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CONSOLIDAÇÃO DO PROJECTO ACTA REUMATOLÓGICA PORTUGUESA

Lúcia Costa*

É com grande satisfação que posso anunciar que a partir do início de 2012 teremos a funcionar de forma definitiva o *site* da Acta Reumatológica Portuguesa (ARP), passando a submissão de artigos a ser feita exclusivamente por este meio. Pensamos ser um passo importante pela forma como permitirá aos autores acompanharem o processo de revisão dos seus trabalhos, evitando a perda de tempo muitas vezes ocasionada por erros nos endereços electrónicos e nos contactos por *e-mail*. Neste número estão já disponíveis as novas instruções aos autores para submissão dos artigos. Por outro lado, a revista *online* permitirá uma melhor difusão, facilitando o acesso ao arquivo de forma fácil. Embora tivesse sido nosso objectivo conseguir prestar este serviço há mais tempo, não deixa de ser curioso que esta melhoria objectiva da ARP vá surgir num ano importante para a Sociedade Portuguesa de Reumatologia (SPR), já que em 2012 a SPR comemora 40 anos de existência.

Um dos nossos objectivos para melhorar o posicionamento da ARP, nomeadamente no aumento do Factor de Impacto (FI), era conseguir um maior número de artigos escritos integralmente em inglês e os autores responderam de forma inequívoca, sendo actualmente a maioria dos artigos publicados nesta língua, o que facilita a difusão da revista, proporcionando maior número de citações.

Em virtude da crescente preocupação com a qualidade dos artigos publicados, tivemos uma taxa de rejeição de perto de 25%, principalmente no que diz respeito a casos clínicos. Essa exigência vai manter-se e o número de casos clínicos a publicar será tendencialmente mais baixo, sendo importante que os relatos submetidos sejam situações raras ou com dificuldades diagnósticas ou de tratamento.

Estando no final do ano, quero agradecer a todos os que contribuíram para a manutenção da qualidade da ARP, nomeadamente os autores que elegeram a Acta Reumatológica como meio de divulgação do seu trabalho.

Agradeço a colaboração fundamental de todo o corpo editorial: Editores Associados, Conselho Editorial, Editor Técnico (João Cavaleiro) e Editora Publisaúde. Um agradecimento especial a todos os que colaboraram revendo de forma cuidada e criteriosa os artigos submetidos, contribuindo para o rigor das publicações: Aikaterini Chatzidionysiou, Ana Azevedo, Ana Cordeiro, Ana Filipa Mourão, Ana M Rodrigues, Ana Rita Cravo, Ana Sofia Roxo, Anabela Barcelos, António Albino Teixeira, António Paulo Encarnação, Augusto Faustino, Cândida Silva, Carmo Afonso, Catarina Resende, Cátia Duarte, Domingos Araújo, Elisabete Martins, Elsa Sousa, Esperanza Naredo, Fernando Pimentel, Filipa Ramos, Filipa Teixeira, Filipe Barcelos, Filipe Vinagre, Graça Pereira, Helena Canhão, Helena Pessegueiro, Helena Santos, Herberto Jesus, Ingrid Moller, J A Pereira Silva, Jaime Branco, Jiri Vencoski, Joana Lopes, João Eurico Fonseca, Joaquim Pereira, Jorge Crespo, Jorge Lains, José Alves, José Carlos Romeu, José Costa, José Miguel Bernardes, Jozélio Carvalho, Luís Graça, M Teresa Terreri, Manuel Gutierres, Manuel Salgado, Manuela Costa, Margarida Espanha, M João Saavedra, M João Salvador, M José Santos, Marta Conde, Márta Péntek, Melo Gomes, Miguel Roberto Jorge, Milton Severo, Mónica Bogas, Patrícia Nero, Paula Araújo, Paulo Coelho, Pedro Machado, Raquel Lucas, Raul Maia Silva, Ricardo Figueira, Sandra Falcão, Sara Cortes, Sara Lourenço, Sofia Pimenta, Sofia Ramiro, Susana Capela, Teresa Monjardino, Teresa Nóvoa, Vaz Patto e Viviana Tavares.

Desejo que, com o contributo de todos, 2012 seja um excelente ano para a Acta Reumatológica Portuguesa.

*Editora-Chefe, Acta Reumatológica Portuguesa

REVIEW OF COMPARATIVE STUDIES BETWEEN BONE DENSITOMETRY AND QUANTITATIVE ULTRASOUND OF THE CALCANEUS IN OSTEOPOROSIS

Michelle Flöter[*], Cíntia Kelly Bittar[**,*], José Luis Amin Zabeu[*], Ana Carolina Ramos Carneiro[*]

Abstract

Objective: To assess the utility of quantitative ultrasound (QUS) of the calcaneus for diagnosing osteoporosis compared to the gold standard, bone densitometry using dual-emission X-ray absorptiometry (DXA), according to published reports.
Design: In this systematic review, the Medline/ /PUBMED, Medline Ovid and Journals@Ovid, and Wilson General Sciences Full Text database were used. The search strategy involved use of the following MeSH descriptors: [osteoporosis AND (densitometry OR ultrasonography)], and 39 articles published between 2001 and April 2010 were assessed. However, only six articles met the inclusion criteria: sensitivity and specificity of QUS, sample (women or men with no treatment or other disease likely to change bone mass index), devices used, comparative T-score between QUS of the calcaneus and DXA. The GE-Lunar Achilles and Hologic Sahara devices were used in most of the tests reported and were effective.
Results: All studies assessed compared QUS of the calcaneus to DXA of the lumbar spine or femoral neck, as the gold standard. QUS sensitivity ranged from 79% to 93% and specificity ranged from 28% to 90% when at the lower threshold. It is a controversial parameter, because the gold-standard threshold (T-score < -2.5, DXA) could not be used for QUS without errors in osteoporosis diagnosis. All studies had a threshold determined by the authors' criteria, with a variability of -1.7 (pDXA T--score) and -2.4 for QUS, leading to the same prevalence of osteoporosis, and a T-score of < -3.65 for QUS was equivalent to a T-score < -2.5 for DXA.
Conclusions: Based on the analysis of seven studies, we conclude that QUS of the calcaneus still cannot be used to confirm diagnosis of osteoporosis by comparing the results to those of patients who had already received such a diagnosis based on DXA. However, further research should be conducted in this area, because it is possible to improve the number diagnoses by varying the cutoff T-score. Furthermore, using QUS of the calcaneus was a helpful tool for assessing pathological fractures, whether or not they were associated with osteoporosis.

Keywords: Densitometry; Bone Mineral Density; Calcaneus/ultrasonography; Osteoporosis.

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Introduction

Osteoporosis is defined by the World Health Organization (WHO) as a disease characterized by reduced bone mass and microarchitectural deterioration of bone tissue, with consequent bone fragility and susceptibility[1-3] to fractures[4,5]. Such criteria have not been defined for men, who have larger bones with thicker cortices, although their density and trabecular architecture is similar to that of women[4]. The WHO's operational definition for osteoporosis is a BMD that is 2.5 SDs (T-scores) or more below the mean for young healthy adult women and the definition of osteopenia is a T-score between -1 and -2.5[1,11].

The disease affects approximately 200 million people worldwide, and is responsible for 1.5 million fractures annually in the USA[1,3]. In Latin America, the vertebral and femoral bones are affected in around 15% of women over the age of 50 years, with great social and economic impact[3].

Considering the increase in life expectancy, prevention and early diagnosis of osteoporosis may avoid frequent complications, such as fractures. Ad-

ditionally, early diagnosis may contribute to reducing public health expenditures and the costs of rehabilitating these patients. In Latin American countries, the direct costs of disease reach US$4500–6000 per month, which may be higher than the per capita income in some of these countries[3].

Bone density evaluation for diagnosing osteoporosis can be performed by various methods, including bone ultrasound, bone densitometry, tomography, and radiographic exams. Bone densitometry using dual-emission X-ray absorptiometry (DXA) remains the gold-standard test for the diagnosis and quantification of osteoporosis, but access to this method is still restricted due to its high cost and limited availability in rural zones[2].

Quantitative ultrasound (QUS) of the calcaneus is a bone ultrasound method that provides a fast diagnosis with no radiation emissions and at relatively low cost[38]; it can also be used to predict the risk of fractures due to osteoporosis[1-3,5,13]. The calcaneus is especially suitable for obtaining a quantitative analysis because of its characteristics: a short, trabecular bone with a thin cortex[6]. It has a high metabolic turnover and a bone pattern similar to that of the spine. Because of its trabecular mechanical characteristics, the calcaneus undergoes static and dynamic stresses from orthostatism and the human walking mechanism. However, there is still no consensus on the accuracy of QUS of the calcaneus for identifying patients with osteoporosis.

QUS uses low-frequency ultrasonic waves to measure different bone properties by means of two parameters: the speed of sound (SOS, expressed as m/s) which means the necessary time to ultrasound waves go through a determined distance inside the calcaneus bone[7,11] and the attenuation of ultrasound broad bands (BUA, expressed by dH/MHz) which is a measure of the ultrasound variation of attenuation with the incident frequency of wave sound[7,11], generating a rigidity index called stiffness[12] of the bone or quantitative ultrasound index (QUI, expressed as a percentage of the result from young adults or the percentage of weight-matched references according to the manufacturer)[7,12]. Estimated Bone Mineral Density (EBMD expressed as g/cm^2) is the result of the combination of BUA and SOS that gives a BMD value, but it is important to note that QUS BMD is inferred from a linear combination of BUA and SOS and it is not an actual measurement of calcaneal BMD[6,41].

Its use has been satisfactorily described in the literature for predicting the risk of fractures[13] resulting from osteoporosis, but it has not been shown to be reliable for monitoring medication treatment of osteoporosis[3] because of differences between the equipment and parameters used[13].

Dual-energy x-ray absorptiometry (DXA) of the lumbar spine and femur head is the gold-standard test for bone evaluation. It generates T-score and Z-score based on the statistical unit of the standard deviation[5]. T-score is the number of standard deviations below the average for a young adult at peak bone density. Z-score is the number of standard deviations below an average person of the same age. There are different T-scores and Z-scores depending on the group used as a reference. BMD (expressed as g/cm^2)[11] calculated as the ratio of bone content to the scanned area is helpful to predict the risk of bone fracture[1,5] and BMC (expressed as kg)[5]. DXA quantifies bone *mass* but is incapable of providing information about bone *quality*. The quality and microarchitecture of the trabeculae correspond to up to 50% of the mechanical strength of bone. This is equivalent to a relationship of 0.43 between bone density and bone strength[6,7]. This relationship explains why in many cases the risk of fracture may be greater than the bone densitometry value would suggest, due to the fragile bone microarchitecture, which is not effectively diagnosed by densitometry. Additionally, it is an expensive test, there is a lack of equipment in places with less infrastructure[8,9], and it is generally difficult to extrapolate hip fracture risk parameters to other points of the skeleton, such as the lumbar spine[8].

