Tibial Pressure Pain - evaluation of its prevalence and correlations

Hugo Manuel Pontes Antunes[1], Dr. João Pedro Vitória Vieira de Matos[2], Prof. Dr. José António Pereira da Silva[3],

[1]Faculdade de Medicina da Universidade de Coimbra

[2]Mestre Psicólogo Clínico

[3] Prof. de Reumatologia da Faculdade de Medicina da Universidade de Coimbra e Director do Serviço de Reumatologia dos Hospitais da Universidade de Coimbra (SRHUC)

Endereço: Hugo Manuel Pontes Antunes – Rua dos Casais, nº740, Rebordões-Souto – 4990-770 Ponte de Lima

E-mail: hugoantunes4@gmail.com

Index of contents

Resumo 4

Abstract 6

1. Introduction 8

2. Materials and Methods 11

2.1. Study Population 11

2.2. Interview and HADS Questionnaire 12

2.3. Physical examination 12

2.4. Blood sample measurements 13

2.5. Questionnaire to physicians 13

2.6. Statistical analysis 14

3. Results 15

3.1. Socio-demographic characteristics 15

3.2. Pressure pain thresholds by groups 16

3.3. Tibial pressure pain and vitamin D status 16

3.4. Tibial pressure pain and Thyroid hormones 17

3.5. Tibial pressure pain and Anxiety and Depression 18

Anxiety 18

Depression 18

3.6. Questionnaire to physicians 18

4. Discussion 20

5. Limitations 24

6. Conclusion 24

Aknowledgments 25

References 26

Appendix 30

Appendix 1 – Socio-demographic Interview 30

Appendix 2 – Hospital Anxiety and Depression Scale (Portuguese version) 32

Appendix 3 – Physical Examination 33

Appendix 4 – Questionnaire to physicians 35

Resumo

Introdução: A dor à pressão tibial, caracterizada pela presença de dor quando se exerce uma pressão digital ligeira sobre a face antero-interna da tíbia (ao pesquisar edema dos membros inferiores, por exemplo), parece ser um achado frequente na prática clínica. Contudo, esta entidade não se identifica na literatura médica nem nos foi possível encontrar quaisquer estudos ou orientações sobre a sua possível etiologia e adequada interpretação clínica. Enquanto alguns clínicos sugerem a relação da dor à pressão tibial com níveis diminuídos de vitamina D, outros defendem que pode ser uma manifestação de fibromialgia; outros ainda entendem não atribuir qualquer relevância clínica a este achado.

Objectivos: O principal objectivo deste estudo foi avaliar a prevalência da dor à pressão tibial. Como objectivos secundários procurámos analisar a associação entre o baixo limiar de dor à pressão tibial e fibromialgia, vitamina D, hormonas tiroideias, ansiedade e depressão.

Métodos: A nossa amostra foi constituída por 63 elementos do sexo feminino, divididos por três grupos de 21 indivíduos: um grupo de pacientes fibromiálgicos, um grupo constituído pelas suas irmãs não fibromiálgicas e outro pelas suas mães. Todos os elementos foram submetidos a colheita de sangue para doseamento dos níveis de 25(OH)D, TSH, T3 e T4 livre. A avaliação do limiar da dor foi efectuada com o recurso a um dolorímetro de pressão. Foram testados os limiares dolorosos da face antero-interna das tíbias, do manúbrio externo e do leito ungueal dos dedos indicadores. Todos os indivíduos preencheram a versão portuguesa do Hospital Anxiety and Depression Scale (HADS).

Resultados: Verificou-se a ocorrência de dor à pressão tibial, a uma pressão menor do que 4 kg/cm^2, em quase dois terços da amostra (61,9%), sendo que 43,6% destes correspondiam a pacientes com o diagnóstico de fibromialgia. A média do limiar de dor à pressão tibial nas pacientes fibromiálgicas (3,01 ± 1,60 Kg/cm^2) mostrou-se significativamente inferior ($p<0,005$) quando comparado com a média do limiar doloroso obtido no grupo das irmãs saudáveis (4,68 ± 1,67 Kg/cm^2) e no grupo das mães (3,92 ± 2,13). Não foram encontradas relações estatísticas significativas ($p>0,05$) entre a presença de dor à pressão tibial e os biomarcadores estudados (níveis de 25(OH)D e hormonas tiroideias), ansiedade ou depressão.

Conclusões: No nosso estudo observámos uma alta prevalência de dor à pressão tibial em todos os grupos. Foi encontrada uma relação estatisticamente significativa entre fibromialgia e dor à pressão tibial. No entanto, mais estudos serão necessários para esclarecer a etiologia da dor provocada pela pressão tibial.

Palavras-chave: Tíbia, Dor à pressão, Fibromialgia, Vitamina D, Tiróide, Ansiedade, Depressão

Abstract

Background: Tibial pressure pain, defined as pain elicited when mild digital pressure is applied to the tibial shins (as when looking for lower limb edema), seems to be a frequent finding in clinical practice. However, we were unable to find any description of this finding in textbooks and no studies or orientations regarding its possible etiology or adequate clinical interpretation seem to be available. Some clinicians associate this phenomenon with reduced vitamin D values while others argue that it could be a manifestation of fibromyalgia (FM); some clinicians disregard it as having no relevant meaning.

