:[2,13] pseudo-acupuncture intervention (such as touching the skin with a toothpick), non-penetrating sham needles devices, superficial needling of appropriate acupuncture points, needling non-channel points and needling "irrelevant" channel points.

As discussed in one of the systematic reviews included in this work, we consider to exist consequences for the sham intervention to be chosen.[2] Trials using pseudo-acupuncture intervention (such as touching the skin with a toothpick, streitberger placebos, shallow 2mm needlings or pyonex controls) the dosage of penetration is zero or low. The use of different numbers of needles in verum and control interventions lead the searchers to compare high dosage of needling in the verum versus low dosage of penetration in controls.[2] Superficial needling of the same acupuncture points needled in the real acupuncture group, and the use of non-penetrating "placebo needle" devices are clearly not inert controls, have marked similarities responses, as already shown by fMRI, and therefore are not suitable for sham control protocols.[12] Needling channel points which are deemed to be clinically irrelevant to the condition treated as form of sham control has its hazards because there is no literary record of which points have no effect on a target action.[12]

In our study we decided to needle non-channel points being aware that they might not be inert and could overlap to some extent with the effects of real acupuncture. However, Wu et al found in a fMRI study, comparing needling channel points with needling non-channel points, some activations/deactivations of brain centers which were seen only in response to needling channel points.[12]

Sham controls not being inert is one problem. When a sham protocol is active, the difference between the real and sham will be reduced by the degree of activity of the sham control. This is a problem not exclusive to acupuncture, but is also a challenge for other complex interventions such as surgery, for which researchers struggle to design a sham protocol which is both credible and inert.[13]

Please discuss the appropriateness and quality of the validation of the algometer for the purposes of the RCT.

Pressure Algometry (PA) can be an outcome that nurses are able to use in the assessment and management of patients' pressure threshold as well as for the research settings to measure and quantify an individual's pain experience by determining the pressure-pain threshold in a chronic disease as RA, whose patients' autonomy is often compromised by pain and decreased hand strength.

Quantification of acupuncture effects for relieving pain and reduce inflammation associated to RA is still a problem. To objectively assess the effects of acupuncture in the pain of the hands of selected patients with RA, we needed to develop a specific device to measure the pain tolerance threshold of these individuals whose features were related to specific Chinese medicine syndromes.[6]

Although there is a wide range of PA devices used to assess the pain tolerance threshold and assist in the management of therapy, according to our previous research, we have no knowledge of a validated and adequate PA device to RA patients that would allow us to measure the force applied in two different situations: the force applied at two points considering the hand grip and the thumb resistance force.

In that way, we developed a specific PA, adapted to a computerized system, with the aim to objectify the variability effects of a standardized acupuncture treatment by a physically measurable parameter. Therefore, we compared the outcome of clinical acupuncture, as measured by VAS and PA, in a sample of 14 RA patients and with a specific vegetative functional state called Turning Point syndrome (TPS), to see whether the methods lead to correlating results.

The methodology to build and validate this device took place in five steps:

Literature review and establishment of a conceptual framework.

Definition of the objectives of the instrument to the population involved.

In strict cooperation with the Biomedical Engineer department of the Engineer Faculty of the University of Porto, we developed a novel pressure-sensitive sensor device which allows to assess and precisely determine the hand pressure tolerated (in Kgf) until the pain starts during the hand grip. This device was built based on adjustments made by experts on the field of Chinese medicine, rheumatology, physiotherapy and biomedical engineering.

A quasi-experimental nature design was developed, to test the device in a group of RA patients with a specific vegetative functional state called TPS before we performed the double-blind randomized controlled trial.

To estimate the validation of the instrument, statistical analysis of the data collected in the experimental study was performed comparing the VAS with the algometry results.

We observed an increase in the pressure tolerated by the hand (objective measurement) and a decrease of the self-reported pain, assessed by VAS score (subjective measurement).[6] The PA device tested have proven to be correctly adjusted to quantify objectively the individual hand grip pressure toleration variability of RA patients before and after the acupuncture treatments.

The validity of an instrument occurs when its construction and applicability allow the faithful measurement of what it is intended to evaluate, that is, if the content of an instrument effectively analyzes the requirements to measure the phenomena to be investigated. To guarantee the quality of an instrument it must guarantee reliability and validity. Reliability is the ability of an instrument to accurately measure a phenomenon. Validity is the ability of an instrument to accurately measure the phenomenon to be studied.[14]

Given these considerations and in the view of the goal proposed to this device, we consider that the instrument has achieved a good level of internal consistency, has content validity (attested by a team of experts and a previous experimental study), showing to have the necessary theoretical attributes required to be used in the RCT designed.

We can say that the PA instrument has been validated, but it is important to note that there may be standard-errors and it may have certain limitations such as the non-applicability to other CM syndromes, a not comparability with devices already created, the fact that it does not have a patient controlled 'stop' button and that we may not have enough data that allows us to define the ideal sample size to satisfactorily estimate how valid this specific device is for other studies.[5]

However, it is noteworthy that the evaluation of the validity of any measuring instrument should be a continuous and permanent process, so as to enable the early detection of any adaptation or reformulation needs, thus enabling its applicability and taking into account the different contexts that appropriate it.[15]

The calculation of the sample size should be presented in full with a clear description of the method used. Please specify the outcome guiding the calculations and the foundations supporting the choice of alfa = 0.2.

We used an alpha of 0.05, as it is the value traditionally applied in the large majority of published papers.

If you may observe in the last paragraph of the Statistical Methods section of our paper,[5] we report: the analyses were performed on IBM SPSS Statistics 24 and on R 3.3.2. The significance level adopted was 0.05. However, it might be unclear on the thesis because in the same paragraph were we state how the sample size was calculated, we report the values of 0,05 for alpha and beta and the value of 0,2 for the effect size considered, which may also be a beta value to take into account.

Thus, the procedure for the sample size determination is better explained below.

We intended to apply a repeated measures ANOVA using a within-between design with 2 measurements (baseline and final) and three groups (Verum, Control and Waiting List) to evaluate changes in the primary outcome, considering a 0 to 10 scale as a quantitative measure as high variability is expected in these values. We used the ANOVA test statistic value (f) as an effect measure, considering that a value of f = 0.2 is a medium effect size, according to Cunningham JB, 2007.[16]

For this expected effect size (f=0.2), which corresponds to a critical F always above 3, we computed the needed sample size using G*Power, version 3.1.9.2, considering a type I error (alpha) of 0,05 and a type II error (beta) ranging from 0.05 to 0.20, corresponding to an expected achieved power of 0.80 to 0.95. We also considered that the correlation between both measurements should range between 0.40 and 0.60 and a nonsphericity correction of 1. For these assumptions we obtained the following:

		0.05	0.10	0.15	0.20
			Beta		
Correlation	0.40	120	99	87	78
between	0.50	102	84	72	66
baseline and final	0.60	81	69	60	54

F tests – ANOVA: Repeated measures, within-between interaction
Number of groups = 3, Number of measurements = 2, Corr among rep measures = 0.5,
Nonsphericity correction ε = 1, α err prob = 0.05, Effect size f = 0.2
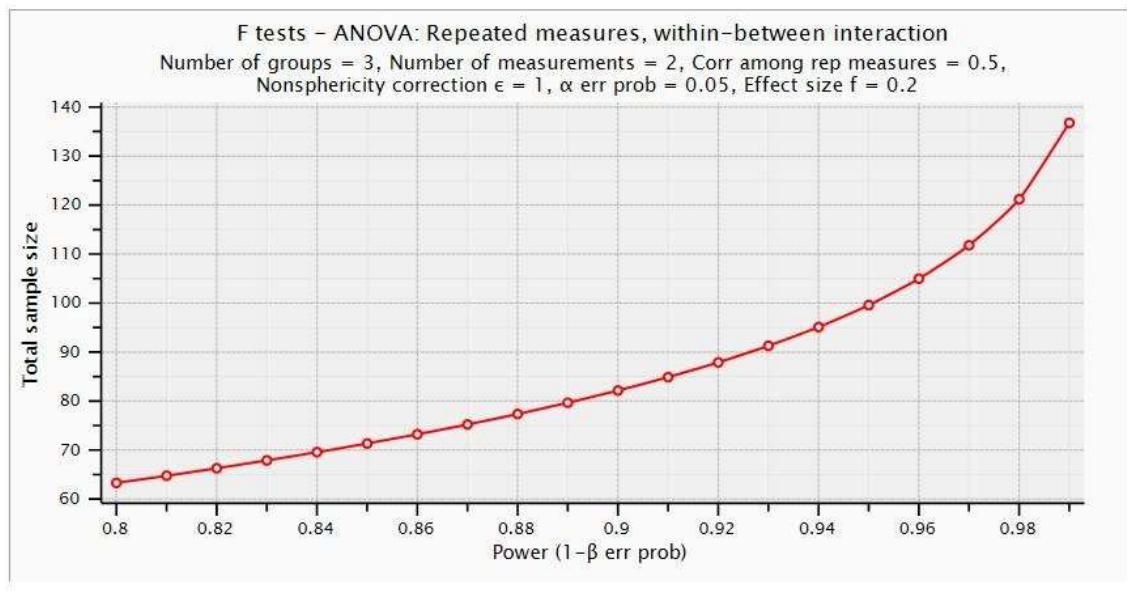
Considering these assumptions, and also that we would achieve a minimal correlation between both baseline and final measurements of 0.5, we would need a 102 sample size to detect a difference in the pain and functions outcomes with a 95% statistical power. However, in these type of follow-up studies it is reasonable to consider a lost to follow-up/dropout rate of 10%. Thus, the actual sample size recommended to the procedure, considering multiples of three in order to achieve a 1:1:1 ratio between sample size groups, should be 111, which is equivalent to have 37 subjects in each one of the three groups.