The association between the DXA and QUS tests has been reported to present a margin of confidence of 90% in specificity and sensitivity[10], suggesting that bone mass density and evaluation performed by QUS may be equally predictive of risk of future fractures[11], since one Standard Desviation decreased in BUA increases two times the risk of hip fractures[3,13]. The aim of this review was to analyze comparative studies between DXA and QUS, verifying their applicability in the diagnosis of osteoporosis according to the WHO criteria, using DXA as the gold-standard technique.

Methods

The Medline/PUBMED, Medline Ovid and Journals@Ovid, and Wilson General Sciences Full Text

databases were used in the literature review. In the search strategy, the following MeSH descriptors were used: [osteoporosis AND (densitometry OR ultrasonography)].

Thirty-nine articles published between 2001 and April 2010 were analyzed, and then either selected or excluded because they did not meet the following inclusion criteria: sensitivity and specificity of QUS compared to DXA, subjects in the sample (women and/or men who were not being treated with drugs that altered bone quality and without other comorbidities that altered the bone mass index), types of equipment, the presence of the QUS equipment brand used in the research, comparative T-score between the methods, and site for the performed test (Table I). As a result, only six studies were included, which included all of the variables discussed here (Table II).

Table I. Compared variables between published articles following or not the inclusion criteria

Variables Articles (author)	Sensitivity DXA/ /QUS	Specificity DXA/ /QUS	Devices used DXA/ /QUS	Subjects in the Sample (N)	BMD (T-Score) DXA/ /QUS	Site where which test were used DXA/QUS	Year of publication
EL Maghraoui et al.[5]	- / -	- / -	+	+	+ / +	+ / +	2009
Camozzi et al.[2]	- / -	- /-	+	+	+ / +	+ / +	2007
Canhão et al.[7]	- / -	- / -	+	+	- / +	- / +	2006
Hans et al. [8]	- /-	- / -	-	+	- / -	+ /+	2004
Frost et al.[6]	- / -	- / -	+	+	+ / +	+ / +	2001
Hans et al.[3]	**+ / +**	**+ / +**	**+**	**+**	**+ / +**	**+ / +**	**2009**
Arana-Arri E et al.[16]	- / +	- / +	-	+	- / +	- / +	2007
Jørgensen et al.[17]	+ / +	+ / +	-	+	+ / +	+ / +	2001
Imashuku et al.[10]	- / -	- / -	+	+	+ / +	+ / +	2007
Hodson, Marsh[18]	- / +	- / +	-	+	+ / +	+ / +	2003
Fukunaga, Sone, Yoshikawa[19]	- / -	- /-	-	-	- / -	+/ -	2006
Soontrapa, Soontrapa, Chaikitpinyo [20]	- / -	- / -	-	-	+ / +	+ / -	2009
Frost, Blake, Fogelman[21]	+ / +	+ / +	-	+	+ /+	+ /+	2002
El-Desouki, Sherafzal, Othman[22]	+ / +	+ / +	-	+	+ /+	+ /+	2005
Glüer et al[23]	- / -	- / -	-	+	- / -	+ / +	2005
Krieg et al[24]	- / +	- / +	-	-	- / -	- / +	2008
Hans, Krieg[25]	- / -	- / -	-	-	- / -	- / +	2008
Gudmundsdottir, Indridason, Franzson, Sigurdsson[11]	**+ / +**	**+ / +**	**+**	**+**	**+ / +**	**+ / +**	**2004**
Ikeda[13]	**+ / +**	**+ / +**	**+**	**+**	**+ / +**	**+ / +**	**2002**
Navas et al.[26]	- / -	- / -	+	+	+ / +	+ / +	2006
Pearson et al.[14]	**+ / +**	**+ / +**	**+**	**+**	**+ / +**	**+ / +**	**2003**
Wüster, Hadji[27]	- / -	- / -	-	-	- / -	- / +	2009
Kraemer, Nelson, Bauer, Helfand[15]	- / -	- / -	-	+	- / -	+ / +	2005
Dubois et al.[28]	+ / +	+ / +	-	+	- / -	+ / +	2001
Glüer et al.[29]	+ / +	+ / +	-	+	- / -	+ / +	2004
Nayak et al.[26]	+ / +	+ / +	-	+	+ / +	+ / +	2006
Stewart, Reid,[30]	- / +	- / +	+	+	+ / +	+ / +	2000
Relation among MRTA, DXA and QUS[31]	- / -	- / -	-	+	- / -	+ / +	2004

continues on the next page

Table I. Compared variables between published articles following or not the inclusion criteria *(continuation)*

Variables Articles (author)	Sensitivity DXA/ /QUS	Specificity DXA/ /QUS	Devices used DXA/ /QUS	Subjects in the Sample (N)	BMD (T-Score) DXA/ /QUS	Site where which test were used DXA/QUS	Year of publication
Schnabel et al[32]	+ / +	+ / +	-	+	+ / +	+ / +	2006
Frediani et al[33]	+ / +	+ / +	-	+	+ / +	+ / +	2005
Diessel et al[34]	- / -	- / -	+	+	- / -	+ / +	2006
Knapp[35]	- / +	- / -	-	-	- / -	- / -	2000
Trimpou et al[12]	**+ / +**	**+ / +**	**+**	**+**	**+ / +**	**+ / +**	**2010**
Mueller, Gandjour[36]	- / -	- / -	-	+	- / -	- / -	2008
Nayak, Roberts, Greenspan[37]	- / -	- / -	-	+	- / -	- / -	2009
VU THI THU HIEN et al[38]	- / -	- / -	+	+	- / +	- / +	2005
ZHU Z.Q.; LIU, W.; XU, C.L.; HAN, S.M.; ZHU, G.J.[39]	- / -	- / -	+	+	- / +	- / +	2008
Boonen et al[9]	**+ / +**	**+ / +**	**+**	**+**	**+/ +**	**+ / +**	**2005**
Mazariegos[40]	- / -	- / -	+	+	+ / +	+ / +	2004

* the article's sequence content is at the References

Table II. Selected published articles following the inclusion criteria

Variables Articles (author)	Sensitivity DXA/ /QUS	Specificity DXA/ /QUS	Devices used DXA/ QUS	Subjects in the Sample (N)	BMD (T-Score) DXA/ /QUS	Site where which test were used DXA/ /QUS	Year of publication
Hans et al[3]	+ / +	+ / +	+	+	+ / +	+ / +	2009
Gudmundsdottir, Indridason, Franzson, Sigurdsson[11]	+ / +	+ / +	+	+	+ / +	+ / +	2004
Ikeda et al[13]	+ / +	+ / +	+	+	+ / +	+ / +	2002
Pearson et al[14]	+ / +	+ / +	+	+	+ / +	+ / +	2003
Trimpou et al[12]	+ / +	+ / +	+	+	+ / +	+ / +	2010
Boonen et al[9]	+ / +	+ / +	+	+	+/ +	+ / +	2005

Results

All studies assessed compared QUS of the calcaneus to DXA of the lumbar spine or femoral neck, as the gold standard. Six articles met our inclusion criteria.

The included studies evaluated the compared specificity and sensibility between QUS and the gold-standard DXA of postmenopausal women, men over 70 years or both, without comorbidities that could influence the cutoffs measured to reach a threshold for QUS diagnosis, described the DXA and QUS equipments used, to assure that the manufacturers reference or the use of the phantom to avoid false-negatives and showed a comparative T--score between methods, according to their cutoffs

Table III. Comparison between the included articles according to the inclusion criteria

Selected Article	Population Characteristics	n. of Patients	Equipment used (QUS and DXA)	Specificity (QUS)	Sensibility (QUS)	Objectives of the study
Trimpou et al[12]	Women with Postmenopausal osteoporosis, aged between 53-73 years	80	Lunar Achilles; LUNAR DXP-L	36 – 57%	76 – 84%	7 years follow-up to validate QUS against DXA, as gold-standard
Boonen et al[9]	Post-menopausal women aged between 50-75 years	221	Hologic Sahara; QDR 4500a fan beam system (Hologic)	70.4%	67.6%	Evaluated the ability of QUS to diagnose osteoporosis
Gudsmundsdottir et al[11]	Random sample aged between 30-85 years (Caucasian population in Iceland)	1630 individuals (1041 females; 589 males)	Lunar Achilles Plus; Hologic QDR 4500	30 -62% for 50-65 years range; 26- 68% for 70-85 years range;(men) 13 – 47% for 70-85 years range	79 – 94% for 50-65 years range; 95- 71% for 70-85 years range; (men) 100–83% for 70-85 years range	Investigate age-related bone decline in men and women measured with QUS and DXA and to find a clinically cutoff level for QUS to detect Osteopenia or Osteoporosis according to DXA
Pearson et al[14]	Women aged between 33-86 years	99	Lunar Achilles Plus; GE Lunar Expert	60 ±10% (when compared to Spine BMD) 84±8% (when compared to Total Hip BMD)	59 ±10% (when compared to Spine BMD) 41±10% (when compared to Total Hip BMD)	Determine the optimal T-score between pDXA and QUS in comparison to DXA
Hans et al[3]	Comparison of 13 studies; women from EPIDOS Study	9561 patients; 5954 from EPIDOS Study	Lunar Achilles/ Hologic Sahara; Hologic QDR 4500 and LUNAR DXP-L	Near to 90% if the threshold is near to inferior parameter of DXA	Near to 90% if the threshold is near to superior parameter of DXA	Review the clinical use of QUS in the following wing settings: 1) the prediction of fracture risk; 2) the diagnosis of osteoporosis; 3) the initiation of osteoporosis treatment or prevention; 4) the monitoring of such treatment; 5) osteoporosis case finding
Ikeda et al[13]	Healthy Japanese women aged between 20-79 years, cohort randomly selected	659	Hologic Sahara; QDR 4500A, Hologic	65- 67% (when compared to Spine BMD) 72 – 74% (when compared to Total Hip BMD)	64- 65% (when compared to Spine BMD) 71% (when compared to Total Hip BMD)	Establish reference values of the QUS indices in healthy Japanese women of various ages and to propose a criterion for diagnosing osteoporosis by means of QUS indices

(Table III).

Several studies evaluated more than one of these parameters, however they were excluded because they did not meet all inclusion criteria. We focused our analysis on the comparison of the QUS of calcaneus and DXA for the diagnosis of Osteoporosis.

The cutoffs variables were measured using the following methods: The mean, standard deviation (S.D.) and the standard error of the mean (S.E.M.) were calculated using conventional methods[12], receiver operating characteristic (ROC) curves[3,9,11,13,14] and the areas under the curves AUCs were computed to determine the optimun T-score threshold for QUS measurements, the sensitivity and the specificity[9] and diagnostic accuracy of osteoporosis of each QUS[13].

Discussion

Six articles published between 2001 and 2010 that satisfied the inclusion criteria were analyzed. Considering that osteoporosis affects around 200 million persons worldwide, QUS has been proposed as a diagnostic tool because of its portability, low cost, and safety, although the gold-standard recommended by the WHO is DXA of the lumbar spine and femur head. In the six studies, the gold--standard was compared to the QUS method.