Objective: The primary outcome of this study was to evaluate the prevalence of tibial pressure pain. As secondary outcomes we investigated its association with fibromyalgia, vitamin D, thyroid hormones, anxiety and depression.

Methods: Our sample was constituted by 63 female subjects divided into three groups of 21 elements. One group was formed by fibromyalgia patients, another by their unaffected sisters and the last by patients' mothers. A fasting blood sample was collected in all subjects. We measured 25(OH)D, TSH, fT3 and fT4 hormones. Pressure pain threshold was assessed at tibial shins, sternal manubrium and nail bed of index fingers. All subjects answered to the Portuguese version of Hospital Anxiety and Depression Scale (HADS).

Results: Tibial pressure pain was present in almost two thirds of our sample (61,9%), at less than 4 kg/cm2 of pressure, and 43,6% of them were FM patients. The last ones had a lower

tibial pressure pain threshold (3,01 ± 1,60 Kg/cm^2) than their sisters (4,68 ± 1,67 Kg/cm^2) and mothers (3,92 ± 2,13) ($p<0,005$). No statistically significant relation ($p>0,05$) was found between reduced pressure pain threshold and either the biomarkers tested (thyroid hormones and 25(OH)D values) or the scores of anxiety or depression.

Conclusions: In our study we observed that tibial pressure pain was highly prevalent in all the groups. We found a statistically significant relation between reduced tibial pressure pain threshold and fibromyalgia. Further studies are needed in order to clarify the etiology of tibial pressure pain.

Keywords: Tibia, Pressure pain, Fibromyalgia, Vitamin D, Thyroid, Anxiety, Depression

1. Introduction

Tibial pressure pain is a commonly observed but poorly understood clinical finding. It is characterized by the presence of pain when mild digital pressure is applied over the tibial shins such as when examining for lower limb edema. Many patients with this problem report spontaneous discomfort or pain due to the local contact of clothes or shoe wear, pressure by bed coverings and also on occasional minor local trauma. Clinical observations suggest that this phenomenon is observed more commonly in middle-aged and elderly women and is associated with multiple nonspecific complaints. Physicians vary considerably in their interpretation of this phenomenon: while some merely disregard it as having no relevant meaning, others take it as a strong suggestion of either vitamin D deficiency/osteomalacia or decreased pain threshold/fibromyalgia. Having performed a careful literature search we conclude that neither the prevalence of tibial pressure pain nor its etiology or clinical interpretation is addressed in current medical information sources. Through clinical discussions based on physiopathological reasoning we elected a few hypotheses for primary consideration: fibromyalgia/primary hyperalgesia; vitamin D deficiency/osteomalacia; thyroid dysfunction; anxiety/depression.

Pain, as a submodality of somatic sensation, has been defined as a complex constellation of unpleasant sensory, emotional and cognitive experiences provoked by real or perceived tissue damage and manifested by certain autonomic, psychological and behavioral reactions [1]. Typically, nociception and perception of pain are evoked only when the pressure is intense enough to potentially injure tissues. However, there is a subgroup of population in which perception of pain appears at lower pressures – a phenomenon designated as hyperalgesia.

The fibromyalgia syndrome is a non-articular rheumatic condition characterized by a variety of symptoms related to pain, no restorative sleep and mood disturbances. The diagnostic criteria of the American College of Rheumatology (ACR) for FMs include wide-spread musculo-skeletal pain lasting for at least 3 months, accompanied by pain on pressure of at least 11 of 18 anatomically defined points. These points do not include the tibial shins. These symptoms are frequently associated with morning stiffness, sleep disorders, fatigue, anxiety and depression, with negative impact in quality of life [2]. Fibromyalgia is nowadays understood as a complex hyperalgesia syndrome, in which abnormalities of central sensory processing interact with peripheral pain generators and psychoneuroendocrine dysfunction producing a wide spectrum of symptoms. Central sensitization includes a reduction in pain threshold, an increased response to painful stimuli and increased pain duration even after the cessation of the stimulation [3]. Although not a predefined tender point, may be the tibial pressure pain be a symptom of FMs?

On the other hand, osteomalacia is a common disorder that may easily escape recognition especially in its early stages because of the often nonspecific symptoms. Osteomalacia is almost always caused by vitamin D deficiency, and rarely by phosphate and calcium depletion [4]. The classic symptoms are bone pain and tenderness, muscle weakness, and difficulty in walking, all of which can often be vague and unremitting. Pain in osteomalacia is dull and poorly localized but clearly felt in the bones rather in the joints and is distinct from muscle pain. It is almost never of a radicular nature and in the absence of fracture there is tenderness on percussion of bones, especially over the tibial shins [5].