However, the lack of assumptions met thrower us to the use of univariate statistics but we have considered that if a sample size is adequate for more elaborated statistical analysis, it would also be adequate for this simpler solutions.

Statistical description and analysis should not be limited to median (IQR) and nonparametric tests, unless normal distribution was never confirmed.

Each categorical variable was described by its absolute and relative frequencies while each quantitative variable was described by its median, 25th percentile and 75th percentile. Chi-square and Fisher tests were used to assess the association between categorical variables. Shapiro-Wilk tests were performed to assess the normality of quantitative variables. When they were normally distributed, ANOVA was used to verify whether statistically significant differences exist between the verum,

control and waiting list groups. When the normality requirements did not hold, Kruskal-Wallis tests were used instead. When the comparisons were performed between only two of the groups, t-Student tests or Mann-Whitney tests were used, as applicable. Within each of the three groups, Wilcoxon tests were used to assess whether quantitative outcomes were altered with statistical significant differences between the baseline and after the last treatment. The analyses were performed on IBM SPSS Statistics 24 and on R 3.3.2. The significance level adopted was 0.05.[5]

The comparison of baseline characteristics between the experimental (verum) and the control group should be discussed as well as the need to perform statistical analysis on these data.

RA patients included in this RCT were randomly assigned in a 1:1:1 ratio to either verum, control or waiting list group. Baseline outcomes were assessed for the first time before acupuncture treatments.[4,5] Demographic, clinical and outcomes assessments and statistical analysis of the participants of the three groups are described in table 6. There were no significant differences in baseline characteristics between the three groups (please see table 6). A detailed analysis and discussion of clinical signs and symptoms relevant for the diagnosis and treatment according to CM has been made and published in the European Journal of Integrative Medicine.[11]

Patients recruitment criteria were a very important requirement of our design, from both western and Chinese medicine's point of view. By that, we were able to homogenize the participants and determine the most appropriate acupuncture treatment for their characteristics.[4]

The comparison of baseline characteristics only between the verum and control groups seems unnecessary to us since in practice randomization was done before the treatments started and, in table 4 the reader can see tests of significance that utilize p-value to determine the statistical significance of the observed baseline difference in patients' characteristics were now added. However, this last practice has suffered wide criticism, and has been regarded as unnecessary, and this is why the tests of significance were not included in the original paper.

According Egbewale B. many authors disapprove of the use of hypothesis tests as means of comparing baseline characteristics across groups. They contest the practice whereby tests of significance are used to assess the comparability in respect of the magnitude of the baseline imbalance. Their argument is that there is no need for such tests, as a proper randomization procedure ensures that groups' differences are entirely due to chance, and all such tests seek to establish is that the observed difference could or could not have been due to chance. They also argue that researchers who use hypothesis tests to compare baseline characteristics report fewer significant results than expected by chance, thus suspecting a foul play in reporting. The procedure of hypothesis tests on baseline characteristics has been described as not only clearly absurd but also as unnecessary and might also be harmful.[17]

The consensus regarding baseline comparison of patients' characteristics appears to be that researchers should present the distributions of such baseline information of treatment groups in a table, thus, allowing readers to see the extent of similarities of the groups.[17]

Table 6: Demographic and clinical characteristics (baseline) (adapted from Seca et al 2018)[5]

		Verum AC (n=35)	Control AC (n=35)	Waiting list Group (n=35)	p-value	Observations
Gender (F:M)		31 (88.6%): 4 (11.4%)	30 (85.7%): 5 (14.3%)	33 (94.3%): 2 (5.7%)	0.625	Monte Carlo chi-square
Age (years)		57.31±11.3	56.46±16.43	57.66±11.07	0.926	One-way ANOVA
Duration of disease (years)		10.5 (5.25, 16.75)	15 (7.5, 21.5)	12 (7, 19)	0.361	Kruskal-Wallis test
Positive serum test for rheumatoid factor, n (%)		23 (74.2%)	24 (72.7%)	20 (58.8%)	0.331	Chi-square test
High blood cholesterol (yes: no)		18 (51.4%): 17 (48.6%)	16 (45.7%): 19 (54.3%)	15 (42.9%): 20 (57.1%)	0.765	Chi-square test
BMI score		26.34 (25, 28)	25.54 (24, 28.384)	25 (24.045, 27.15)	0.298	Kruskal-Wallis test
History of joint surgeries (yes: no)		16 (45.7%): 19 (54.3%)	17 (48.6%): 18 (51.4%)	15 (42.9%): 20 (57.1%)	0.891	Chi-square test
Erosive Disease (yes: no)		21 (61.8%): 13 (38.2%)	20 (64.5%): 11 (35.5%)	23 (65.7%): 12 (34.3%)	0.941	Chi-square test
Early morning stiffness (minute)		15 (10, 25)	10 (0, 27.5)	15 (7.5, 20)	0.268	Kruskal-Wallis test
Pharm.Treat.	NSAID (yes: no)	27 (77.1%): 8 (22.9%)	31 (88.6%): 4 (11.4%)	33 (94.3%): 2 (5.7%)	0.144	Monte Carlo chi-square
	BIOLOGICAL (yes: no)	17 (48.6%): 18 (51.4%)	15 (42.9%): 20 (57.1%)	22 (62.9%): 13 (37.1%)	0.226	Chi-square test
	DMRAD (yes: no)	29 (82.9%): 6 (17.1%)	32 (91.4%): 3 (8.6%)	32 (91.4%): 3 (8.6%)	0.577	Monte Carlo chi-square
	ANALGESICS (yes: no)	22 (62.9%): 13 (37.1%)	22 (62.9%): 13 (37.1%)	22 (62.9%): 13 (37.1%)	1.000	Chi-square test
Use of non-pharmacological treatments (yes: no)		22 (62,9%): 13 (37.1%)	21 (60.0%): 14 (40.0%)	29 (82.9%): 6 (17.1%)	0.081	Monte Carlo chi-square
PRIMARY OUTCOMES						
Hands Grasp Strength (Kgf)		13.45 (8.6, 18.28)	12.45 (8.66, 19.48)	11.47 (7.72, 16.95)	0.488	Kruskal-Wallis test
Arm Strength (Kgf)		9.34 (7.873, 14.24)	10.06 (7.14, 16.65)	8.47 (8.41, 9.79)	0.872	Kruskal-Wallis test