Based on the studies analyzed, the sensitivity of QUS compared to DXA showed a range of values: 86–93%[12], 79%[14], 90% for the superior parameter[3], 65-67% (when compared to Spine BMD) and 72–74% (when compared to Total Hip BMD)[13], and 67.6% for the 95% confidence interval[9]. Regarding specificity, the following values were reported: 28–44%[12], 64-65% (when compared to Spine BMD) and 71% (when compared to Total Hip BMD)[13], 90% for the inferior parameter[3], 65.8%[14], and 70.4%[9], demonstrating that variation in sensitivity depends on the change thresholds used for measuring deviation. However, when the sensitivity values were high, the method had an excellent negative predictive value (around 90%[9]) and median specificity value, which also improved when the threshold was reduced (although this slightly decreased its sensitivity).

According to Hans *et al.*[3], the highest number of reported tests have been performed using the GE--Lunar Achilles and Hologic Sahara machines, which have proven to be more effective than other devices. GE-Lunar Achilles was used in studies reported by Trimpou *et al.*[12], Pearson *et al.*[14], and Gudmundsdo *et al.*[11,12,15]. Hologic Sahara was mentioned by Ikeda *et al.* as performing well, and was also used by Boonen *et al.*, in conjunction with the Meditech DTU-One machine, for which no evidence has been reported for evaluating the risk of hip fractures, according to Hans *et al.*[3]. In their study, it was observed that the GE-Lunar Achilles was used in the majority of populations to evaluate the risk of fractures of the hip, spine, and other sites in the body, whereas the Hologic Sahara had been used with Caucasian and Japanese populations[3]. Regarding to WHO criteria, which is not applicable to QUS, women were also classified into WHO groups using the revised criteria for QUS that have been shown applicable to Sahara and DTUone devices[41], creating a standard T-score for these machines, however the different models were not comparable each other (Hologic Sahara and Lunar Achilles), even for the same index[13].

According to Ikeda *et al.*[13], 659 Healthy Japanese women aged between 20-79 years, from a second survey of a larger cohort study (JPOS study), that involved 2 cohorts in the northeastern part of Honshu main island and in Shikoku, were selected to establish reference values of the QUS indices and to propose a criterion for diagnosing osteoporosis by means of QUS indices. The vaue of Sahara as a diagnostic tool would be increased if the optimal site is determined to be the total hip in the future, however, the method did not increase sensitivity and specificity, making the diagnostic accuracy of QUS indices not superior than age which can be obtained very easily without any expensive machines.

In Hans *et al.*[3] a sample of 5,954 women ≥ 75 years participating in the EPIDOS study, analyzed using the same previously mentioned specificity and sensitivity values, showed 11% false positives and 13% false negatives. This suggests that the QUS method could be used to identify individuals with many or few risk factors for osteoporosis, and for values between the superior and inferior limits, and that DXA could be used as the definitive test and for follow-up in therapy.

In Pearson *et al.*[14], both methods did not show significant differences in performance, with the prevalence of osteoporosis of 46% at the spine and 24% at the total hip for the group measured with the QUS, very similar to those obtained by DXA measurements: 46% at the spine and 25% at the total hip, when applied to 99 women aged 33–86

years who had been referred to the bone metabolism clinic.

In Trimpou *et al.*[12] 80 women aged 53–73 years with osteoporosis or fractures were followed for a period of 7 years. They found that the sensitivity of the method was high, despite the low specificity, and concluded that DXA must be used as a diagnostic test, if available, before beginning the treatment of osteoporosis but the treatment may be initiated without this method if QUS shows a T-score < -3.65, particularly in the presence of fractures.

In Gudsmundsdottir *et al.*[11] a random sample of 1,630 individuals (1,041 women, 589 men) aged 30–85 years showed that loss of bone mass in relation to age was significantly higher when using QUS than when using DXA. Although QUS is not incorporated into the diagnosis of osteoporosis by the WHO, in the study, it was possible to exclude this diagnosis in 30–40% of the cases.

Boonen *et al.*[9] evaluated 221 post-menopausal women aged 50–75 years who had been referred to the Leuven University Center for Metabolic Bone Diseases for DXA, among whom 9 patients were receiving therapy for osteoporosis. It was possible to observe, within the 95% confidence intervals, a mean negative predictive value (NPV) of 89.8% and a mean positive predictive value (PPV) of 33.4%, indicating that the method was useful for diagnosing osteoporosis in the age range studied, compared to the gold-standard method. Nevertheless, the authors noted that a limitation of their study is the lack of a random sample, suggesting that care should be taken when attempting to generalize their data. Also, some of the subjects were receiving treatment for osteoporosis.

A point of controversy with regard to all of the studies is the cut-off point for the diagnostic determination of osteoporosis with the QUS method. No direct relationship can be made between the threshold accepted for DXA (a T-score < -2.5) and QUS without there being discrepancies between the number of patients diagnosed with osteoporosis by each method[3], in addition to variation in calibration of the machines, and the use (or not) of a phantom, a device incorporated at the quantitative ultrasound of calcaneus that calculate the interval of the transmitted wave between the device to the bone and the way back[3] which minimizes the possibility of error in the QUS readout, that also vary with porosity of this incorporated device[13].

In the studies analyzed, it was noted that the authors set a cut-off point determined at their discretion, ranging from -1.7 (pDXA T-score) and -2.4 for QUS, so as to define the same prevalence of osteoporosis[14]. In comparison to the gold-standard spine BMD the QUS T-Score vary from -1,51 to -1,58 and in comparison to gold-standard total hip BMD it vary from -1,88 to -1,90, and, when applied WHO criteria to QUS, the prevalence of osteoporosis appeared to be much lower than that for spine BMD.[13] Another study found that the T-score for QUS should be -1.61 to -1.72 compared to the threshold for DXA accepted by the WHO[9]. In a study on women aged 50–65 years, a T-score > -1.0 for QUS was applied for identifying normal BMD, whereas in the age range of 70–85 years, a T-score < -2.5 for women and < -0.6 for men were considered reasonable cut-off values for identifying normal BMD[12]. It has been reported that T-scores, and particularly a T-score value below -1.55 by QUS, have adequate discriminative power for the diagnosis of osteoporosis[13].

One limitation of this study was the difficulty in finding reports that satisfied all of the inclusion criteria, suggesting that better-designed, more standardized studies should be conducted. An important point, although it is not the main objective of the present study, is that QUS is a helpful tool for evaluating patients with pathological fractures, whether or not they present risk factors for osteoporosis. This reveals good utility for this diagnostic method, which may be used as a tool in triage for the evaluation of fractures due to osteoporosis and later referral of patients to a specialized center that uses DXA, for therapy and monitoring, if necessary.

Conclusions

QUS cannot yet be used to reliably confirm a diagnosis of osteoporosis by the gold-standard DXA test[1]. Indeed, there is great variation in the sensitivity and specificity of QUS, which results in more or fewer diagnoses depending on the T-score, both age and gender dependent, generating confusion. However, there was a large compatibility between the two methods based on the studies assessed in the present study. Further studies on the subject are necessary to determine criteria and a reliable correlation between QUS and DXA.

Nevertheless, with the technological advance, it is possible to improve the QUS devices to be used

at the patients during the clinical treatment of Osteoporosis[3], since this method has good assessment of the quality of the bone and a high correlation with the clinical fracture risks[2], it can be used to exclude healthy individuals from further examinations.

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FREQUENCY OF RHEUMATIC DISEASES IN PORTUGAL: A SYSTEMATIC REVIEW

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Abstract

Objectives: To describe the frequency of rheumatic diseases in Portugal through a systematic review of published literature, critically appraising available information and identifying data collection gaps.
Methods: We systematically reviewed the literature to retrieve data on the occurrence of rheumatic diseases in Portugal through MEDLINE and *Índex das Revistas Médicas Portuguesas* searches, PhD theses, and national health surveys reports. Original articles in English or Portuguese published between 1 January 2000 and 31 December 2010 were included.
Results: We retrieved information for the prevalence of rheumatic diseases, osteoarthritis, back pain, work-related musculoskeletal disorders (WRMDs), osteoporosis, fibromyalgia, rheumatoid arthritis, spondyloarthritis and other systemic rheumatic diseases and for the incidence of back pain, osteoporotic fracture and other systemic rheumatic diseases.

The prevalence of rheumatic diseases ranged from 16.0% to 24.0% and the prevalence of osteoarthritis was 11.1% (95% confidence intervals (95%CI): 9.4-13.1) in the knee and 5.5% (95%CI: 4.3-7.0) in the hip. Regarding back pain, period prevalence ranged from 8.0% (95%CI: 6.1-10.1) to 29.5% (95%CI: 23.4-36.2) in children and from 12.3% (95%CI: 10.5-14.3) to 51.3% (95%CI: 48.6--53.9) in adults. The prevalence of WRMDs ranged from 5.9% to 84.2% (95%CI: 80.8-87.3). The yearly incidence of osteoporotic fracture (per 100 000) ranged from 93.3 to 481 (95%CI: 407-564) in women and from 31.9 to 154 (95%CI: 106-218) in men. The prevalence of osteoporosis in women ranged from 11.0% to 15.4% (95%CI: 13.4-17.6) and in men from 1.1% to 16.8% (95%CI: 12.2-22.3). The prevalence of fibromyalgia ranged from 3.6% (95%CI: 2.0-5.2) to 3.7% (95%CI: 2.0-5.4). The prevalence estimates of ankylosing spondylitis and of spondyloarthritis were 0.6% and 1.6% (95%CI: 0.8-2.7), respectively. The prevalence of systemic lupus erythematosus was estimated in 0.2% (95%CI: 0.1-0.8).
Conclusions: There is a broad spectrum of information available that indicates an important burden of rheumatic diseases in the general Portuguese population. Gaps were identified particularly regarding inflammatory arthropathies and other systemic rheumatic diseases.

Keywords: Rheumatic Diseases; Burden of Disease; Frequency; Prevalence; Incidence; Portugal.

Introduction

Rheumatic diseases are conditions and functional disorders of the musculoskeletal system of non--traumatic causes. These diseases are a diverse group of conditions with regard to pathophysiology which are linked not only by the musculoskeletal structures affected but by their association with pain and consequent reduction in the range of motion and function[1,2]. They encompass a wide spectrum of conditions, from those of acute onset and short duration to chronic progressive course disorders including osteoarthritis, rheumatoid arthritis, osteoporosis and low back pain[3].

Rheumatic conditions are a major cause of morbidity throughout the world[3,4]. They represent an important social and economic problem inflicting enormous costs on health and social care systems[4,5]. They cause more pain and disability than any other group of conditions with consequent organ dysfunction, limitation in activity and restriction in social participation[4]. In Europe, nearly one quarter of adults are affected by longstanding musculoskeletal problems that limit daily activities[6]. Although affecting all ages, rheumatic diseases become increasingly common with ageing. Conside-

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ring the increasing number of old people throughout the world and the observed trends in lifestyles, which promote the occurrence of musculoskeletal disorders, the burden of these conditions on public health tends to rise[4,6].