Pretibial myxedema is an uncommon manifestation of Graves's disease resulting from a local autoimmune response in cutaneous connective tissues probably caused by thyroid-stimulating hormone receptor antibodies [6]. The characteristic abnormality of circumscribed

localized myxedema is thickening of the skin, which usually is limited to the pretibial area [7], and usually painless. However, the lesions may be painful and pruritic [8]. In severe forms associated with thyroid acropachy, the periosteal reaction causes bone pain [9]. Thus, thyroid hormones may also play a role in pretibial pain.

Finally, psychiatric disorders such as depression and anxiety have been correlated to disturbances of pain perception. Pain and depression are supposed to share common neuroanatomical pathways and neurobiological substrates, which might explain the increased vulnerability to pain complaints in depression and vice versa [10,11].

In this paper, we will address the prevalence of tibial pressure pain. We will also explore the potential relationship of tibial pressure pain with the fibromyalgia syndrome (FMs), vitamin D deficiency, thyroid hormone values and anxiety and depression. Lastly, we will assess if physicians frequently recognize this finding in their clinical practice.

2. Materials and Methods

2.1. Study Population

This study was performed as part of a larger scale investigation designated as FMScan, which recruited female patients with fibromyalgia paired with their mother and an unaffected sister.

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

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

All research proceedings were performed in the morning. After receiving an explanation of the study procedures and having an opportunity to present any questions and discuss all issues, participants signed an informed consent form.

2.2. Interview and HADS Questionnaire

All subjects were submitted to a demographic questionnaire (appendix 1) which asked date of birth, nationality, marital status, job, years of education, duration of disease and date of FM diagnosis (when applicable), medication and co-morbidities. Family members were assessed for the ACR criteria for FM.

The Hospital Anxiety and Depression (HADS) Questionnaire adapted to the Portuguese language (appendix 2) was used [11]. The questionnaire consists of two subscales, one measuring anxiety, with seven items, and one measuring depression, also with seven items, which are scored separately. It takes 2-5 minutes to complete. Each item is answered by participants on a 4-point (0-3) response category, and the possible score for each subscale ranges from 0 to 21. A score of 0 to 7 in either subscale is regarded as being in the normal range, a score of 11 or highest as probable presence of the mood disorder, and a score of 8 to 10 as being just suggestive of the presence of the respective state [12].

2.3. Physical examination

Increasing mechanical pressure, was applied by a pressure threshold meter (PTM)(10): the examiner placed the rubber tip on the examination site and gradually increased the pressure at a rate of approximately 1 kg/cm^2 per second until the patient described pain. Pressure pain threshold (PPT) was defined as the minimum pressure applied which induced pain and is described in Kg/cm^2. Pain threshold was measured and recorded (appendix 3) twice in tibial shins, sternal manubrium and nail bed of index fingers. We categorized patients as having tibial pressure pain if the mean of tibial PPT measurements was lower than 4 kg/cm^2, based on other studies in which this value was considered the cut-off point [13, 14].

2.4. Blood sample measurements

A fasting blood sample was collected in all subjects. Breakfast was offered to participants before the other procedures were started. Serum was extracted by centrifugation at 5000 rpm for 10 minutes and stored frozen at -20ºC until analysis, which was performed less than a month after sample collection. Serum 25-OH-D, TSH, fT3 and fT4 were measured by a chemiluminescence immunoassay - DiaSorin LIAISON® in the Hormonology Laboratory of Hospitais da Universidade de Coimbra. Serum 25-OH-D levels are expressed in ng per milliliter. Euthyroidism was defined as concentrations of TSH and fT4 within the normal reference ranges of 0,4–4,0 mU/L and 0,8–1.9 ng/dL, respectively. Subclinical hypothyroidism and overt hypothyroidism were defined as normal and low fT4 concentration, respectively, and elevated TSH (>4,0 mU/L). Hyperthyroidism was defined as decreased concentrations of TSH (< 0,4 mU/L) associated with fT3 above 4,2 ng/dl and/or fT4 above 1,9 ng/dl. Finally, subclinical hyperthyroidism was considered when there was a low TSH concentration and a normal fT3 and fT4 concentrations.

2.5. Questionnaire to physicians

In order to assess whether pretibial pain is identified as a clinical finding by practicing physicians, we asked medical doctors at Hospital of University of Coimbra about their estimated incidence of pretibial pain and its clinical its clinical interpretations (appendix 4). We addressed this questionnaire to cardiologists, rheumatologists, nephrologists, internists, neurologists and physiatrists.

2.6. Statistical analysis

Data were analyzed using statistical package SPSS version 18.0. A significance level lower than 5% (p value < 0,05) was considered as statistically significant in all tests.

Variables were described within study groups according to frequency, means, SD and percentages.

Friedman test was used to evaluate differences of PPTs between the three tested groups. Student-t test was used in continuous variables which satisfied the required normality assumptions and Mann-Whitney test in continuous variables which didn't satisfy the normality assumptions. In order to verify the correlation between variables, we used bivariate correlation of Pearson or Spearman (depending on the existence of normality of the variables).