VAS (0–10, 10 worst health)	6 (4, 7)	5 (4, 7)	5 (4, 6)	0.304	Kruskal-Wallis test
Pressure Algometry (Kgf)	0.315 (0.20, 0.42)	0.37 (0.26, 0.52)	0.38 (0.30, 0.50)	0.074	One-way ANOVA
SECUNDARY OUTCOMES					
Health Related Quality of Life (SF-36 ITEMS) (0–100, 0 worst health)	Physical function	40 (25, 52.5)	40 (12.5, 62.5)	35 (27.5, 50)	0.966	Kruskal-Wallis test
	Role- physical	25 (0, 25)	25 (0, 62.5)	25 (12.5, 50)	0.135	Kruskal-Wallis test
	Bodily pain	31 (22, 41)	36.5 (22, 51)	41 (32, 46.5)	0.012	Kruskal-Wallis test
	General health	35 (27.5, 43.5)	35 (22.5, 42.5)	40 (30, 43.5)	0.642	Kruskal-Wallis test
	Vitality	30 (20, 47.5)	40 (22.5, 55)	40 (37.5, 50)	0.161	Kruskal-Wallis test
	Social Function	50 (37.5, 75)	62.5 (50, 81.25)	50 (37.5, 62.5)	0.189	Kruskal-Wallis test
	Role- Emotional	33.3 (33.3, 66.67)	33.33 (0, 66.67)	33.33 (16.5, 83.335)	0.575	Kruskal-Wallis test
	Mental Health	56 (40, 68)	56 (42, 84)	52 (42, 64)	0.427	One-way ANOVA
HAQ (1–4, 4 worst health)		1.375 (1, 1.8125)	1.25 (0.4375, 1.625)	1.125 (0.875, 1.375)	0.062	One-way ANOVA
Swollen Joints		2 (0, 2.5)	1 (0, 2)	1 (0, 2.5)	0.257	Kruskal-Wallis test
Tender Joints		2 (1, 4)	1 (0, 3)	1 (0, 2)	0.033	Kruskal-Wallis test
ESR		8 (2.25, 17.5)	8 (3, 14)	5 (2, 15)	0.710	Kruskal-Wallis test
CRP (mg/l)		0.28 (0.07, 1.05)	0.22 (0.1, 0.33)	0.17 (0.05, 0.28)	0.360	Kruskal-Wallis test

F (Female); M (Male); BMI (Body Mass Index); NSAID (Nonsteroidal anti-inflammatory drugs); DMRAD (Disease-Modifying Drugs); Kgf (kilogram force); VAS (visual analogue scale); SF-36 (Short Form 36); HAQ (Health assessment Questionnaire); ESR (*erythrocyte sedimentation rate*); CRP (*C-reactive protein).* Data are presented as number (frequency); mean ± SD (standard deviation) or median (1st quartile, 3rd quartile). *p-value* (probability value) adopted was 0.05. There was no significant difference in any of the characteristics between the three groups.

A statistical comparison of results should be made solely between the verum and the control group (excluding the waiting list group).

As figure 3 in our original paper summarizes, strength (arm strength and hand grip strength) and pain (VAS and PA) changes during acupuncture treatments in verum acupuncture and control acupuncture groups (please see below figure 4).[5]

Pressure Algometry

Visual Analogue Scale - Self-reported Pain
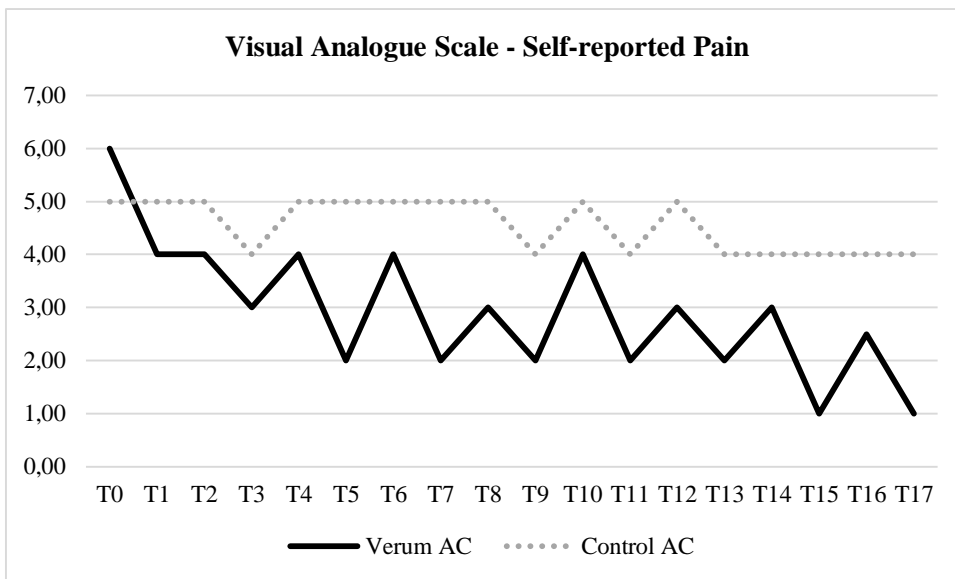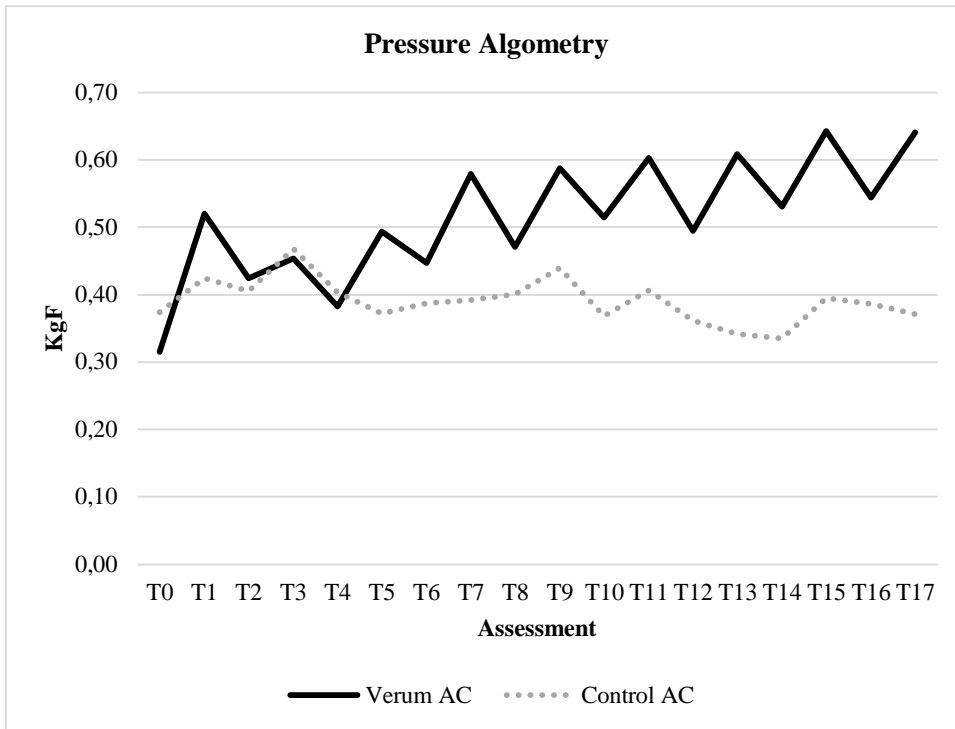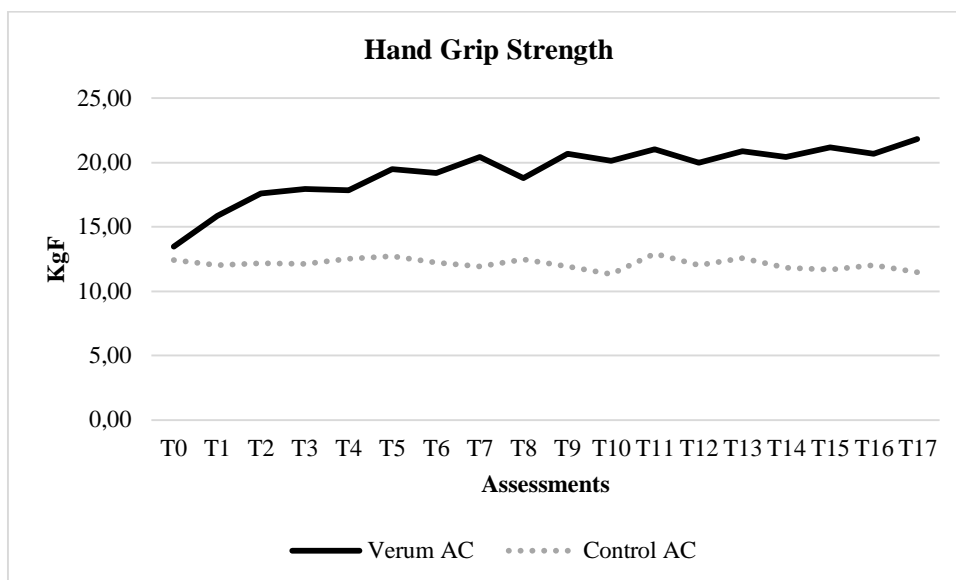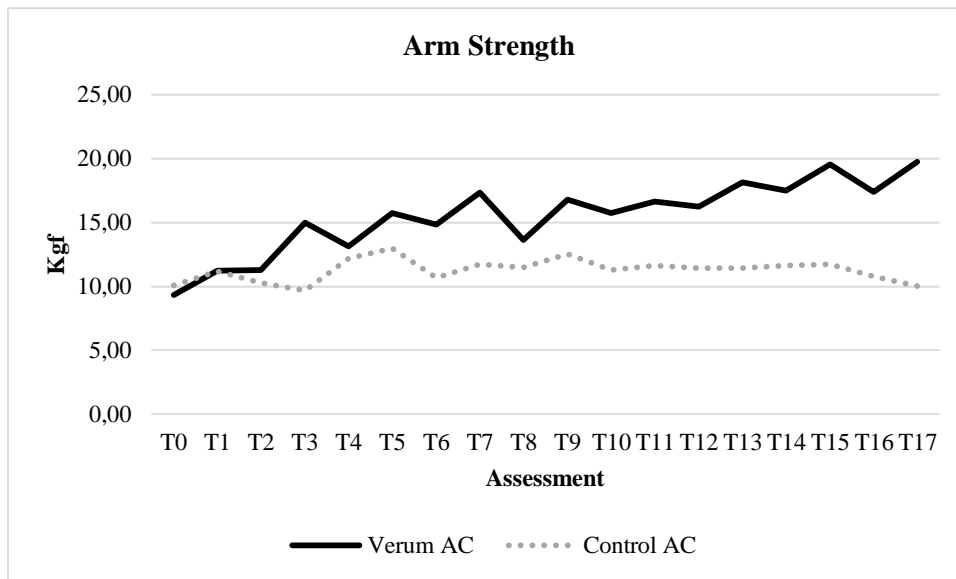
Figure 4: Primary outcomes changes for the groups treated with acupuncture (adapted from Seca et al 2018)[5].