Individual and population impact of rheumatic diseases is certainly high in Portugal according to estimates obtained in other developed societies. However, it is important to systematically collect indicators of the current burden of musculoskeletal conditions in our population, in order to monitor trends and guide health policies[7]. Although in Portugal, narrative reviews on the frequency of rheumatic diseases, individually or as a group, have been published[5,8-10], we believe that the knowledge about these conditions will benefit from a systematic approach.

We were interested in original studies estimating the prevalence and/or incidence of rheumatic diseases targeted by the *National Program against Rheumatic Diseases* because of their predicted impact at population level, either related to their high frequency or to their strong association with adverse health outcomes[2,11]. These conditions are osteoarthritis, back pain, periarticular rheumatic diseases, including work-related musculoskeletal disorders, osteoporosis and osteoporotic fracture, fibromyalgia, microcrystal-related arthropathies, rheumatoid arthritis, spondyloarthritis, other systemic rheumatic diseases and pediatric rheumatic diseases.

Objectives

We aimed to systematically review published scientific literature on the frequency of rheumatic diseases in Portugal, to critically appraise the available information and to identify the gaps in data collection.

Methods

Following the 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[12], data on the occurrence of rheumatic diseases in Portugal were obtained through MEDLINE and *Índex das Revistas Médicas Portuguesas* (Index RMP) searches using the expressions presented in Table I (Date of last search: 30th August 2011). We also reviewed PhD theses in the Index RMP bibliographic database, periodic general health surveys such as the *4th National Health Survey* and publications including information on rheumatic diseases. In addition to this strategy, we also performed a cross references search and a full manual search in the journals *Acta Reumatológica Portuguesa*, *Acta Médica Portuguesa*, *Revista Portuguesa de Saúde Pública*, *Revista Portuguesa de Clínica Geral* and *Arquivos de Medicina*. Since a review on the studies before 2000 estimating the prevalence of rheumatic diseases in Portugal was published in 2002[5] and to optimize the relation between the sensitivity desired and the resources available, original articles in English or Portuguese published between 1 January 2000 and 31 December 2010 were included.

For rheumatic diseases, 1 049 articles were retrieved by MEDLINE and Index RMP bibliographic databases. We identified 170 articles for osteoarthritis, 261 articles for back pain, 86 articles for periarticular rheumatic diseases, 260 articles for work-related musculoskeletal disorders, 345 articles for osteoporosis and osteoporotic fracture, 32 articles for fibromyalgia, 66 articles for microcrystal-related arthropathies, 200 articles for rheumatoid arthritis, 158 articles for spondyloarthritis, 853 articles for other systemic rheumatic diseases and 52 articles for pediatric rheumatic diseases.

Two reviewers (TM and RL) screened all the references. After reviewing the titles and abstracts and/or the full articles, we excluded those that were clearly unrelated to the study subject, (e.g. studies not estimating prevalence or incidence of the condition of interest) or that had a sampling strategy which did not include a random or consecutive sample of Portuguese subjects).

For rheumatic diseases that almost inevitably lead to hospitalization or medical appointments, such as osteoporotic fracture and juvenile idiopathic arthritis, studies estimating prevalence and/or incidence based on hospital records were also included.

Through the MEDLINE and Index RMP searches, and after exclusions were made, two studies were included for rheumatic diseases[13,14], one study for osteoarthritis[13], five studies for back pain[13,15-18], two studies for work-related musculoskeletal disorders[19,20], seven studies for osteoporosis and osteoporotic fracture[13,21-26], one study for fibromyalgia[27], two studies for rheumatoid arthritis[13,28], two studies for spondyloarthritis[13,29], three studies for other systemic rheumatic diseases[13,28,30] and one

Table I. Search expressions and systematic review results about rheumatic diseases occurrence

Diseases	Bibliographic database	Search expression	Number of results after duplicates removed	Excluded articles by title and abstract	Number of included articles and references
Rheumatic diseases	Medline	Publication Date - from 2000/1/01 to 2010/12/31: (musculoskeletal disease OR musculoskeletal disorder OR rheumatic diseases OR skin and connective tissue diseases OR calcium metabolism disorder) AND (Portugal OR Portuguese) AND (prevalence OR incidence OR occurrence OR frequency)	1 049	Not incidence/prevalence studies of rheumatic diseases: n=1 041 Not Portuguese general population based studies: n=6	2[13,14]
	Index RMP	Articles and PhD theses from 2000 to 2010: doença AND reumática AND prevalência doença AND reumática AND incidência patologia AND reumática AND prevalência patologia AND reumática AND incidência patologia AND musculo AND prevalência patologia AND musculo AND incidência patologia AND osteoarticular AND prevalência patologia AND osteoarticular AND incidência			
Osteoarthritis	Medline	Publication Date - from 2000/1/01 to 2010/12/31: (arthritis OR osteoarthritis OR arthrosis OR osteoarthrosis) AND (Portugal OR Portuguese) AND (prevalence OR incidence OR occurrence OR frequency)	170	Not incidence/prevalence studies of osteoarthritis: n=167 Not Portuguese general population based studies: n=2	1[13]
	Index RMP	Articles and PhD theses from 2000 to 2010: osteoartrose AND prevalência osteoartrose AND incidência artrose AND prevalência artrose AND incidência			
Back pain	Medline	Publication Date - from 2000/1/01 to 2010/12/31: (back pain OR back ache) AND (Portugal OR Portuguese) AND (prevalence OR incidence OR occurrence OR frequency)	261	Not incidence/prevalence studies of back pain: n=251 Not Portuguese general population based studies: n=5	5[13,15-18]
	Index RMP	Articles and PhD theses from 2000 to 2010: raquialgia AND prevalência			

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Table I. *(continuation)*

Diseases	Bibliographic database	Search expression	Number of results after duplicates removed	Excluded articles by title and abstract	Number of included articles and references
		raquialgia AND incidência cervicalgia AND prevalência cervicalgia AND incidência dor AND cervical AND prevalência dor AND cervical AND incidência lombalgia AND prevalência lombalgia AND incidência dor AND lombar AND prevalência dor AND lombar AND incidência			
Periarticular rheumatic diseases	Medline	Publication Date - from 2000/1/01 to 2010/12/31: (soft tissue injury OR bursitis OR tendinitis OR tenosynovitis OR enthesopathy OR capsulitis) AND (Portugal OR Portuguese) AND (prevalence OR incidence OR occurrence OR frequency)	86	Not incidence/prevalence studies of periarticular rheumatic diseases: n=85	0
	Index RMP	Articles and PhD theses from 2000 to 2010: patologia AND periarticular AND prevalência patologia AND periarticular AND incidência tendinite AND prevalência tendinite AND incidência tenossinovite AND prevalência tenossinovite AND incidência entesite AND prevalência entesite AND incidência bursite AND prevalência bursite AND incidência capsulite AND prevalência capsulite AND incidência ligamentite AND prevalência ligamentite AND incidência		Not Portuguese general population based studies: n=1	

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Table I. *(continuation)*

Diseases	Bibliographic database	Search expression	Number of results after duplicates removed	Excluded articles by title and abstract	Number of included articles and references
Work-related musculoskeletal disorders	Medline	Publication Date - from 2000/1/01 to 2010/12/31: (occupational OR work) AND musculoskeletal disease) AND (Portugal OR Portuguese) AND (prevalence OR incidence OR occurrence OR frequency)	260	Not incidence/prevalence studies of work-related musculoskeletal disorders: n=248 Not Portuguese general population based studies: n=10	2[19,20]
	Index RMP	Articles and PhD theses from 2000 to 2010: reumatologia AND ocupacional AND prevalência reumatologia AND ocupacional AND incidência les* AND musculo AND prevalência les* AND musculo AND incidência LMERT AND prevalência LMERT AND incidência LMELT AND prevalência LMELT AND incidência			
Osteoporosis and osteoporotic fracture	Medline	Publication Date - from 2000/1/01 to 2010/12/31: (osteoporosis OR osteoporotic fracture) AND (Portugal OR Portuguese) AND (prevalence OR incidence OR occurrence OR frequency)	345	Not incidence/prevalence studies of osteoporosis and osteoporotic fracture: n=330 Not Portuguese general population based studies: n=8	7[13,21-26]
	Index RMP	Articles and PhD theses from 2000 to 2010: osteoporose AND prevalência osteoporose AND incidência fractura AND prevalência fractura AND incidência			
Fibromyalgia	Medline	Publication Date - from 2000/1/01 to 2010/12/31: (fibromyalgia OR fibromyositis OR chronic fatigue syndrome) AND (Portugal OR Portuguese) AND (prevalence OR incidence OR occurrence OR frequency)	32	Not incidence/prevalence studies of fibromyalgia: n=30 Not Portuguese general population based studies: n=1	1[27]
	Index RMP	Articles and PhD theses from 2000 to 2010: fibromialgia AND prevalência fibromialgia AND incidência sindrome fibromiálgico AND prevalência sindrome fibromiálgico AND incidência «fadiga crónica» AND prevalência «fadiga crónica» AND incidência			

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Table I. *(continuation)*

Diseases	Bibliographic database	Search expression	Number of results after duplicates removed	Excluded articles by title and abstract	Number of included articles and references
Microcrystal--related arthropathies	Medline	Publication Date - from 2000/1/01 to 2010/12/31: (gout OR chondrocalcinosis OR crystal arthropath*) AND (Portugal OR Portuguese) AND (prevalence OR incidence OR occurrence OR frequency)	0	Not incidence/prevalence studies of microcrystal-related arthropathies: n=66	66
	Index RMP	Articles and PhD theses from 2000 to 2010: artropatia AND prevalência artropatia AND incidência gota AND prevalência gota AND incidência pirofosfato AND cálcio AND prevalência pirofosfato AND cálcio AND incidência			
Rheumatoid arthritis	Medline	Publication Date - from 2000/1/01 to 2010/12/31: rheumatoid arthritis AND (Portugal OR Portuguese) AND (prevalence OR incidence OR occurrence OR frequency)	200	Not incidence/prevalence studies of rheumatoid arthritis: n=198	2[13,28]
	Index RMP	Articles and PhD theses from 2000 to 2010: artrite AND prevalência artrite AND incidência			
Spondylo-arthritis	Medline	Publication Date - from 2000/1/01 to 2010/12/31: (spondyloarthropathies OR spondylarthropath* OR psoriatic arthritis OR arthritic psoriasis OR ankylosing spondylitis OR bechterew disease OR reiter OR reactive arthritis OR postinfectious arthritis) AND (Portugal OR Portuguese) AND (prevalence OR incidence OR occurrence OR frequency)	158	Not incidence/prevalence studies of spondyloarthritis: n=155 Not Portuguese general population based studies: n=1	2[13,29]
	Index RMP	Articles and PhD theses from 2000 to 2010: espondil* AND prevalência espondil* AND incidência psoria* AND prevalência psoria* AND incidência sindrom* AND Reiter AND prevalência sindrom* AND Reiter AND incidência SAPHO AND prevalência SAPHO AND incidência			