3. Results

3.1. Socio-demographic characteristics

The screening criteria described above, reduced the potential population to 317 individuals, which were contacted by phone. Of these, 278 were excluded for the following reasons: 121 did not have an unaffected sister, 27 their sister lived too far away to attend, 73 were already orphans or their mother was not capable or participating, 57 were not reachable through the phone. Of the remaining 39 families, satisfying inclusion criteria, 11 refused to participate and 6 never made themselves available to attend the research centre.

Of the remaining 22 families that were included in the overall project, in this paper we excluded one of them because both patient and her sister had FM criteria.

Their demographic characteristics are presented in table 1.

Table I. Baseline characteristics of the study's population

	FM patients	**Sisters**	**Mothers**
Age (years)			
Mean ± SD	40,9 ± 10,3	40,1 ± 10,3	67,6 ± 11,1
Range	18-54	19-52	46-85
Age at first symptoms (years)			
Mean	33,1± 12,7	-	39,7 ± 11,2 (n=3)
Range	15-49	-	30-52
Age at diagnosis (years)			
Mean ± SD	39,7 ± 10,5	-	-
Range	17-54	-	-
Delay in diagnosis (years)			
Mean	7,5 ± 6,5	-	-
Range	0-23	-	-
Education (years)			
Mean ± SD	12,6 ± 4,2	12,1 ± 5,4	4,1 ± 3,5
Range	5-21	4-24	0-11

3.2. Pressure pain thresholds by groups

We observed that PPT in FM patients was lower in all points tested, with statistically significant differences to all locations tested. Table II shows the mean pain threshold measured in each site. We verified that 52,4% (n=33) of all studied subjects had tibial pressure pain in both legs. The prevalence was highest among the FM patients' group (66,7%). On the other hand, the sisters' group showed the lowest percentage of tibial pressure pain (28,6%). The mothers presented an intermediary frequency (61,9%).

Considering people affected by tibial pressure pain who had PPT < 4kg/cm^2 in one leg at least, we found a prevalence of tibial pressure pain of 61,9% (n=39) in our study population, 43,6% of them being FM patients, 35,9% mothers and 20,5% sisters. We observed that patients presenting tibial pressure pain had also reduced sternal and nail's PPTs, presenting a high positive correlation (r>0,636 in all cases; p=0,000). We also tested if PPT was correlated with age. No statistically significant correlation was found between age and PPT (p=0,688).

Table II. Comparison of measured PPT in the three groups studied.

	FM patients	**Sisters**	**Mothers**	*p* value
Tibia midpoint				
Mean ± SD, (kg/cm2)	3,01 ± 1,60	4,68 ± 1,67	3,92 ± 2,13	0,047
Sternal Manubrium				
Mean ± SD, (kg/cm2)	1,91± 1,46	3,16 ± 1,21	2,78 ± 1,66	0,015
Index nail bed				
Mean ± SD, (kg/cm2)	3,12 ± 1,76	4,89 ± 1,89	4,61 ± 2,66	0,013

3.3. Tibial pressure pain and vitamin D status

We didn´t find a statistically significant correlation between vitamin D status and tibial PPT (p=0,411). When the 25(OH)D values of superior and inferior tertiles of tibial PPT were

compared, we also did not find significant differences. The means ± SD of 25(OH)D to superior and inferior PPT's tertiles are shown in table III.

Table III. PPT's mean of superior and inferior PPT tertiles and comparison of their 25(OH)D means.

	Inferior tertile	**Superior tertile**	*p* value
PPT (kg/cm^2)			
Mean ± SD	1,95 ± 0,61	5,93 ± 1,23	0,000
Range	0,85 – 2,65	4,95 - 9,00	
25(OH)D (ng/ml)			
Mean ± SD	15,21 ± 5,50	16,30 ± 6,50	0,434

3.4. Tibial pressure pain and Thyroid hormones

Among the 63 subjects enrolled, 88,89% had normal thyroid function and 7,94% (n=5) were subclinically hypothyroid. One subject (1,59%) had hyperthyroidism and also one subject had subclinical hyperthyroidism. We didn´t observe statistically significant correlation between tibial PPT and thyroid hormone values (p>0,05). When compared the thyroid hormones values between the subjects of superior and inferior tertiles of tibial PPT (table IV), we also didn´t find statistically significant differences (p>0,05). Figure 3 compares TSH and fT4 values between tibial PPT tertiles.

Table IV. Comparison of thyroid hormones between superior and inferior tertiles of tibial PPT.

	Inferior tertile	**Superior tertile**	p value
TSH (mU/L)			
Mean ± SD	2,12 ± 0,87	2,43 ± 1,88	0,772
fT3 (ng/dl)			
Mean ± SD	3,25 ± 0,33	3,30 ± 0,43	0,800
fT4 (ng/dl)			
Mean ± SD	1,09 ± 0,18	1,17 ± 0,35	0,729

3.5. Tibial pressure pain and Anxiety and Depression

Anxiety

There was no statistically significant correlation between anxiety (measured by HADS questionnaire) and tibial PPT (p=0,197). The level of anxiety of subjects of superior and inferior tertiles of tibial PPT was not also statistically different (p=0,126). The mean ± SD of HADS anxiety questionnaire score was 9,95 ± 4,50 in lowest tibial PPT tertile and 8,48 ± 3,60 in superior PPT tertile.