A new table is included in this chapter in which the reader can see the patients progress during the treatments (please see table 7). Patients in the verum acupuncture group showed significantly better outcomes compared to the control acupuncture group for all outcomes measures, in particular after the second treatment (T3) for VAS, after the third treatment (T5) for PA, after the fourth treatment (T7) for AS, and two weeks after the first treatment (T11) for HGS.[5]

Table 7: Primary outcomes changes for the groups treated with acupuncture (adapted from Seca et al 2018)[5]

	Verum AC (n=35)	Control AC (n=35)	p-value	Observations
Hands Grasp Strength (Kgf)				
Baseline	13.45 (8.6, 18.275)	12.45 (8.655, 19.475)	0.488	Kruskal-Wallis test
5 min. post 1st treatment (T1)	15.85 (11, 21.825)	12.05 (8.975, 19.5)	0.344	Mann-Whitney U test
24 hours post 1st treatment (T2)	17.6 (11.425, 21.05)	12.2 (9.388, 18.688)	0.173	Mann-Whitney U test
5 min. post 2nd treatment (T3)	17.95 (12.275, 21.725)	12.125 (9.1, 19.038)	0.122	Mann-Whitney U test
72 hours post 1st treatment (T4)	17.85 (12, 21.9)	12.545 (8.438, 21.45)	0.235	Mann-Whitney U test
5 min. post 3rd treatment (T5)	19.5 (12.75, 22.55)	12.74 (8.625, 22.662)	0.195	Mann-Whitney U test
7 days post 1st treatment (T6)	19.2 (10.1, 22.888)	12.205 (8.712, 19.975)	0.187	Mann-Whitney U test
7 days post 1st treatment (T7)	20.425 (10.838, 22.562)	11.95 (9.475, 21.488)	0.146	Mann-Whitney U test
14 days post 1st treatment (T10)	20.125 (10.975, 23.762)	11.35 (9.1, 18.488)	0.093	Mann-Whitney U test
14 days post 1st treatment (T11)	21.05 (13.05, 24.688)	12.95 (9.338, 18.362)	0.045	Mann-Whitney U test
21 days post 1st treatment (T14)	20.425 (12.95, 23.838)	11.825 (8.5, 18.462)	0.028	Mann-Whitney U test
21 days post 1st treatment (T15)	21.175 (14.262, 24.2812)	11.675 (9.038, 17.981)	0.014	Mann-Whitney U test
28 days post 1st treatment	20.7 (13.838, 23.6)	12.05 (8.95, 19.35)	0.058	Mann-Whitney U test
Changes from baseline to post last treatment	6.2 (8.8, 4.65)	-0.045 (-1.95, 1.55)	<0.001	Kruskal-Wallis test
Statistical value (Wilcoxon Z)	**-5.086**	**-0.243**		
P value	**<0.001**	**0.808**		
Arm Strength (Kgf)				
Baseline	9.34 (7.872, 14.238)	10.06 (7.14, 16.645)	0.872	Kruskal-Wallis test
5 min. post 1st treatment (T1)	11.23 (9.72, 18.998)	11.17 (7.792, 17.701)	0.551	Mann-Whitney U test
24 hours post 1st treatment (T2)	11.3 (9.74, 17.56)	10.282 (5.925, 16.07)	0.216	Mann-Whitney U test
5 min. post 2nd treatment (T3)	14.995 (10.69, 18.742)	9.682 (6.056, 18.764)	0.067	Mann-Whitney U test
72 hours post 1st treatment (T4)	13.12 (10.512, 17.885)	12.172 (5.56, 17.962)	0.380	Mann-Whitney U test
5 min. post 3rd treatment (T5)	15.74 (11.79, 18.932)	12.968 (5.464, 17.286)	0.108	Mann-Whitney U test
7 days post 1st treatment (T6)	14.8225 (10.558, 18.71)	10.695 (6.833, 15.629)	0.066	Mann-Whitney U test
7 days post 1st treatment (T7)	17.3325 (11.828, 20.375)	11.75 (6.763, 16.653)	0.024	Mann-Whitney U test

14 days post 1st treatment (T10)	15.745 (12.57, 19.919)	11.2625 (4.385, 15.856)	0.008	Mann-Whitney U test	
14 days post 1st treatment (T11)	16.6525 (13.371, 21.622)	11.635 (4.912, 16.779)	0.005	Mann-Whitney U test	
21 days post 1st treatment (T14)	17.4925 (11.338, 22.818)	11.6125 (5.522, 15.685)	0.006	Mann-Whitney U test	
21 days post 1st treatment (T15)	19.54 (13.081, 22.429)	11.738 (5.861, 16.885)	0.003	Mann-Whitney U test	
28 days post 1st treatment	17.3675 (13.304, 23.06)	10.76 (6.12, 16.13)	0.005	Mann-Whitney U test	
Changes from baseline to post last treatment	7.128 (-10.654, -5.186)	0.27 (-0.91, 2.135)	<0.001	Kruskal-Wallis test	
Statistical value (Wilcoxon Z)	**-5.086**	**-0.027**			
P value	**<0.001**	**0.979**			
VAS (0–10, 10 worst health)					
Baseline	6 (4, 7)	5 (4, 7)	0.304	Kruskal-Wallis test	
5 min. post 1st treatment (T1)	3.943±1.924	4.6±1.988	0.165	t-Student test	
24 hours post 1st treatment (T2)	4 (3, 5)	5 (3, 6.75)	0.123	Mann-Whitney U test	
5 min. post 2nd treatment (T3)	2.857±1.972	4.382±2.0002	0.002	t-Student test	
72 hours post 1st treatment (T4)	4 (3.5, 5)	5 (3, 6.75)	0.033	Mann-Whitney U test	
5 min. post 3rd treatment (T5)	2 (1, 4)	5 (3, 6)	<0.001	Mann-Whitney U test	
7 days post 1st treatment (T6)	4 (2, 5)	5 (3, 7)	0.010	Mann-Whitney U test	
7 days post 1st treatment (T7)	2 (1, 3)	5 (2.25, 6)	<0.001	Mann-Whitney U test	
14 days post 1st treatment (T10)	4 (2, 5)	5 (4, 7)	0.010	Mann-Whitney U test	
14 days post 1st treatment (T11)	2 (1, 2.75)	4 (3, 5.25)	<0.001	Mann-Whitney U test	
21 days post 1st treatment (T14)	2.868±1.463	4.562±1.95	<0.001	t-Student test	
21 days post 1st treatment (T15)	1 (0.25, 2)	4 (2, 5.25)	<0.001	Mann-Whitney U test	
28 days post 1st treatment	2.5 (2, 3)	4 (3, 6)	<0.001	Mann-Whitney U test	
Changes from baseline to post last treatment	1 (0, 3)	4 (3, 6)		Mann-Whitney U test	
Statistical value (Wilcoxon Z)	**5.099**	**3.674**			
P value	**<0.001**	**<0.001**			
Pressure Algometry (Kgf)					
Baseline	0.31±0.16	0.39±0.2	0.074	One-way ANOVA	
5 min. post 1st treatment (T1)	0.509±0.212	0.432±0.232	0.151	t-Student test	
24 hours post 1st treatment (T2)	0.436±0.191	0.418±0.21	0.717	t-Student test	
5 min. post 2nd treatment (T3)	0.5123±0.191	0.4765±0.250	0.508	t-Student test	