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Table I. *(continuation)*

Diseases	Bibliographic database	Search expression	Number of results after duplicates removed	Excluded articles by title and abstract	Number of included articles and references
Other systemic rheumatic diseases	Medline	Publication Date - from 2000/1/01 to 2010/12/31: (systemic rheumatic disease OR connective tissue diseases OR autoimmune diseases OR myositis OR vasculitis OR skin diseases, vascular) AND (Portugal OR Portuguese) AND (prevalence OR incidence OR occurrence OR frequency)	853	Not incidence/prevalence studies of other systemic rheumatic diseases: n=850	3[13,28,30]
	Index RMP	Articles and PhD theses from 2000 to 2010: doença AND reumática AND sistémica AND prevalência doença AND reumática AND sistémica AND incidência doença AND tecido AND conjuntivo AND prevalência doença AND tecido AND conjuntivo AND incidência conectivite AND prevalência conectivite AND incidência doença AND autoimune AND prevalência doença AND autoimune AND incidência esclerose AND sistémica AND prevalência esclerose AND sistémica AND incidência polimiosite AND prevalência polimiosite AND incidência dermatomiosite AND prevalência dermatomiosite AND incidência vasculite AND prevalência vasculite AND incidência lúpus AND eritematoso AND sistémico AND prevalência lúpus AND eritematoso AND sistémico AND incidência Sjogren AND prevalência Sjogren AND incidência			
Pediatric rheumatic diseases		Publication Date - from 2000/1/01 to 2010/12/31: (pediatric rheumatic diseases OR juvenile arthritis) AND (Portugal OR Portuguese) AND (prevalence OR incidence OR occurrence OR frequency)	52	Not incidence/prevalence studies of pediatric rheumatic diseases: n=51	1[31]

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Table I. *(continuation)*

Diseases	Bibliographic database	Search expression	Number of results after duplicates removed	Excluded articles by title and abstract	Number of included articles and references
	Index RMP	Articles and PhD theses from 2000 to 2010: artrite AND idiopática AND prevalência artrite AND idiopática AND incidência reumatismo AND juveni* AND prevalência reumatismo AND juveni* AND incidência			

study for pediatric rheumatic diseases[31].

For their relevance in population-based measures and indicators we obtained also data from the *4th National Health Survey*, carried out by the National Health Institute Doutor Ricardo Jorge (INSA, IP) and Statistics Portugal (INE, IP)[32], from the *ECOS project (Em Casa Observamos Saúde)*, an observation tool created by INSA, IP[14,33], and from the *Network of Sentinel Doctors,* a primary care surveillance system from the National Institute of Health based on a network of general practitioners[18,34,35].

Through the cross references search and full manual search we additionally identified two studies for back pain[36,37] and seven studies for work-related musculoskeletal disorders[38-44].

For each study, we extracted information on first author, year of publication, period of data collection, data collection method, case definition used, study population addressed, characteristics of the subjects evaluated (gender and age of the participants), sample size, participation/response rate and a summary of the estimates. Researchers were contact directly when studies did not present results in a format that could be used in the incidence and prevalence tables. A summary of the characteristics of the studies included in this systematic review and results on the frequency of rheumatic diseases are presented in Tables II to XI.

We conducted a thorough assessment of the methodological quality of the included studies using the checklist for incidence and prevalence studies of chronic diseases (Methodological Evaluation of Observational Research)[45]. For each study, the report firstly lists flaws and issues not reported related to external validity followed by flaws and issues not reported related to internal validity. The authors of this checklist did not propose numerical rating of quality, quantitative values for criteria or numerical weighting of flaws. We did not appraise the methodological quality of two articles estimating the frequency of acute low back pain[18,35] since it is not a chronic disease and of one article providing prevalence of several rheumatic diseases[28], since it was based on secondary data combining information from patients followed by specialists and the prevalence of these diseases in other countries.

Results

We identified 32 studies reporting the incidence or the prevalence of rheumatic diseases in the Por-

Table II. Frequency of rheumatic diseases (studies characteristics and results)

First author, publication year, reference	Period of data collection	Collecting data method	Case definition	Study population	% males	Sample size	% participation	Age distribution	Estimates
INSA, IP/INE, IP, 2009[32]	2005-2006	Face to face interview	To have or have had any rheumatic disease/Previous medical or nursing diagnosis of a rheumatic disease/To have or have had any rheumatic disease in the previous year (all self-reported)	Residents in Portugal familiar dwellings	48.4%	41 193 individuals (15 239 dwellings)	76%	Age groups (years): <15: 15.6% 15-24: 12.4% 25-34: 15.6% 35-44: 14.8% 45-54: 13.3% 55-64: 11.2% 65-74: 9.6% 75-84: 5.9% ≥85: 1.5%	Lifetime prevalence: Both sexes: 16.0% M: 11.1%; F: 20.5% Lifetime prevalence (medical or nursing diagnosis): Both sexes: 14.6% Prevalence in the previous year: Both sexes:14.5%
Branco M, 2005[14]	2004	Telephone interview	To have a rheumatic disease (self-reported)	Residents in Portugal mainland familiar dwellings with landline (Portugal Telecom)	47.4%	2 820	82.1%	Age groups (years) 0-4: 2.8% 5-9: 4.3% 10-14: 4.8% 15-24: 12.6% 25-34: 12.6% 35-44:12.8% 45-54:14.4% 55-64: 14.8% 65-74: 12.6% >75: 8.2%	Point prevalence: Both sexes: 24.0% (95%CI:22.4-25.7) M: 18.3% (95%CI:16.2-20.6) F: 29.1% (95%CI:26.7-31.7)
Costa L, 2004[13]	1999-2003	Face to face interview	History of medical diagnosed of, at least, one of these diseases: rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, psoriatic arthritis, hip osteoarthritis, knee osteoarthritis and chronic low back pain (self-reported)	Adult population of the city of Porto	36.4%	1 238	70.0%	Age groups (years): ≤40: 33.9% 41-59: 36.2% >59: 29.9%	Lifetime prevalence: Both sexes: 23.0% M: 13.1% (95%CI:10.2-16.6) F: 28.7% (95%CI:25.6-32.0)

INSA, IP/INE, IP – National Institute of Health/Statistics-Portugal; M – males; F – females; 95%CI - 95% confidence intervals.

Table III. Frequency of osteoarthritis (studies characteristics and results)

First author, publication year, reference	Period of data collection	Collecting data method	Case definition	Study population	% males	Sample size	% participation	Age distribution	Estimates
Costa L, 2004[13]	1999-2003 interview	Face to face	History of medical diagnosed hip osteoarthritis or knee osteoarthritis (self-reported)	Adult population of the city of Porto	36.4%	1 238	70.0%	Age groups (years): ≤40: 33.9% 41-59: 36.2% >59: 29.9%	Lifetime prevalence (hip osteoarthritis): Both sexes: 5.5% (95%CI:4.3-7.0) M: 2.2% (95%CI: 1.1-4.2) F: 7.4% (95%CI:5.7-9.5) Lifetime prevalence (knee osteoarthritis): Both sexes: 11.1% (95%CI:9.4-13.1) M: 5.9% (95%CI:3.9-8.6) F: 14.2% (95%CI:11.8-16.9)

M – males; F – females; 95%CI - 95% confidence intervals.

tuguese population and published during the last decade.

Rheumatic diseases

Two studies meeting our inclusion criteria describing the overall prevalence of rheumatic diseases were identified from the bibliographic database search[13,14]. Additionally we identified the *4th National Health Survey* from which we calculated the lifetime prevalence of rheumatic diseases[32] (Table II).

The number of subjects evaluated ranged from 1 238, 36.4% males, in Costa *et al* (2004)[13] to 41 193, 48.4% males, in the *4th National Health Survey*[32]. Branco *et al* (2005)[14] and the *4th National Health Survey* described samples with wide age ranges (from childhood to over 75) while Costa *et al* (2004) enrolled participants over 18 years. In these three studies the cases of rheumatic disease were defined according the participant's self-reported history of any medically-diagnosed rheumatic disease. Overall, the prevalence of self-reported rheumatic disease ranged from 16.0%[32] to 24.0%[14]. In women estimates ranged from 20.5% [32] to 29.1% (95% confidence intervals (95%CI): 26.7-31.7)[14] and in men these ranged from 11.1% [32] to 18.3% (95%CI: 16.2-20.6)[14].

Osteoarthritis

The prevalence of osteoarthritis was obtained from the aforementioned study by Costa et al (2004)[13] (Table III). Cases were defined according to self-reported history of clinically diagnosed hip and/or knee osteoarthritis. Overall the prevalence of self-reported osteoarthritis was higher in the knee [11.1% (95%CI: 9.4-13.1)] than in the hip [5.5% (95%CI: 4.3-7.0)].

Back pain

We identified two studies estimating the incidence[18,35] and seven studies estimating the prevalence of back pain[13,15-17,33,36,37] (Table IV). Both studies estimating incidence were performed by the *Network of Sentinel Doctors* through registration of new episodes of acute low back pain in 2003[18] and in 2004[35]. In 2004, in 124 709 patients (47.8% males), the global yearly incidence was 1 817.8 per 100 000 population, higher in women (2 157.4) than in men (1 446.7)[35]. Prevalence studies described samples that ranged from 215 [Vital *et al* (2006)[37]] to 4 817 participants [Matos *et al* (2006)[36]] and a male proportion varying from 35.4% [Rabiais *et al* (2003)[33]] to 55.8% [Vital *et al* (2006)]. These

Table IV. Frequency of back pain (studies characteristics and results)