Depression

No statistically significant correlation was found between depression and tibial PPT (p=0,489). The difference of HADS score between tertiles was not also statistically significant (p=0,369). The means ± SD of HADS score in inferior and superior tibial PPT's tertiles were 6,29 ± 4,45 and 5,43 ± 3,52, respectively.

3.6. Questionnaire to physicians

One-hundred questionnaires were distributed to clinicians of University Hospital of Coimbra. However, only thirty-three physicians were available to answer to our questionnaire. Their distribution by medical specialties is shown in table V. Twenty-two of respondents (66,7%) recognized tibial pressure pain as a common finding in their clinical practice. Twenty out of these 22 (90,9%) considered that tibial pressure pain had a higher prevalence in female than in male subjects. Table VI presents the most plausible causes of tibial pressure pain in the view of the respondents.

Table V. Distribution of respondents by medical specialty.

Medical Specialty	Number (%)
Cardiology	4 (12,12%)
Physiatry	3 (9,09%)
Internal Medicine	12 (36,36%)
Nephrology	5 (15,15%)
Neurology	4 (12,12%)
Rheumatology	5 (15,15%)

Table VI. Tibial pressure pain's causes advocated by respondents.

Etiology	Percentage
General hyperalgesia	24,49%
Anxiety	16,33%
Fibromyalgia	14,29%
Neurogenic pain	12,24%
Skin's diseases	12,24%
Osteoporosis	8,16%
Periostitis	6,12%
Osteomalacia	4,08%
Depression	2,04%
Hyperthyroidism	0%
Hypothyroidism	0%

4. Discussion

We found tibial pressure pain in almost two thirds of our sample (61,9%), defined as tibial PPT's mean lower than 4 Kg/cm^2. All tested groups had subjects who presented tibial pressure pain. The group with highest prevalence was FM patients. Of all subjects with tibial pressure pain, 43,6% were FM patients. This result suggests a possible connexion between tibial pressure pain and FM. The generalized lowering of PPTs in FM patients may explain this finding. Although, more than half of subjects presenting tibial pressure pain did not have FM, suggesting than other causes should interfere with pathophysiology of this sign. Indeed, the mothers' group showed a prevalence of tibial pain similar to FM patients. This finding may indicate that biological changes associated with age play a role in the etiology of tibial pressure pain. We have to note that three mothers had FM symptoms which could have affected the results. Many factors are known that produce variations in pain threshold such as race, sex, analgesics, subject and observer interaction, genetic and personality [15-18]. These factors are expected to influence PPTs in general, not only in the tibial area. Indeed, we observed that patients presenting tibial pressure pain had also reduced sternal and nail PPTs in most cases. Therefore, tibial pressure pain could be seen as a part of a generalized decrease of PPT. This statement is in accordance with the questionnaire made to physicians in which the general hyperalgesia was the most advocated cause by respondents to justify tibial pressure pain. Some factors may explain that pain at the tibia may have caught more attention over other sites, i.e. tibia is a frequently site assessed to evaluate presence of edema; it is a bone with a residual subcutaneous tissues between the skin and the bone itself which enhances its exposure; and it is a bone under the load of the body.

In this study, we observed that FM patients had lower PPTs than the other two tested groups. This finding is in accordance with previous studies [13, 19-21]. Tunks *et al*. [21]

found that pressure pain thresholds in nontender points were significantly lower in fibromyalgia patients than in controls. The fact that FM patients have augmented pain sensitivity could possibly be explained by a combination of factors including biochemical and nociception disorders and psychological characteristics, although these etiological factors still require further clarification [19].

Experimental data on age-related changes in pain perception have so far been contradictory. One study dated from 1976 showed that the pain threshold increases with the age [1]; another study [22] presented opposite results showing an inverse correlation between age and PPT. In our study we have compared the PPTs between mothers' and sisters' groups. The average of mothers' age was 27,52 years superior than sisters' age. In accordance with some studies, we observed that elder people had lower PPTs than younger; however, differences were not statistically significant. FM patients were not included due to expected reduced PPTs related to their condition attempting to eliminate bias.

Vitamin D is a steroid hormone that is essential in the homeostasis of calcium and phosphorus and for the functioning of the musculoskeletal system. Vitamin D deficiency in adulthood compromises bone mineralization and may cause osteomalacia which is characterized by bone loss, fractures, deformities bone pain, and generalized proximal myopathy [23]. We performed serum 25(OH)D assay in order to analyze if PPTs were associated with levels of vitamin D. Althought 25(OH)D mean's was lower in subjects who belong to the inferior tibial PPT tertile, no statistically significant differences were found. No studies correlating vitamin D and PPTs were found in literature. However, some experts suggest that vitamin D plays a role in musculoskeletal pain thus supporting a potential association with tibial pressure pain. The way vitamin D acts on the musculoskeletal system, associated with the symptoms related to its deficiency, has led researchers to question if

reductions in lower levels could be responsible for diffuse musculoskeletal pain [24-26]. Straube et al. [27] conducted a critical analysis on this issue. They identified three observational studies exploring differences in 25(OH)D levels between patients with and without chronic musculoskeletal widespread pain. Two of these were very small studies (104 patients in total) [28,29] that claimed significantly reduced 25(OH)D levels in patients with pain compared to controls. However, in a recent large study [30], a significant association between 25(OH)D levels and musculoskeletal increased pain was found in only one of the several analyses. The presently available evidence is not conclusive establishing a relation between vitamin D level and PPTs reduction. Nevertheless, the link between reduced 25(OH)D values and osteomalacia and osteoporosis symptoms make us believe that a possible relationship between reduced 25(OH)D values and decreased tibial PPTs could exist. More studies with larger samples are needed to clarify whether an effective association exists.