72 hours post 1st treatment (T4)	0.3825 (0.327, 0.487)	0.403 (0.208, 0.512)	0.627	Mann-Whitney U test
5 min. post 3rd treatment (T5)	0.494 (0.386, 0.63)	0.3717 (0.289, 0.475)	0.001	Mann-Whitney U test
7 days post 1st treatment (T6)	0.479±0.175	0.383±0.189	0.034	t-Student test
7 days post 1st treatment (T7)	0.564±0.176	0.424±0.21	0.004	t-Student test
14 days post 1st treatment (T10)	0.512±0.156	0.368±0.184	0.001	t-Student test
14 days post 1st treatment (T11)	0.594±0.163	0.370±0.175	<0.001	t-Student test
21 days post 1st treatment (T14)	0.542±0.192	0.34±0.177	<0.001	t-Student test
21 days post 1st treatment (T15)	0.655±0.189	0.37±0.155	<0.001	t-Student test
28 days post 1st treatment	0.568±0.176	0.364±0.171	<0.001	t-Student test
Changes from baseline to post last treatment	0.34 (0.24, 0.41)	-0.02 (-0.08, 0.06)	<0.001	t-Student test
Statistical value (Wilcoxon Z)	**-5.086**	**0.545**		
P value	**<0.001**	**0.586**		

Please discuss the duration of the effect of acupuncture and how this was evaluated.

Detailed information regarding the research methods of this study can be found in chapters 5 and 8. Reporting to our study protocol, patients allocated to the verum and control groups were treated with the exact same number, depth and stimulation of needles, but participants of the verum group were treated with a specific choice of points of the affected conduits (i.e. real acupuncture points) and control group patients' were treated not according to the CM diagnosis on points allocated in areas close to the real acupoints but at non-acupoints (i.e. false acupuncture points).

Acupuncture effects were assessed with objective outcomes and with patient reported outcomes, as defined in our study design.

Analysis of our results have shown a quick onset of symptomatic relief within five minutes, that continued to improve throughout the period of four weeks. As shown by the verum acupuncture group, patients improved their functional ability and the HRQoL with less pain. Acupuncture, a non-pharmacologic and nontoxic technique, was an effective and well-tolerated treatment.

Our findings have also shown that after the first week, in which acupuncture treatments were done three times and with shorter intervals, the frequency was gradually reduced and less frequency of the acupuncture treatment achieved as good follow-up outcomes in the patients with chronic pain as those with a higher frequency. Our findings are highly consistent with some trials and analysis available in the literature.[18]

As the reader can see in table 7, at baseline, there were no significant differences in the primary outcomes between the groups. At the end of the treatment, all patients treated with verum acupuncture significantly improved the function of the hands (assessed with a Jamar® Hydraulic Hand Dynamometer), self-reported pain (assessed with the VAS) and pressure threshold tolerated (assessed with the pressure algometer). The patients treated with false or sham acupuncture showed that only

self-reported pain improved significantly, VAS (p= <0.001). Changes from baseline to post last treatment, in all the primary outcomes between groups were significant (p= < 0.001).

Patients treated with real acupuncture points showed significantly better outcomes compared to sham acupuncture for all outcomes measures, in particular: 24 hours after the first treatment (after the second treatment = T3) for VAS; 72 hours after the first treatment (after the third treatment = T5) for PA, one week after the first treatment (after the fourth treatment = T7) for arm strength, and two weeks after the first treatment (after the sixth treatment = T11) for hand grasp strength.

Secondary outcomes analyzed after four weeks showed that Health assessement questionnaire (HAQ) scores significantly decreased in the verum group, while there was no change in the group treated with sham acupoints; verum acupuncture improved significantly 7/8 SF-36 domains, while sham acupuncture improved significantly only 5/8 SF-36 domains. The number of swollen and tender joints significantly decreased in the group treated with real acupoints, while there was no change in the sham group.

We carefully evaluated our results and provided the following recommendations:

1. The treatment underlying our study was developed in the Heidelberg School of CM, where treatments of RA have frequently been performed for two decades in a similar manner as standard intervention. After the intensive treatment of four weeks, frequency is gradually reduced to one session every three weeks and symptoms remain on a comparable level. However, this should be examined and objectified by follow-up future studies.[5]

2. Further research is needed to explore whether long-term effects can be obtained and if treatment variations may be necessary to achieve this.[5]

3. Our study followed the revised STandards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA),[3] published to encourage the publication protocol of precise interventions methods used in trials of acupuncture. The recommendations emphasized the need to provide rationed detailed protocol information, such as needling, treatment regimen, co-interventions, practitioners background, and control interventions. However, the range of duration of each acupuncture treatment session, number of treatment sessions, and total duration of treatment in weeks for diseases, should be added in STRICTA to evaluate the quality of performed randomized controlled trials

Discuss the results, and the mechanisms involved, from the point of view of western medicine, given that the thesis was submitted to a Faculty of (Western) Medicine.

I would like to remember the reader that this was a trial developed to assess the effects of an intervention with potential to be used by nurses. Since this work was developed within the context of the doctoral program in Health Sciences, branch in Nursing, it was not our aim to assess mechanisms associated with the technique studied (acupuncture). Rather, we aimed to assess the effect of that treatment regime, according to the defined methodology, on pain, function and quality of life of selected patients with RA.

The acupuncture treatment underlying our study was developed in the Heidelberg School of CM, where treatment of RA is common and frequently based on a classical Chinese medical theory – the Shang Han Lun – which is systemized in the Algor Leadens Theory (ALT) of the Heidelberg Model of CM. According to the clinical experience gained over two decades, we know that comparable patients are treated in the same manner as the patients of the standard group in our study.

Below these results are discussed in two parts: in part one they will be discussed from the point of view of nursing care and in part two the possible mechanisms that are involved in the effects according to western medicine are outlined.

- **How acupuncture can serve nurses in their care of RA patients**

In the last years there have been drastic improvements in the treatment of RA, not only by developing new drugs (such as biological drugs) but also in the development of new treatment strategies (such as ''Treat-to-Target [T2T]'' strategy).[1] Although remission of the disease, i.e. complete abrogation of inflammatory activity, has become a viable option for most patients with a recent diagnose,[1] there is no cure for RA and a considerable proportion (14% to 38%) of patients who are in biological remission, i.e. without objective signs of relevant inflammation, still report significant levels of disease impact, higher levels of pain, functional deficits and poor quality of life, similar to those with active disease.[1]

Effective control of the inflammatory process through immunosuppressive therapy, which is the cornerstone of current medical intervention, provides a major contribution to improve RA symptoms. However, this so called ''near-remission'' is at least as frequent as remission and typifies a common failure of the disease process strategy to achieve the ultimate goal of therapeutic intervention: to enable the patient to fully enjoy his/her life.[1]

To fully grasp the dimensions affected by the disease and the psychosocial context, RA patients will not have their condition improved sufficiently by additional immunosuppressive therapy.

An optimal care of RA patients requires a life-long holistic management by a multidisciplinary team as a basis for personalized adjunctive interventions that go beyond pharmacological treatment and control of the domains underlying the persisting impact of the disease.[1,19]

Nurses, as part of the multidisciplinary team, are the professionals that spend more time with patients in many health care settings than any other person, and they can play an important role in treating or educating patients about the field of non-pharmacological interventions to relieve RA disease symptoms.

Acupuncture, a non-pharmacological intervention, is one of the various complementary and alternative medicines (CAM) that is increasingly popular among patients with RA,[20] but also in the general public as well as health care workers like nurses.