First author, publication year, reference	Period of data collection	Collecting data method	Case definition	Study population	% males	Sample size	% participation	Age distribution	Estimates
Network of Sentinel Doctors, 2006[35]	2004	New cases of disease notified by the physicians network	Clinical criteria for the diagnosis of acute low back pain	Clients of mainland Portugal health care centers	47.8%	124 709 patients (129 general practic-tioners)	2.3% of general practictioners in Portugal	Age groups (years): 0-4: 5.8% 5-9: 5.2% 10-14: 5.4% 15-24: 12.9% 25-34: 15.9% 35-44: 14.6% 45-54: 12.5% 55-64: 10.2% 65-74: 9.9% ≥75: 7.6%	Yearly incidence rate: Both sexes: 1 817.8 per 100 000 M: 1 446.7 per 100 000 F: 2 157.4 per 100 000
Rabiais S, 2003[33]	2002	Telephone interview	Low back pain in the previous week (at least one day)	Adult residents in Portugal mainland familiar dwellings with landline (Portugal Telecom)	35.4%	1 414	84.6%	Age groups (years): 18-24: 5.8% 25-34: 8.3% 35-44: 18.0% 45-54: 19.9% 55-64: 20.8% 65-74: 17.4% ≥75: 9.7% Not specified: 1.3%	Prevalence in the previous week: Both sexes: 51.3% (95%CI:48.6-53.9) M: 36.5% (95%CI:32.2-40.9) F: 59.4% (95%CI:56.2-62.6)
Costa L, 2004[13]	1999-2003	Face to face interview	History of medical diagnosed chronic low back pain (lasting more than 3 months) (self-reported)	Adult population of the city of Porto	36.4%	1 238	70.0%	Age groups (years): ≤40: 33.9% 41-59: 36.2% >59: 29.9%	Lifetime prevalence: Both sexes: 12.3% (95%CI:10.5-14.3) M: 6.4% (95%CI:4.4-9.2) F: 15.6% (95%CI:13.2-18.4)
Ponte C, 2005[15]	2004	Telephone interview	Low back pain in the previous 6 months	Adult users of a health center of Porto	52.0%	296	98.6%	Age groups (years): 18-29: 19.6% 30-39: 24.3% 40-49: 22.0% 50-65: 34.1%	Prevalence in the previous 6 months: Both sexes: 49.0% (95%CI: 43.3-54.7) M: 44.2% (95%CI:36.2-52.4) F: 54.2% (95%CI:45.7-62.6)

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Table IV. ***(continuation)***

First author, publication year, reference	Period of data collection	Collecting data method	Case definition	Study population	% males	Sample size	% participation	Age distribution	Estimates
Matos M, 2006[36]	2006	Self administrated questionnaire	Back pain in the previous 6 months (almost every day pain or more than once a week)	6th, 8th and 10th grades Portuguese students	49.6%	4 817	1,6% of the population of students enrolled in academic year 2005/2006	Mean age: 14 years	Prevalence in the previous 6 months: Both sexes: 12.9% M: 9.5% F: 16.2%
Costa M, 2002[16]	1999-2000	Face to face interview by a rheumatologist	Back pain in the previous 3 months	Public school students from the metropolitan region of Lisbon	45.6%	767	n/av	Mean age (standard deviation); [range]: 10.6 (2.4) years; [6-17]	Prevalence in the previous 3 months: Both sexes: 8.0% (95%CI: 6.1-10.1) M: 4.3% (95%CI:2.4-7.0) F: 11.0% (95%CI:8.2-14.4)
Coelho L, 2009[17]	2005-2006	Self administrated question-naire	All and any kind of painful complaint in the lumbar region which has lasted at least 24 hours	Young people resident in the Greater Lisbon area and attending educational establishments there (both state-run and private)	47.6%	439	n/av	Mean age (standard deviation); [range]: 13.0 (1.1) years; [11-15]	Annual prevalence: Both sexes 20.5% (95%CI:16.8-24.6) M: 11.0% (95%CI:7.1-16.0) F: 29.2% (95%CI:23.3-35.5) Point prevalence: Both sexes: 16.3% (95%CI:5.2-10.4) Lifetime prevalence: Both sexes: 25.5% (95%CI:21.5-29.9)
Vital E, 2006[37]	2003-2004	Self administrated question-naire	Back pain in the previous 6 months (almost every day pain or more than once a week)	5th grade students from two Portugal Center region municipalities	55.8%	215	97.3%	Age (years): 10: 53.0% 11: 31.2% 12: 12.6% 13: 3.3%	Prevalence in the previous 6 months: 29.5% (95%CI:23.4-36.2)[I] Prevalence in the previous 6 months (first episodes): Both sexes: 16.3 (95%CI:11.6-22.1)[II]

n/av – Not available; M – males; F – females; 95%CI – 95% confidence intervals; I, II – Estimates calculated from the results presented in the study

Table V. Frequency of work-related musculoskeletal disorders (studies characteristics and results)

First author, publication year, reference	Period of data collection	Collecting data method	Case definition	Study population	% males	Sample size	% participation	Age distribution	Estimates
Cunha--Miranda L, 2010[19]	2006	Questionnaire sent to the occupational physician	Clinically relevant WRMDs	Large dimension companies in Portugal (over 250 employees)	48.4%	410 496 workers (515 companies)	62.3%	Mean age (standard deviation): M: 39.5 (5.7) years F: 37.9 (5.1) years	Point prevalence: 5.9% (total WRMDs clinically relevant) Back pain: 4.2% Cervical pain: 1.1% Dorsal pain: 0.8% Low back pain: 2.3% Upper limb: 1.6% Shoulder tendonitis: 0.6% Carpal tunnel syndrome: 0.3% Elbow tendonitis: 0.3% Hand tendonitis: 0.4% Lower limb tendonitis: 0.1%
Parent--Thirion A, 2007[38]	2005	Face to face interview	Backache or muscular pains in shoulders, neck and/or upper/lower limbs related to occupational activity	Residents in Portugal in paid employment (employees and self-employed), during the field-work period (over 15 years old)	n/av	1 000	67%	n/av	Point prevalence of backache: 30.7% Point prevalence of muscular pains in shoulders, neck and/or upper/lower limbs: 28.8%
Carnide F, 2006[20]	2004	Interview and a clinical exam conducted by an occupational medical doctor	WRMSs (presence of pain or paraesthesia during the last year, with episodes lasting for at least 1 week or occurring at least once a month, with no previous acute trauma)/ /WRMDs evaluated by an occupational medical doctor	Automobile industry workers (paint area production)	n/av	29	n/av	Mean age (standard deviation): 37.7 (8.2) years	Point prevalence: Neck: WRMSs: 10.3% (95CI%:2.2-27.4) WRMDs: 58.6% (95%CI:38.9-76.5) Right shoulder: WRMSs: 24.1% (95%CI:10.3-43.5) WRMDs: 20.7% (95%CI:8.0-39.7) Left shoulder: WRMSs: 6.9% (95%CI:0.8-22.8)

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Table V. *(continuation)*

First author, publication year, reference	Period of data collection	Collecting data method	Case definition	Study population	% males	Sample size	% participation	Age distribution	Estimates
									WRMDs: 10.3% (95%CI:2.2-27.4) Right elbow: WRMSs: 17.2% (95%CI:5.8-35.8) WRMDs: 24.1% (95%CI:10.3-43.5) Left elbow: WRMSs: 0.0% (95%CI:0.0-12.0) WRMDs: 3.4% (95%CI:0.1-17.8) Right wrist: WRMSs: 27.6% (95%CI:12.7-47.2) WRMDs: 24.1% (95%CI:10.3-43.5) Left wrist: WRMSs: 6.9% (95%CI:0.8-22.8) WRMDs: 17.2% (95%CI:5.8-35.8) Right hand: WRMSs: 10.3% (95%CI:2.2-27.4) WRMDs: 17.2% (95%CI:5.8-35.8) Left hand: WRMSs: 0.0% (95%CI:0.0-12.0) WRMDs: 10.3% (95%CI:2.2-27.4)
Serranheira F, 2003[39]	2001	Self-administered questionnaire	WRMSs in the previous year/week (adaptation of the Standardised Nordic questionnaire for the analysis of musculoskeletal symptoms)	Automobile components industry workers (industry in Setubal peninsula)	16.1%	574	63.2%	Modal class [range]: 26-33 years [18-65]	Prevalence in the previous year: Cervical region: 83.0% Shoulders: 57.5% Elbows: 21.4% Wrists/hands: 66.7% Upper back region: 50.3% Low back region: 55.4% Hips/thigh: 31.1% Legs/knees: 71.2% Ankles/feet: 63.7% Prevalence in the previous week: Cervical region: 29.1%

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Table V. *(continuation)*

First author, publication year, reference	Period of data collection	Collecting data method	Case definition	Study population	% males	Sample size	% participation	Age distribution	Estimates
									Shoulders: 24.2% Elbows: 8.3% Wrists/hands: 32.1% Upper back region: 21.4% Low back region: 23.5% Hips/thigh: 14.5% Legs/knees: 35.3% Ankles/feet: 30.2%
Uva A, 2005[40]	2002	Self-administrated questionnaire	Back pain related to occupational activity (physicians, nurses, health care allied professionals and clerks working in health facilities, in government agencies and in other sectors not directly related to the provision of care)	Ministry of Health workers	25%	1 754	41%	Age groups (years): <20: 1.1% 20-29: 20.9% 30-39: 30.7% 40-49: 25.7% 50-59: 18.6% ≥60: 2.3% Not specified: 0.7%	Point prevalence: Both sexes: 47%
Carneiro P, 2005[41]	2003	Self-administered questionnaire	Pain or discomfort related to occupational activity	Portuguese dentists	44%	697	16.6%	Mean age (standard deviation): M: 36.1 (8.3) years F: 32.1 (6.2) years	Prevalence in the previous year: M: 75.5% (95%CI:69.8-80.5) F: 83.3% (95%CI:79.0-87.0)
Vilão S, 2005[42]	2000	Self-administered questionnaire	Have suffered at least one WRMDs (self-reported)	Physiotherapists working in Portugal Center region hospitals	13%	41	n/av	Age groups (years): 21-30: 50% 31-40: 42% 41-60: 8%	Lifetime prevalence: Both sexes: 58.5% (95%CI:42.1-73.7)
Fonseca R, 2006[43]	2004	Self-administered questionnaire	WRMSs (Standardised Nordic questionnaire for the	Nurses working in Porto hospitals	16%	507	56%	Median [range]: 31 years [22-63]	Prevalence in the previous year: Both sexes: 84.2% (95%CI: 80.8-87.3)

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Table V. ***(continuation)***

First author, publication year, reference	Period of data collection	Collecting data method	Case definition	Study population	% males	Sample size	% participation	Age distribution	Estimates
			analysis of musculoskeletal symptoms)						Prevalence in the previous week: Cervical region: 53% Shoulders: 61% Elbows: 33% Wrists/hands: 45% Dorsal region: 62% Low back region: 58% Thighs: 54% Knees: 56% Ankles/feet: 71%
Martins J, 2008[44]	2007	Self-administered questionnaire	WRMSs (Standardised Nordic questionnaire for the analysis of musculoskeletal symptoms)	Nurses working in one hospital (medicine, surgery and orthopedics services)	18.2%	176	80%	Mean age (standard deviation); [range]: 33.4 (7.5) years; [23-66]	Prevalence in the previous year: Both sexes: 81.3% (95%CI:74.7-86.7) M: 71.9% (95%CI:53.2-86.2) F: 83.3% (95%CI:76.2-89.0)

n/av – Not available;WRMDs – work-related musculoskeletal disorders;WRMSs – work-related musculoskeletal symptoms; M – males; F – females; 95%CI – 95% confidence intervals

studies used distinct definitions of back pain and different prevalence estimates (point prevalence[17], period prevalence in previous specified days/ /months/years[15-17,33,36] or lifetime prevalence[13,17]). In four studies samples of children and adolescents (6 to 17 years) were evaluated[16,17,36,37] and three studies enrolled adults[13,15,33]. Among children and adolescents, the prevalence of back pain ranged from 8.0% (95%CI: 6.1-10.1), if classified as pain in the previous three months[16], to 29.5% (95%CI: 23.4-36.2), if classified as pain in the previous six months[37]. In adults, low back pain prevalence ranged from 12.3% (95%CI: 10.5-14.3), when evaluated as lifetime low back pain lasting more than three months[13], to 51.3% (95%CI: 48.6-53.9), when classified as at least one day of pain in the previous seven days[33].