We found no correlation between thyroid hormones' values and tibial PPTs. It is important to note that only 11,11% of our sample's subjects presented abnormal thyroid hormones values. This fact was a limitation of this assay.

We did not measure thyroid antibodies. This is an important fact to take in account in future studies about this issue. Indeed, some studies had associated musculoskeletal complaints with presence of thyroid microsomal antibodies [31]. Bazzichi *et al*. [32] suggest a relationship between thyroid autoimmunity and FM, and highlight also the association between thyroid autoimmunity and allodynia. Other studies have similarly demonstrated that thyroid autoimmunity was associated with FM and musculoskeletal widespread pain [31, 33]. It would be interesting to evaluate a possible association between tibial PPTs and thyroid antibodies based on these statements.

In our study, the HADS score to anxiety and depression were higher in subjects who belonged to the inferior tertile of tibial PPT than those belonging to the superior tertile but the differences did not reach statistical significance. We expected that higher anxiety levels would be associated with lower tibial PPTs. This idea is supported by researches that showed an association between anxiety and pain modulation [34, 35].

As mentioned above, no association between tibial PPT and depression was found in our study. Controversial results have been published about this issue. Euteneuer *et al*. [36] showed that depressed patients exhibited significantly decreased PPTs when compared with controls. This finding of increased pain sensitivity in major depression is in accordance with some studies [37] but not all studies. Klauenberg *et al* [38] in their study verified that nearly all depressed patients showed normal mechanical pain and mechanical pain threshold.

5. Limitations

Methodological limitations should be considered when interpreting our results. The first limitation resides the relatively small sample size and the presence of FM symptoms in three mothers. Moreover, we did not include male subjects in present study. It would be important verify whether tibial pressure pain's prevalence differs significantly between men and women. A further important methodological limitation is related to measurement of PPTs. In order to reduce examiner variability, all PPTs should be measured by the same examiner. The reported results may have also been affected by the patients' medication which possibly influences the testing procedures such as slower reaction-time and antinociceptive effects induced by antidepressants. This was not accounted for.

6. Conclusion

Tibial pressure pain was highly prevalent in our sample. However, in most cases, this occurs in the context of generalized hyperalgesia as translated as reduced PPT at other sites. This finding may indicate that tibial pressure pain is a manifestation of a generalized decreased pressure pain syndrome. We found an association between FM involvement and reduced PPTs. Thus, FM and tibial pain provoked by pressure may be related. Despite of this, other causes may interfere with PPT reduction. Further studies are needed in order to clarify the etiology of tibial pressure pain.

Aknowledgments

Agradeço ao Professor Doutor José António Pereira da Silva e ao Dr. João Pedro Vitória Vieira de Matos pela orientação e co-orientação deste trabalho e pelo contributo na minha formação académica e científica. Pelo apoio e suporte que me prestaram, o meu muito obrigado.

Agradeço às enfermeiras Andreia Marques, Andreia Gonçalves, Marisa Lourenço, Marta Martins e à secretária, Dª Ana Abrantes pela colaboração nas colheitas sanguíneas e no apoio logístico prestado a este estudo.

Agradeço à Dra. Fátima Leitão e ao Laboratório de Hormonologia dos Hospitais da Universidade de Coimbra pela colaboração nos doseamentos sanguíneos necessários a este projecto.

Agradeço ao Laboratório de Bioestatística e Informática Médica e, particularmente ao Dr. Pedro Serranho pela ajuda no tratamento estatístico dos dados recolhidos.

Agradeço aos meus colegas de trabalho final do 6º ano médico, Diogo Monteiro, Hugo Paiva, Joana Melim, João Matias, Marta Peixoto, Miguel Pereira, Patrícia Rodrigues e Pedro Silva, pela colaboração no desenho deste estudo e na recolha dos dados necessários à realização do mesmo.

À Rita, por completar os meus dias e pela compreensão e carinho nos momentos mais difíceis. É muito bom estar ao teu lado!

À minha família, por serem o meu grande apoio. Por serem uma família de verdade. Todo este trabalho só foi possível graças ao vosso amor e compreensão.

Aos meus amigos e colegas de curso, um bem-haja!

References

1. O'Driscoll SL: Pain threshold analysis. Clin Rheum Dis 1976;2:27-35.

2. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. Arthritis Rheum. 1990 Feb;33(2):160-72.