Use of CAM is a part of nursing's heritage. However, as nurses began to be employed primarily in hospitals that largely supported the Western biomedical approach to medical care, most of the nurses' time was allocated to collaborative activities associated with the medical care plan including the

monitoring of the patient's status. Due to lack of time nurses had less opportunity to administer these aspects of nursing that included complementary therapies.[21]

In the late 1950s, the nursing process was introduced. In Portugal registered nurses are educated at the graduate level to provide primary, acute, chronic, and specialty care to patients of all ages. Their training covers disease prevention, coordination of care, and health promotion. Currently, the nursing process contemplate the assessment, evaluation, diagnosis, planning and prescription of nursing treatment plans.[21]

In addition to the honing of assessment skills, the process also drew attention to interventions. Distinction was often made between dependent or collaborative actions and independent actions or interventions. As graduate education of nurses for clinical practice increased, interest in and use of independent nursing interventions grew.[21] Complementary therapies, as acupuncture, are one of these field of interventions.

Acupuncture comes very close to the underlying philosophy, ethics and core training of the nurse profession and allows nurses to demonstrate to care in a holistic approach of persons and health care, which is a key characteristic of nursing. In contrast to the Cartesian philosophy of medicine, acupuncture and nursing are people-oriented with the goal to provide the best care based on physical, psychological, social, cultural and spiritual needs of the people.

Nurses' use of evidence-based therapies is imperative to support safe therapeutic decisions. To use acupuncture or to advise patients on its use, the nurses must adhere to evidence-based principles, have adequate training and supervision necessary to administer acupuncture, consider the appropriateness of the therapy to both the condition of the patient and any co-existing treatments, ensure that the patient is aware of the therapy and are given informed consent, and follow the established practice protocols and standards of care and practices within the local legal requirements.[21]

Once working in partnership with the patient and health-care team to determine the suitability of a therapy, nurses can administer acupuncture in conjunction with a biomedical treatment rather than as a replacement for it.[21] Research in evidence-based acupuncture still needs to be continued, especially concerning its inclusion in the field of nurses' interventions, to develop a better scientific base for the use of acupuncture with RA patients.

Living with RA can be a frightening, exhausting, and demanding experience. RA patients are already for some time looking for and using acupuncture to relief the remain symptoms that are not being successfully reliefed by biological therapies, which suggests that we should not dismiss the use of acupuncture; rather we should investigate further the benefits that can be obtained.

In this RCT with selected RA patients we found out that acupuncture decreases pain, increases physical function and improves the HRQoL in all the domains. Clear allocation criteria for acupoints according to CM functional diagnosis, applied by a qualified therapist with over 9 years of intensive training in the Heidelberg School of Chinese Medicine, were extremely relevant to show the effects of acupuncture in a patient group that had been primarily defined by a "western" medicine diagnosis.

In this context, the integration of acupuncture in RA patients nursing care, if respecting the allocation of individual acupoints according to the scientific rules quoted, seems to have a great potential to integrate CM and western medicine, and should therefore be considered.

Nurses' philosophy and core competencies have a unique position in the assessment and management of the holistic view on the RA patient, placing his/her needs at the center of the decision-making process. By incorporating acupuncture to treat pain and disability into the field of interventions for RA, the nurses can greatly improve the patients' autonomy in their daily living activities and their health condition and thereby their quality of life.[22]

Acupuncture can supplement, extend, enrich and improve the nursing skills and the quality of nursing care in the management and health education of patients with RA. The advantages and effects of acupuncture on preventive care, postoperative rehabilitation and chronic disease care are becoming increasingly distinct and significant, thereby increasing the economic returns for hospitals, improving clients' satisfaction with medical service, and enhancing the sense of achievement of nurses.

RA patients that have tried acupuncture alongside with conventional medical care reported that this choice helped to reinforce their attendance, perception and satisfaction with conventional care.[23]

Nurses, as part of the health-care team, are frequently in the position of giving information and advice about the disease management. That is why they should understand the need for symptom relief and the physiological benefit that may derive from acupuncture, but they also need to be able to explain the ambiguous evidence base for this therapy, particularly with regard to their effects, side effects and potential interactions with conventional RA therapies.[19]

A full understanding of acupuncture and the implications of its use by nurses can avoid many potentially important consequences to RA patients that do not inform their physicians that they are looking for acupuncture,[20] like to try non-qualified acupuncturists, read unreputable sources or being introduced to therapists who may be acting irresponsibly.

With this study, our goal to use a systematic strategy to collect scientific evidence regarding the base of acupuncture treatments has been achieved but we recognize that we still need to continue carrying out further clinical trials on their use in RA.

In trying to represent our commitment to continue to contribute to further progress in the prevention and management of RA by giving visibility and social usefulness to our results, we are already continuing our work by developing a larger sample size RCT, to study the long-term effects, safety, and cost-effectiveness of acupuncture, and if treatment variations may be necessary.

- **Neurophysiological mechanisms of acupuncture and their relevance to RA**

As part of the discussion of our results, including the reasons of the selection of the verum acupoints, specific diagnostic technical terms and possible mechanisms are quoted, and if necessary described with an auxiliary Western medical explanation in brackets, in the following paragraphs.

In response to the treatment of the vegetative nervous system with acupuncture we found a statistical significant change in pain and physical disability. This is the first RCT assessing the effects of

acupuncture on the hands of selected patients with RA, including western and Chinese medicine diagnosis as inclusion criterion.[5]

The neuro-immune signs and symptoms that come with the vegetative functional state of selected RA patients were interpreted according to a classical Chinese medical theory – the Shang Han Lun – which is systematized in the Algor Leadens Theory (ALT) of the HM of CM.[24] According to this theory pain and disability in RA arises from a relative hypoxis of a tissue and its disrupted microcirculation due to an attack of the "immunological algor" (regional disturbance of microcirculation following an immune responses due to adhesion molecules, coupling of complement and coagulation systems within the capillaries of inflamed areas, e.g. fibrin formation and vasospasmic reflexes) in six stages (please see Chapter 2).[25]

Signs and symptoms of the pattern (specific neuro-affective pattern with defined physical signs) presented by the selected RA patients, i.e. with hand pain worsened by handgrip, indicated a so-called Turning Point syndrome (which is systematized in the ALT of the HM of CM). This diagnose of the vegetative functional status according to CM was our basis for the individualized selection of acupuncture points in the verum acupuncture group.[11,25]

The Turning Point syndrome helps us to understand the signs and symptoms surrounding our RA patients sample. According to Western understanding, local and systemic increase of microcirculation occurs as a result of the inflammatory response in order to eliminate the pathogen "immunological algor".[25] This leads to a couple of local pathophysiological consequences and sensations well described or shown by our sample,[11] like (1) red tongue (the tongue is considered an embryological somatotopic system); (2) sensation of warmth (by increase of capillary flow); (3) pre-inflammatory state, leading to pain modalities like "worse if pressed", as inflammation tend to be increasingly painful under pressure; (4) reddish skin, the mechanisms by which this is induced may include the release of substance P, therefore accompanied by burning sensation.[5,11,26] Systemic pathophysiological consequences may include a relative lack of fluids in the larger vessels, as fluid supplies peripheral capillary flow, leading to water saving mechanisms (thirst, dry mucosa and mouth, dry skin, dry stool, yellow and sparse urine), sympathetic stimulation with higher pulse rate, and inner tension.[5,11,26]

However, if the pathological factor "immunological algor" invades further and the activation of specific immunological mechanisms failed, eventually a generalized decrease in microcirculation appears leading to loss of muscular power and stiffness, for example.[11,25]

If the pathogen algor attack persists over time, the infection process may become chronic.[24] The main symptoms such as retarded flexion and extension, deformity and contracture of the bones and muscles may will appear.[27] Overtime, a yin deficiency may arise, i.e. a labile neurovegetative regulation due to an overall deficiency of functional tissue

A yin deficiency results in an imbalance that results in sudden changes on the vegetative system, making it difficult for the body to adjust, so dysregulated immunological reactions and disrupted microcirculation problems can continue to happen.

The distal and local acupuncture points that were selected to treat the RA patients in the verum acupuncture group are considered as acupoints having specifical therapeutic effects in the treatment of the aforementioned Turning Point syndrome, especially on the underlying systemic inflammatory process as well as on the treatment of a set of physiological imbalances and/or disordered metabolic processes that alternate continuously and are an underlying mechanism of an immune response in these RA patients.[11]

Acupuncture's anti-inflammatory effects played an important part in its analgesic mechanisms, biomechanical improvement and, can even activate self-healing mechanisms. Below complementary information, based in human neuroimaging, animal and human experiments, regarding the mechanisms of action of acupuncture for RA, are addressed.