Work-related musculoskeletal disorders

We identified nine studies estimating the prevalence of work-related musculoskeletal disorders (WRMDs)[19,20,38-44] (Table V). To define cases of WRMDs Cunha-Miranda *et al* (2010)[19] and Carnide *et al* (2006)[20] considered only clinically relevant disorders, with medical diagnosis, while other studies considered work-related musculoskeletal symptoms (WRMSs) as reported by workers[38-44]. The sample sizes ranged from 29 [Carnide *et al* (2006)] to 1 000 (Parent-Thirion *et al* 2007[38]) when workers were inquired directly while, in the study by Cunha-Miranda *et al* (2010) addressing 515 occupational health doctors, a coverage of 410 496 workers was achieved[19]. The proportion of males ranged from 13.0% [Vilão *et al* (2005)[42] to 48.4% (Cunha-Miranda *et al* (2010)], (the gender distribution was not available for two studies[20,38]), and Parent-Thirion *et al* (2007) included workers from the age of 15. Cunha-Miranda *et al* (2010), Parent-Thirion *et al* (2007) and Uva *et al* (2005)[40] presented data on the prevalence on WRMDs for several professional categories whereas other studies focused on particular occupational activities (e.g. industrial workers[20,39], health care providers[41-44]). The prevalence of WRMDs ranged from 5.9%, considering clinically relevant disorders in several occupational activities[19], to 84.2% (95%CI: 80.8-87.3) regarding symptoms reported by hospital nurses[43].

Table VI. Frequency of osteoporosis or osteoporotic fracture (studies characteristics and results)

First author, publication year, reference	Period of data collection	Collecting data method	Case definition	Study population	% males	Sample size	% participation	Age distribution	Estimates
Pina M, 2008[23]	2000-2002	Selection of admissions from the National Hospital Discharge Register, (Health Informatics and Financial Management Institute)	Hip fracture diagnosis according the ICD9-CM classification (codes ICD9-CM 820.x) caused by a low or moderate fall	Residents in Portugal mainland (over 50 years old)	n/ap	n/ap	n/ap	n/ap	Yearly incidence rate: M: 129.4 per 100 000 F: 351.9 per 100 000
Network of Sentinel Doctors, 2009[34]	2007	New cases of fracture reported to the physicians network	Medical diagnosis of hip fracture	Clients of mainland Portugal health care centers	47.9%	111 129 patients (141 general practictioners)	2.3% of general practictioners in Portugal	Age groups (years): 0-4: 5.3% 5-9:5.3% 10-14: 5.1% 15-24: 11.7% 25-34: 15.7% 35-44:14.8% 45-54:13.2% 55-64:10.8% 65-74:9.6% ≥75: 8.4%	Yearly incidence rate: Both sexes: 63.9 per 100 000 M: 31.9 per 100 000 F: 93.3 per 100 000
Costa J, 2009[25]	2007	Clinical report consultation of patients hospitalized	Hip fracture occurring spontaneously or from a fall no greater than standing height	Residents in Viana do Castelo district (over 65 years old)	n/ap	n/ap	n/ap	n/ap	Yearly incidence rate: Both sexes: 351 per 100 000 (95%CI:302-406) M: 154 per 100 000 (95%CI:106-218) F: 481 per 100 000 (95%CI:407-564)
Cruz M, 2009[21]	2004-2006	Clinical report consultation of patients hospitalized	Proximal femur fracture after a low impact fall	Residents in the catchment area of Caldas da Rainha Hospital (over 50 years old)	n/ap	n/ap	n/ap	n/ap	Yearly incidence rate: 2004: 80 per 100 000 2005: 100 per 100 000 2006: 80 per 100 000

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Table VI. *(continuation)*

First author, publication year, reference	Period of data collection	Collecting data method	Case definition	Study population	% males	Sample size	% participation	Age distribution	Estimates
INSA, IP/INE, IP, 2009[32]	2005-2006	Face to face interview	To have or have had osteoporosis/Previous medical or nursing diagnosis of osteoporosis/To have or have had osteoporosis in the previous year (all self-reported)	Residents in Portugal familiar dwellings	48.4%	41 193 individuals (15 239 dwellings)	76%	Age groups (years): <15: 15.6% 15-24: 12.4% 25-34: 15.6% 35-44: 14.8% 45-54: 13.3% 55-64: 11.2% 65-74: 9.6% 75-84: 5.9% ≥85: 1.5%	Lifetime prevalence: Both sexes: 6.2% M: 1.1% F: 11.0% Lifetime prevalence (medical or nursing diagnosis): Both sexes: 6.1% Prevalence in the previous year: Both sexes: 5.6%
Marantes I, 2004[26]	2001-2002	Telephone interview	Self-reported osteoporosis	Adult women residents in Portugal mainland	0%	1 800	n/av	Age groups (years): 18-29: 13.8% 30-39: 16.0% 40-49: 19.6% 50-59: 16.3% 60-69: 17.6% 70-79: 12.9% ≥80: 3.8%	Point prevalence: 15.4% (95%CI:13.4-17.6) of which 96.8% (95%CI:93.1-98.8) had diagnostic exams that confirm the disease
Bernardo A, 2003[24]	2001-2002	Bone density measurement	WHO operational definition of osteoporosis based on the BMD values measured by DXA (lower spine and hip)	Males clients of one health care center of the city of Porto (over 20 years old)	100%	226	n/av	Mean age (standard deviation); [range]: 57.2 (16.0) years; [21-87]	Point prevalence (osteoporosis): 16.8% (95%CI:12.2-22.3) Point prevalence (osteopenia): 50.9% (95%CI:44.2-57.6)
Lucas R, 2008[22]	1994-1995	Bone density measurement	WHO operational definition of osteoporosis based on the BMD values measured by DXA (non-dominant distal forearm)	Caucasian adult males residents in Portugal mainland	100%	739	n/av	Age groups (years): 20-39: 12.2% 40-49: 28.3% 50-59: 33.7% 60-69: 17.9% ≥70: 8.0%	Point prevalence: >39 years: 4.3% (95%CI:2.9-6.2) 40-49 years: 1.9% (95%CI:0.5-4.8) ≥70 years: 18.6% (95%CI:9.7-30.9)

n/ap – Not applicable; M – males; F – females; 95%CI – 95% confidence intervals; INSA, IP/INE, IP – National Institute of Health/Statistics-Portugal; n/av – Not available; WHO – World Health Organization; BMD – bone mineral density; DXA – dual energy X-ray absorptiometry.

Osteoporosis and osteoporotic fractures

Four studies estimated the incidence of osteoporotic fracture[21,23,25,34] (Table VI). Data collection methods included the search of hospital admissions records with hip fracture[21,23,25] or cases of fracture reported by primary care patients to the *Network of Sentinel Doctors*[34]. All studies included both males and females and the yearly incidence of fracture (per 100 000 inhabitants) in women ranged from 93.3[34] to 481 (95%CI: 407-564)[25] and in men from 31.9[34] to 154 (95%CI: 106-218)[25].

Data on osteoporosis prevalence were obtained from three studies[22,24,26] and calculated using the *4th National Health Survey*[32] (Table VI). The number of subjects evaluated ranged from 226 [Bernardo *et al* (2003) [24]] to 41 193 (*4th National Health Survey*). The *4th National Health Survey* included both sexes (48.4% males), Marantes *et al* (2004)[26] included only females while Bernardo *et al* (2003)[24] and Lucas *et al* (2008)[22] included only males. Most studies evaluated samples of adults but the *4th National Health Survey* included participants with a wide age range (from childhood to over 85). Case definition was based on actual bone density measurement[22,24] or self-reported history of osteoporosis[26,32]. Among women the prevalence of self-reported osteoporosis ranged from 11.0%[32] to 15.4% (95%CI: 13.4-17.6)[26]. Among men it ranged from 1.1% when self-reported[32], to 16.8% (95%CI: 12.2--22.3) based on actual bone mineral density measurements[24].

Fibromyalgia

One study by Branco *et al* (2010) estimated the prevalence of fibromyalgia[27] (Table VII). A positive screen case was considered if meeting the 4-pain criteria of the *London Fibromyalgia Epidemiological Study Screening Questionnaire* (LFESSQ-4), or meeting both the 4-pain and the 2-fatigue criteria (LFESSQ-6). This study included 4 517 participants over 15 years (48% males) and the prevalence of fibromyalgia in the general population was estimated by applying the positive-predictive values obtained in a rheumatology clinic-based sample to eligible community subjects (i.e., positive screens). In the Portuguese general population the estimated overall prevalence was 3.7% (95%CI: 2.0--5.4) based on positive screens for LFESSQ-4, and 3.6% (95%CI: 2.0-5.2) based on positive screens for LFESSQ-6[27].

Rheumatoid arthritis

Two studies described the prevalence of rheumatoid arthritis[13,28] (Table VIII). In the aforementioned study by Costa *et al* (2004) the prevalence of self--reported rheumatoid arthritis in women was 2.5% (95%CI: 1.5-3.9) and in men was 0.0% (95%CI: 0.0--1.1)[13]. Abreu *et al* (2006) estimated the prevalence of rheumatoid arthritis based on secondary data combining information from patients followed by Internal Medicine specialists and the prevalence of other countries. The proposed prevalence for Portugal was 0.5 to 1%[28].

Spondyloarthritis

Two studies provided estimates of the prevalence of ankylosing spondylitis[13,29] (Table IX). In the aforementioned study of Costa *et al* (2004)[13] participants were questioned about medical diagnosis of ankylosing spondylitis while Bruges-Armas *et al* (2002) studied recruited subjects over 50 years (52.0% males) by clinical examination[29]. Although different data collection methods were used, the estimated prevalence of ankylosing spondylitis was 0.6% in both studies. The prevalence of spondyloarthritis assessed by dorsal, lumbar, and pelvic radiography, was 1.6% (95%CI: 0.8-2.7)[29]. No cases of psoriatic arthritis were identified[13].