3. Grossman SA. Assessment of cancer pain: a continuous challenge. Support Care Cancer. 1994 Mar;2(2):105-10.

4. Parfitt AM. Osteomalacia and related disorders. In: Avioli LV, Krane SM, editors. Metabolic bone disease and clinically related disorders. Philadelphia: WB Saunders; 1990;329-96.

5. Bhan A, Rao AD, Rao DS. Osteomalacia as a result of vitamin D deficiency. Endocrinol Metab Clin North Am. 2010 Jun;39(2):321-31.

6. Kriss JP. Pathogenesis and treatment of pretibial myxedema. Endocrinol Metab Clin North Am. 1987 Jun;16(2):409-15.

7. Fatourechi V, Pajouhi M, Fransway AF. Dermopathy of Graves disease (pretibial myxedema). Review of 150 cases. Medicine (Baltimore). 1994 Jan;73(1):1-7.

8. Schwartz KM, Fatourechi V, Ahmed DD, Pond GR. Dermopathy of Graves' disease (pretibial myxedema): long-term outcome. J Clin Endocrinol Metab. 2002 Feb;87(2):438-46.

9. Fatourechi V, Ahmed DD, Schwartz KM. Thyroid acropachy: report of 40 patients treated at a single institution in a 26-year period. J Clin Endocrinol Metab. 2002 Dec;87(12):5435-41.

10. Adler G, Gattaz WF. Pain perception threshold in major depression. Biol Psychiatry. 1993 Nov 15;34(10):687-9.

11. Pais-Ribeiro, J., et al. Validation study of a portuguese version of the Hospital Anxiety and Depression Scale. Psychol Health Med. 2007;12(2):225-235; quiz 235-7.

12. Snaith, RP. The Hospital Anxiety and Depression Scale. Health Qual Life outcomes. 2003. 1:p.29.

13. Fischer AA. Pressure algometry over normal muscles. Standard values, validity and reproducibility of pressure threshold. Pain. 1987 Jul;30(1):115-26.

14. Smythe HA: Fibrositis and other diffuse musculoskeletal syndromes, Textbook of Rheumatology. Second edition. Edited by WN Kelley, ED Harris Jr, S Ruddy, CB Sledge. Philadelphia, WB Saunders, 1985.

15. Lacroix-Fralish ML, Mogil JS. Progress in genetic studies of pain and analgesia. Annu Rev Pharmacol Toxicol. 2009;49:97-121.

16. Foulkes T, Wood JN. Pain genes. PLoS Genet. 2008;4(7):e1000086.

17. Eccleston C. Role of psychology in pain management. Br J Anaesth. 2001 Jul;87(1):144-52.

18. Mogil JS. The genetic mediation of individual differences in sensitivity to pain and its inhibition. Proc Natl Acad Sci U S A. 1999 Jul 6;96(14):7744-51.

19. Mikkelsson M, Latikka P, Kautiainen H, Isomeri R, Isomaki H. Muscle and bone pressure pain threshold and pain tolerance in fibromyalgia patients and controls. Arch Phys Med Rehabil. 1992 Sep;73(9):814-8.

20. Jensen R, Rasmussen BK, Pedersen B, Lous I, Olesen J. Cephalic muscle tenderness and pressure pain threshold in a general population. Pain. 1992 Feb;48(2):197-203.

21. Tunks E, Crook J, Norman G, Kalaher S. Tender points in fibromyalgia. Pain. 1988 Jul;34(1):11-9.

22. Lautenbacher S, Kunz M, Strate P, Nielsen J, Arendt-Nielsen L. Age effects on pain thresholds, temporal summation and spatial summation of heat and pressure pain. Pain. 2005 Jun;115(3):410-8.

23. Pedrosa MA, Castro ML. Role of vitamin D in the neuro-muscular function. Arq Bras Endocrinol Metabol. 2005 Aug;49(4):495-502.

24. Mascarenhas R, Mobarhan S. Hypovitaminosis D-induced pain. Nutr Rev. 2004 Sep;62(9):354-9.

25. Heaney RP. Nutrition and chronic disease. Mayo Clin Proc. 2006 Mar;81(3):297-9.

26. Perez-Lopez FR. Vitamin D and its implications for musculoskeletal health in women: an update. Maturitas. 2007 Oct 20;58(2):117-37.

27. Straube S, Andrew Moore R, Derry S, McQuay HJ. Vitamin D and chronic pain. Pain. 2009 Jan;141(1-2):10-3.

28. Benson J, Wilson A, Stocks N, Moulding N. Muscle pain as an indicator of vitamin D deficiency in an urban Australian Aboriginal population. Med J Aust. 2006 Jul 17;185(2):76-7.

29. Lotfi A, Abdel-Nasser AM, Hamdy A, Omran AA, El-Rehany MA. Hypovitaminosis D in female patients with chronic low back pain. Clin Rheumatol. 2007 Nov;26(11):1895-901.

30. Atherton K, Berry DJ, Parsons T, Macfarlane GJ, Power C, Hypponen E. Vitamin D and chronic widespread pain in a white middle-aged British population: evidence from a cross-sectional population survey. Ann Rheum Dis. 2009 Jun;68(6):817-22.