Acupuncture stimulation induce systemic and local molecular and cellular changes at and around the location of the acupoint, as also various neurophysiological mechanisms occur in peripheral and central nervous system through its corresponding afferent pathways and generated efferent signals on autonomic nervous system. Several studies found that these mechanisms are clearly different from pain mechanisms, stimulation at non-acupoints or surrounding tissues.[28,29]

In the present investigation, we clearly demonstrated that using acupoints selected specifically according to the vegetative functional state of the patient led to significant pressure threshold tolerance and physical function improvement.[5] The fact that the needling of false acupuncture points differ in these effects in the present study indicates that it considerably matters which acupoints are used and contradicts the view that acupuncture might not only mediate nonspecific skin stimulation, which may or may not exceed placebo effects. If acupoints are understood as reflex points that elicit specific neurovegetative alterations, it can be speculated that they might only yield satisfactory treatment results if they match the current vegetative status of patient (which is expressed in the CM diagnosis).

Different modes of action may account to relieve inflammation, chronic pain and physical disability. A great number of human neuroimaging studies have reported cerebral hemodynamic responses in the pre-frontal cortex, somatosensory cortex and limbic system during acupuncture stimulation at acupoints.[28,29,30] Some of these responses, such as, secretion of spinal opioids and serotonin, may mediate its effects on pain, anxiety and stress-related diseases.[30,31]

Acupuncture can restore the hypothalamus-pituitary-adrenal (HPA) axis by down-regulate serum cortisol levels and upregulate the release adrenocorticotrophic hormone (ACTH) that activates the zona fasciculate of the adrenal glands to produce glucocorticoids.[32]

Release of vascular and immunomodulatory factors with acupuncture stimulation can ease pain by triggering a natural painkilling chemical called adenosine, and the extracellular signal-regulated kinase (ERK) pathway.[28,33,34]

According to CM, acupuncture is believed to restore the balance between yin and yang and this can be understood in the Western medicine terminology as a synergistic modulation of the equilibrium between parasympathetic and sympathetic activity.[30] Acupuncture appears to activate the sympathetic

regulation of the immune system by inducing either local or systemic catecholamine secretion, for example, norepinephrine, which provide clinical advantages for treating inflammatory disorders such as arthritis by preventing systemic immunosuppression and susceptibility to secondary infections.[35] Previous studies shown that acupuncture stimulate effects mediated by the vagus nerve, for example, induce the release of acetylcholine, appears to reduce serum levels of inflammatory cytokines as TNF-α, IL-1b, and IL-6, and increase anti-inflammatory cytokines such as IL-4 and IL-10 in RA serum and joints.[33,35]

Acupuncture itself is a type of local microtrauma on the tissues at the body surface and applying appropriate sensory stimulation (affected by acupoint selection, different needling means or stimulation parameters) can trigger or strengthen the body's self-inflammatory reflex to alleviate inflammation. These include mast cell involvement, the release of vasoactive substance such as substance P, calcitonin gene related peptide (CGRP), nitrous oxygen (NO), adenosine, prostangladin, etc, in which, upon the activation of A-δ and C-fibers via axon reflex, resulting in vasodilatation in small vessels, increased blood flow, and triggered local inflammatory and anti-inflammatory response, i.e, the inflammation reflex induced by acupuncture though stimulation at the affected area or distal acupoints is a process that automatically limits inflammation by breaking the "inflammatory-anti-inflammatory equilibrium" that originally exists in the local area, which commonly exists in chronic inflammatory diseases.[28,35]

When an acupoint is stimulated adequately, the blood perfusion of this point continued to increase and improve local microcirculation, improve tissue oxygenation and decreases oxidative stress in specific organs and tissues, together with other sympathetic nerve activity mechanisms, like skin temperature, heat production in muscles and brown adipose tissue will counteract heat loss or heat gain via the skin. Following the same stimulation, the blood perfusion of a non-acupoint only changed slightly.[28,29,36]

It has been proposed that the acupuncture points are located on sites with high concentration of connective tissue, nerve endings and biochemical/bioelectrical signaling phenomena, (including movement, metabolism, signaling and information exchange) located on the fascia network.[29,30]

The biomechanical signaling through the connective tissue, and the changes in matrix composition along the fascial system network, with effects on blood flow and cytokines synthesis, may result in a long-term modulation of the activity of sensory afferents inside the connective tissue (whose sensitization is involved in many chronic diseases, such us neurogenic inflammation and chronic pain) and/or changes in central synapses, indeed in a neuromodulation cascade that follows the processing of the mechanical sensory stimuli after needling of acupoints.[30,37]

The pulling of collagen toward the needle induces an active cellular response in connective tissue fibroblasts up to several centimeters away from the needle. This cellular response consisted of an active cytoskeletal reorganization of proteins and fibroblasts cells, actomyosin contractility as well as Rho and Rac.[37] Proteins and fibroblast cells modulation in connective tissue have profound effects on reducing local connective tissue inflammation and fibrosis via direct mechanical effects of the

stretched tissues,[38] restore tissue integrity, and induce functional changes in local microcirculation to increase waste removal and adequate nutrient delivery to chondrocytes.[33]

Extensive evidence from cultured cell models and in vivo model of adjuvant- induced arthritis (AIA) rats have shown acupuncture effects on the protection of inflammation and related signs and cartilage degradation.[33] Cell shape and cytoskeletal remodeling are key components of mechanotransduction responses during acupuncture-needle manipulations linking the cell's mechanical environment to fundamental events such as gene transcription, cartilage extracellular matrix proteins up-regulation, and cell-adhesion dynamics.[23,33]

This thesis is more one work that demonstrated together with other previously studies,[34,39,40,41,42] that acupuncture, according to the HM concepts and treatment principles, may lead to pain reduction and physical function improvement. These outcomes were already described in conjunction in RCTs showing the clinical efficacy of acupuncture over sham/placebo treatment for chronic low back pain, gait improvement of patients with Multiple Sclerosis, pain-induced after sternotomy, Osteoarthritis and Peripheral Neuropathy. [34,39,40,41,42,43]

Greater usage of non-pharmacologic therapies like acupuncture in conjunction with conventional pharmaceutical approaches may be helpful in chronic pain treatment and management. Acupuncture research groups have already created a scientific path to understand the physiologic effects of acupuncture and to prove that the typical dogma of acupuncture being a "glorified iplacebo" is a viewpoint that is clearly not supported by the scientific evidence. As a result important data from acupuncture research done in the last two decades, along with the safety data showing that acupuncture is well tolerated, supported the decision in January 2020 of a mainstream medical payer in the USA to cover acupuncture for low back pain for up to 20 sessions over 12 months.

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Chapter 11

Overview and future directions

Overview and future directions

In this final chapter we summarize the main findings of the studies presented in this thesis, discuss their relevance and implications in an integrated overview and explore future perspectives.

This endeavour was structured to establish the best evidence of the effects of acupuncture on Rheumatoid Arthritis (RA) based on clear allocation criteria of acupoints, objective assessment of effects and valid, double-blind controls.

Of the 284 RA patients enrolled, 94 were excluded because they did not meet the inclusion criteria. 151 (79.5%) RA patients showed worsening hand pain, as induced by handgrip, more than in the knuckles or thumb. Of those 151 eligible patients, the 105 RA patients with a Turning Point syndrome (TPS), according Chinese Medicine (CM), were randomized into three groups.

Our results clearly indicate a relevant clinical effect of acupuncture in RA of the hand in patients suffering from TPS. As the effects were shown in a double-blind manner, a mere placebo or suggestive effect can be excluded and effects can therefore be considered to be specifically induced by the acupoints used. The rigorous design of this randomized controlled clinical trial also avoids major other problems of acupuncture studies such as weak allocation of acupoints or lack of objective assessment of effects. The results may therefore provide helpful information for those involved in decision-making within the healthcare systems and support a more active role of acupuncture as an option for RA treatment.

Our publications have the innovative feature of providing the reader with scientific evidence accumulated through the work described, providing the basis for recognizing and realizing the benefits of integrating acupuncture in the treatment of RA. We are very proud that it has received approval for publication in renowned scientific journals, which suggests its international relevance.

The methodological issues and limitations of our studies have been openly discussed in the respective chapters. Although research will always be open to criticism and amenable to improvement, we believe that we have performed state of the art research, following the best and most recent recommendations and quality filters.