31. Aarflot T, Bruusgaard D. Association between chronic widespread musculoskeletal complaints and thyroid autoimmunity. Results from a community survey. Scand J Prim Health Care. 1996 Jun;14(2):111-5.

32. Bazzichi L, Rossi A, Giuliano T, De Feo F, Giacomelli C, Consensi A, et al. Association between thyroid autoimmunity and fibromyalgic disease severity. Clin Rheumatol. 2007 Dec;26(12):2115-20.

33. Ribeiro LS, Proietti FA. Interrelations between fibromyalgia, thyroid autoantibodies, and depression. J Rheumatol. 2004 Oct;31(10):2036-40.

34. Feeney SL. The relationship between pain and negative affect in older adults: anxiety as a predictor of pain. J Anxiety Disord. 2004;18(6):733-44.

35. Chapman, C.R. and Turner, J.A. Psychological control of acute pain, J.Pain Sympt. Manage. 1 (1986) 9-20

36. Euteneuer F, Schwarz MJ, Hennings A, Riemer S, Stapf T, Selberdinger V, et al. Depression, cytokines and experimental pain: Evidence for sex-related association patterns. J Affect Disord. 2010 Dec 15.

37. Vaccarino AL, Sills TL, Evans KR, Kalali AH. Multiple pain complaints in patients with major depressive disorder. Psychosom Med. 2009 Feb;71(2):159-62.

38. Klauenberg S, Maier C, Assion HJ, Hoffmann A, Krumova EK, Magerl W, et al. Depression and changed pain perception: hints for a central disinhibition mechanism. Pain. 2008 Nov 30;140(2):332-43.

Appendix

Appendix 1 – Socio-demographic Interview

INQUÉRITO DEMOGRÁFICO

Data: ____/____/_____

Nº: 00 A

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

Data de nascimento: _____/___/___

Nacionalidade: _____

Residiu no estrangeiro até aos 18 anos? _____

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

Número de irmãos: _____

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

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

(do mais velho para o mais novo)

Tem filhos? Sim ☐ Não ☐

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

Filhos falecidos: ____

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

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

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

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

Estado civil: _____

Profissão:

Por conta própria ☐ Por conta de outrem ☐

Desempregada ☐ Reformada ☐ Com que idade? _____ anos

Anos de educação formal: _____ Concluídos em: ____ anos

Critérios de Fibromialgia: Sim ☐ Não ☐

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

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

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

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

_____
_____
_____
_____
_____
_____

Se tem outras doenças, indique quais:

_____
_____
_____
_____

Que tratamentos faz para estas doenças?

_____
_____
_____
_____

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

_____
_____
_____
_____

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

_____

Appendix 2 – Hospital Anxiety and Depression Scale (Portuguese version)

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

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

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

Appendix 3 – Physical Examination

EXAME FÍSICO

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

Nº de pontos dolorosos: ____

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

Massa gorda:

a. Perímetro abdominal:
(na linha que passa nas cristas ilíacas, numa expiração normal)

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

b. Perímetro do braço:

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

c. Perímetro da coxa:

A	**B**	**C**	**Média**

_____cm _____cm _____ cm _____ cm

d. Prega bicipital:
(medida três vezes no braço não dominante)

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

e. Prega tricipital:
(medida três vezes no braço não dominante)

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

f. Prega subescapular:
(medida três vezes no braço não dominante)

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

g. Prega da coxa:

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

h. Bio-impedância

Appendix 4 – *Questionnaire to physicians*

Dor pré-tibial – uma avaliação sumária

Definição: dor espontânea ou desencadeada por pressão ligeira/moderada(*) na face antero-interna da tíbia.

* como a exercida na pesquisa de sinal de godet por edema

1. **Reconhece este problema na sua prática clínica?**
   Sim /n

Se sim:

2. **Parece-lhe mais frequente em:**
   Homens /Mulheres

3. **Com que frequência aproximada admite que esteja presente esta dor à palpação nos seguintes grupos etários, considerando a sua casuística habitual**

MULHERES

Idade	**Percentagem**
<20 ●	● 0
21-40 ●	● 1-10%
41-60 ●	● 10-20%
>60 ●	● 20-30%
	● >30%

HOMENS

Idade	**Percentagem**
<20 ●	● 0
21-40 ●	● 1-10%
41-60 ●	● 10-20%
>60 ●	● 20-30%
	● >30%

4. Na sua prática clínica como interpreta este sintoma? Isto é: a que o atribui?

_____
_____

Vire, sff

5. Qual das seguintes explicações lhe parecem mais plausíveis. Escolha duas (círculo)

- Ansiedade
- Depressão
- Doenças da pela /tecido celular subcutâneo
- Dor neurogénica
- Fibromialgia
- Hiperalgesia geral
- Hipertireoidismo
- Hipotireoidismo
- Osteomalácia
- Osteoporose
- Periostite

A sua especialidade é: _____

Muito Obrigado,

Hugo Antunes

José António Pereira da Silva (Reumatologia)