The research described in this thesis constitutes, we believe, a very coherent and comprehensive body of work and evidence, sufficient to support a much needed paradigm change in Nursing care. These results will certainly promote new challenges and provide novel opportunities to demonstrate and reinforce the role that acupuncture may play in the management and prevention of RA health issues in the individual and public spheres.

We need to respond effectively to the new demands in the health care system and to diversify resources, not simply accepting the current quality as good enough.

To integrate the complementary and alternative medicines (CAMs), in particularly acupuncture, into the health care system, will give RA patients the chance to enjoy an integrative care approach with the most appropriate treatments and well-trained professionals. To use acupuncture, following the CM diagnosis as criteria to decide the most adequate acupoints and tecniques, proved to be an effective strategy to effectively relieve pain and discomfort, improve the patient's physical status and quality of life with few side effects and even may have a broad range of intervention possibilities in situations where the restricted use of Western medicine would be limited.

The CAMs are used in combination with conventional treatments and not as replacement. They have been used for thousands of years in both Western and Eastern civilizations, evidencing benefits in the health/well-being of people.

Since the 1970s, several scientific studies have been developed to prove the efficacy of one of the most widely used CAM, acupuncture. In 1979, the World Health Organisation (WHO) published a list of 41 diseases that had excellent results with the treatment of acupuncture and after twenty-five years of research in several institutions in the world, the WHO published the document Acupuncture: Review and analysis of reports on controlled clinical trials, in which it exposes the results of these surveys.

Since 2002, the WHO has recommended the provision of acupuncture in the public network as a primary or complementary treatment for various pathologies. The General Guidelines for Methodologies on Research and Evaluation of Traditional Medicine state the various reasons why traditional medicine practices should be used by its member countries.

The mechanisms and effects of acupuncture have a vast field of effects namely, immune system regulation, increased pain threshold and improved microcirculation. It may assume great importance in the control or relief of signs and symptoms, for example, anxiety, pain (including phantom pain), nausea and vomiting, may have an anesthetic effect in minor surgical procedures, and decrease pharmacological side effects and drug interactions, either by reducing the need for some medications, or acting in the affected organ or system in order to protect it.

In trying to represent our commitment to continue to contribute to further progress in the prevention and management of RA, giving visibility and social usefulness to our results, our next goal is to continue to explore these results in a longitudinal observational study and, incorporate and implement the possibility that RA patients may choose to be treated with acupuncture, a technique with low cost and reduced side effects, and which if implemented by welltrained CM professionals may guarantee a model that prioritizes humanized and integral care, quality, efficiency and safety in use.

Currently acupuncture is widely used in hospitals in several countries. In China 95% of the hospitals have units of Chinese medicine. A brief look at what is going on in Europe, shows that in Portugal since 2003 there is a regulation for the practice of non-conventional therapies,

including acupuncture, but these are not yet part of the national health system. In the United Kingdom, as in the United States of America, CM is practised in state hospitals and taught in state universities. In Germany it is still mostly used in private establishments but with a significant contribution from social security and insurance.

The inclusion of acupuncture in health care systems derives from several advantages: the necessary resources, specially the instruments, have low cost; the rooms and units in health care institutions can be easily adapted to acupuncture treatments; almost total independence from hospital medical technology; applicability in the field of preventative and curative medicine could contribute to reduce the waiting lists in public health systems, and the costs associated with expensive drugs, invasive techniques and hospital admissions.

In the countries where these treatments have been integrated in their health care services, there is a strong tendency towards an increase of the number of departments that are implementing it because of the high satisfaction of the patients who have had access.

We are going through a time of cost containment, more than ever techniques that had proven to be effective and of low cost should be an available resource in health care. In the Ordinance nº163/2013 of April 24th, the prices to be practised by the different interventions available in the National Health Care system of Portugal are defined. Acupuncture is included in this file and €28.30 is the price stipulated for each appoiment, a price much lower than that of most invasive interventions.

Following the desire to improve the evidence demonstrated by clinical experiences and now translated by these results, I believe that to integrate acupuncture into the range of nurse treatment options on offer to RA patients could be an important project with good prospects for implementation, which may be a great benefit to the person and community and, the health care services could benefit from indirect cost reduction and achieve visibility by extending forms of prevention and restoration of health they make accessible to users.

List of Abbreviations and Acronyms

AC	Acupuncture
ACPA	anti-citrullinated protein antibodies
ACR	American College of Rheumatology
ADR	adverse drug reaction
AGL	acid gamma linolenic
AIA	adjuvant- induced arthritis
ALT	Algor Leadens Theory
AS	arm Strength
AT	autogenic training
ATDS	automatic Tongue Diagnosis System
BINGO	Biological NetworkGene Ontology
CAC	control acupuncture
CAM	Complementary and Alternative Medicine
CASP	Critical Appraisal Skills Programme
CGI	Clinical Global Impression
CGRP	calcitonin gene related peptide
CM	Chinese Medicine
CTLA-4	cytotoxic T-lymphocyte-associated antigen-4
COX	Cyclooxygenase
CRP	c-reactiv protein
DAS	Disease Activity Score
DAS28	Disease Activity Score in 28 joints
DB	Database

DHEAS	dehydroepiandrosterone sulfate
DMARD	disease-modifying antirheumatic drug
DIP	distal interphalangeal joints
DNA	deoxyribonucleic acid
EA	Electroacupuncture
EFA	essential fatty acid
EMA	European Medicines Agency
ERK	extracellular signal-regulated kinase
ESR	erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
FFA	free fatty acids
GARS	Groningen Activity Restriction Scale
GC	guiding criterion
GC-MS	gas chromatography mass spectrometry
GI	gastro intestinal
GSZD	Guizhi-Shaoyao-Zhimu decoction
HAQ	Health Assessment Questionnaire
HGS	hand grip strength
HLA	human leukocyte antigen
HM	Heidelberg Model
HPA	Hypothalamic Pituitary Adrenal
HRQOL	Health Related Quality of Life
IFN	Interferon
IL	Interleucine

JBI-MASTARI	Joanna Briggs Institute Meta-Analysis of Statistics Assessment and Review Instrument
LC-MS	liquid chromatography-mass spectrometry
LLP	level of lipid peroxidation
LPO	level of serum lipid peroxide
MAPK	mitogen-activated protein kinase
MCP	Metacarpophalangeal
MHIQ	McMaster Health Index Questionnaire
MRI	Magnetic Resonance Imaging
MTP	Metatarsophalangeal
MTX	Methotrexate
NEI	neuro-endocrine-immune
NK	natural killer
NO	nitrous oxygen
NSAID	non-steroidal anti-inflammatory drug
NF	nuclear factor
PA	pressure algometry
PC	Phosphatidylcholine
PDI	pain disability index
PE	phosphatidylethanolamine
PF	physical function
PGADA	patient's global assessment of disease activity
PIP	proximal interphalangeal
PLT	total effective rate platelet
PPAR	peroxisome proliferator-activated receptor

PPI	protein-protein interactions
PRO	patient reported outcomes
PUFA	polyunsaturated fatty acids
QOL	quality of life
RA	Rheumatoid Arthritis
RAQOL	Rheumatoid Arthritis Quality of Life instrument
RBC	red blood cell count
RCT	randomized controlled trial
RF	rheumatoid factor
RNA	ribonucleic acid
SD	satisfaction degree
SOD	activity of superoxide dismutase
STAT4	signal transducer and activator of transcription 4
SE	shared epitope
SF-36	36-item Short-Form Health Survey
SHL	Shang Han Lun
SSZ	Sulfasalazine
STRICTA	Standards for Reporting Interventions in Clinical Trials of Acupuncture
TA	traditional acupuncture
TAS	tellegen absorption scale
TCA	traditional Chinese acupuncture;
TCM	Traditional Chinese Medicine
TENS	transcutaneous electrical nerve stimulator
TH	t-helper
TJC	tender joint count

TLR	toll-like receptor
TNF-A	tumor necrosis factor alpha
TNFAIP	tumor necrosis factor alpha induced protein
TGP	total glucosides of peony
TPS	Turning Point Syndrome
TE	*Tripterygium wilfordii* Hook F extract
UICISA: E	Health Sciences Research Unit - Nursing
US	Ultrasound
VAC	verum acupuncture
VAS	visual analogue scale
VASG	visual analogue scale of patient's global assessment.
VEGF	vascular endothelial growth factor
WBC	white blood cell count
WHO	World Health Organisation
WM	Western medicine