Other systemic rheumatic diseases

We identified three studies reporting on the prevalence of other systemic rheumatic diseases[13,28,30] (Table X). The study aforementioned by Costa *et al* (2004) estimated the self-reported prevalence of systemic lupus erythematosus in 0.2% (95%CI: 0.1-0.8)[13]. Gouveia *et al* (2005), reporting cases in children under 5 years diagnosed at a single hospital (Hospital Fernando Fonseca), provided a yearly incidence of Kawasaki disease of 8.2 per 100 000 children[30]. In the aforementioned study of Abreu *et al* (2006) the proposed prevalence, for Portugal, for systemic lupus erythematosus ranged from 0.015 to 0.05%, for scleroderma ranged from 0.04 to 0.25% , for Sjögren's syndrome was 3% and for Behçet's disease ranged from 0.01 to 0.3%[28].

Pediatric rheumatic diseases

In 2004, Salgado *et al* reported prevalence and incidence estimates of pediatric rheumatic diseases and juvenile idiopathic arthritis[31] (Table XI). The patients were identified in the pediatric rheumatology outpatient clinic and cases were defined according the International League of Associations for Rheumatology criteria. Among children under 16 years of age, one in every 1 785 children had or

Table VII. Frequency of fibromyalgia (studies characteristics and results)

First author, publication year, reference	Period of data collection	Collecting data method	Case definition	Study population	% males	Sample size	% participation	Age distribution	Estimates
Branco J, 2010[27]	2003-2006	Telephone interview	Diagnostic criteria from the LFESSQ	General population (over 15 years old)	48%	4 517	n/av	Mean age (standard deviation): 45.0 (17.0) years	Point prevalence (positive screens for LFESSQ-4): Both sexes: 3.7% (95%CI:2.0-5.4) M: 2.3% (95%CI:2.1-2.5) F: 5.1% (95%CI:4.8-5.4) Point prevalence (positive screens for LFESSQ-6): Both sexes: 3.6% (95%CI:2.0-5.2) M: 1.8% (95%CI:1.6-2.0) F: 5.2% (95%CI:4.9-5.5)

LFESSQ - *London Fibromyalgia Epidemiological Study Screening Questionnaire;* n/av – Not available; LFESSQ-4 – meeting the 4-pain criteria alone from the LFESSQ; LFESSQ-6 – meeting both the 4-pain and the 2-fatigue criteria from the LFESSQ; M – males; F – females; 95%CI - 95% confidence intervals.

had had a pediatric rheumatic disease, and one in 3 225 children had or had had juvenile idiopathic arthritis. The incidence was calculated for the previous three years using the pediatric catchment population (<16 years) and was 8.4 per 100 000 children-year for pediatric rheumatic diseases and 4.3 per 100 000 children-year for juvenile idiopathic arthritis[31].

No studies estimating the frequency of periarticular rheumatic diseases or microcrystal-related arthropathies in Portugal were identified from the literature search.

Methodological quality appraisal

Overall the studies included were of low reporting and methodological quality. Major flaws jeopardizing external validity of these studies were related to low response rates in total sample[41] while minor flaws were related to random samples restricted to geographic area[13,21,24,25,30,31] and to lack of assessment and address of sampling bias[13-17,19,20,22,24,26,27,29-31,35,37,39,40,42-44]. External validity was also compromised by poor reporting in these issues: response rate, exclusion rate from the analysis or whether sample bias was address. Low internal validity was related to major flaws in the definition of incidence or prevalence (e.g. when severity of the disease could have been relevant but was not assessed)[13-17,19,22,24,26,36-38,41,42,44] and to the use of not validated methods[13-17,26,29,32-34,36,37,39,40,42-44]. Minor flaws in internal validity included use of methods poorly validated[27] and access to unreliable data sources to measure prevalence/incidence[19,21,23,25,30,31]. In almost every study, low internal validity was also consequence of not reported information about validity and/or reliability of the methods employed.

Discussion

In Portugal, a large amount of information is available derived from a wide variety of methods resulting in broad ranges of frequency estimates. We identified 32 studies reporting the incidence or the prevalence of rheumatic diseases in the Portuguese population and published during the last decade. This systematic review retrieved information for nine of the 11 rheumatic conditions targeted by the *National Program against Rheumatic Diseases.* Most studies computed prevalence, being back pain and work-related musculoskeletal disorders

Table VIII. Frequency of rheumatoid arthritis (studies characteristics and results)

First author, publication year, reference	Period of data collection	Collecting data method	Case definition	Study population	% males	Sample size	% participation	Age distribution	Estimates
Costa L, 2004[13]	1999-2003	Face to face interview	History of medical diagnosed rheumatoid arthritis (self-reported)	Adult population of the city of Porto	36.4%	1 238	70.0%	Age groups (years): ≤40: 33.9% 41-59: 36.2% >59: 29.9%	Lifetime prevalence: Both sexes: 1.6% (95%CI:1.0-2.5) M: 0.0% (95%CI:0.0-1.1) F: 2.5% (95%CI:1.5-3.9)

M – males; F – females; 95%CI - 95% confidence intervals.

the most frequent rheumatic conditions assessed.

The timeline of the search was selected aiming to optimize the relation between the sensitivity desired and the resources available, in order to improve yield as much as feasible. We identified a review of studies estimating the prevalence of rheumatic diseases in the Portuguese population, performed since 1976, and published in 2002[5]. From this review we were able to learn that there were few studies published before 2000 and most of their results were published outside widely available journals (grey literature). To appraise these and other studies published before 2000 would require an extensive search of the grey literature available in Portugal, a time-consuming process with a very low efficiency. Bearing in mind the aim of this paper we think that limiting the timeline of the research strategy did not substantially decrease the quality and the yield of the search.

Rheumatic diseases

The overall prevalence of rheumatic diseases in Portugal varied between 14.5% and 24.0%. The difference in the estimates found in the Portuguese population could be related to the definition of the rheumatic disease but also to survey design factors and to the age and gender distribution of the study population[46].

Comparability of frequency measures from different populations is limited owing to methodological and cultural differences. For instance, the use of a list of rheumatic diseases is expected to produce higher prevalence estimates than an open and more general description of rheumatic disease[46]. The description and meaning of different rheumatic diseases differ between medical specialists and general public, from different cultures and languages, and can also result in highly different estimates[46]. A recent study performed in the general Portuguese population showed that there are incorrect beliefs about rheumatic diseases being the identification of rheumatic disease the major flaw[47].

The main limitation of national health surveys, such as the *4th National Health Survey*, remains in the impossibility of using standard clinical criteria to define cases, and rather relying on self-reported symptoms and diagnoses. The estimate of frequency obtained by self-report reflects much more than the occurrence of the condition. It reflects a set of constructs such as symptoms, access to health care and the awareness of disease. If, on the one hand, validation studies have supported the

Table IX. Frequency of spondyloarthritis (studies characteristics and results)

First author, publication year, reference	Period of data collection	Collecting data method	Case definition	Study population	% males	Sample size	% participation	Age distribution	Estimates
Bruges-Armas J, 2002[29]	1994	Clinical examination	European Spondiloarthropathy Study Group diagnostic criteria to spondyloarthritis and modified New York diagnostic criteria to ankylosing spondylitis	Caucasian residents of Terceira Island, Azores (over 50 years old)	52.0%	490	52.4%	Mean age: M - 66 years F - 67 years	Spondyloarthritis prevalence: Both sexes: 1.6% (95%CI:0.8-2.7) M: 2.7% (95%CI:1.1-5.6) F: 0.4% (95%CI:0.0-2.5) Ankylosing spondylitis prevalence: Both sexes: 0.6% (95%CI:0.1-1.8) M: 1.2% (95%CI:0.2-3.4) F: 0.0% (95%CI:0.0-1.6)
Costa L, 2004[13]	1999-2003	Face to face interview	History of medical diagnosed ankylosing spondylitis or psoriatic arthritis (self-reported)	Adult population of the city of Porto	36.4%	1 238	70.0%	Age groups (years): ≤40: 33.9% 41-59: 36.2% >59: 29.9%	Lifetime prevalence (ankylosing spondylitis): Both sexes: 0.6% (95%CI: 0.3-1.3) M: 0.4% (95%CI:0.1-1.8) F: 0.8% (95%CI:0.3-1.7) Lifetime prevalence (psoriatic arthritis): Both sexes: 0.0% (95%CI:0.0-0.4) M: 0.0% (95%CI:0.0-1.1) F: 0.0% (95%CI:0.0-0.6)

M – males; F – females; 95%CI - 95% confidence intervals.

Table X. Frequency of other systemic rheumatic diseases (studies characteristics and results)

First author, publication year, reference	Period of data collection	Collecting data method	Case definition	Study population	% males	Sample size	% participation	Age distribution	Estimates
Gouveia C, 2005[30]	1996-2003	Clinical report consultation of patients hospitalized	*American Heart Association* diagnostic criteria for Kawasaki disease	Residents in the catchment area of Fernando da Fonseca Hospital (children under 5 years old)	n/ap	n/ap	n/ap	n/ap	Yearly incidence rate: 8.2 per 100 000
Costa L, 2004[13]	1999-2003	Face to face interview	History of medical diagnosis of systemic lupus erythematosus (self-reported)	Adult population of the city of Porto	36.4%	1 238	70.0%	Age groups (years): ≤40: 33.9% 41-59: 36.2% >59: 29.9%	Lifetime prevalence: Both sexes: 0.2% (95%CI:0.1-0.8) M: 0.2% (95%CI:0.0-1.4) F: 0.3% (95%CI:0.0-1.0)

n/ap – Not applicable ; M – males; F – females; 95%CI - 95% confidence intervals.

accuracy of self-report to measure prevalent chronic conditions and severe diseases which require treatment[48], on the other, one study which assessed the agreement between musculoskeletal diseases' self-reporting, with six months in between, reached different conclusions[46]. Although case ascertainment from self reports has sub-optimal accuracy, for the assessment of diseases that are characterized by pain and functional limitation, individual subject is our single best source of information[46].

One of the solutions to improve diagnostic validity in population studies seems to be the collection of information on medication to confirm self-reported cases[49,50]. However, when we use medications to define disease in an epidemiologic study, we assume that all cases of the disease have been properly diagnosed and treated. This excludes undiagnosed, untreated, misdiagnosed, and mistreated cases and limits the study of early manifestations of disease. Using this approach to define disease also requires a meticulous medication data collection[49].

Case definition using clinical and complementary diagnostic examination provides better sensitivity and specificity. However, many rheumatic conditions still have no accepted universal case definition and clinical diagnosis methods are not easily applicable to general population samples.

Osteoarthritis

Costa *et al* (2004) estimated the prevalence of osteoarthritis in the Portuguese population based on self-reported history of disease[13]. Frequently, estimates of the prevalence of osteoarthritis are based on radiographic surveys[6,48,51] which hampers comparisons with this study. In fact, there is a dissociation in the prevalence estimates between self-reported diagnosis of osteoarthritis and studies employing clinical and radiological criteria[4].

The prevalence of osteoarthritis is usually higher in the knee than in the hip[4] and those results were found in the Portuguese population. Comparing to a Dutch study, which used a similar methodology, the prevalence of knee and hip osteoarthritis in Portugal was slightly lower, except for knee osteoarthritis in women[46].

Back pain

Numerous studies on back pain epidemiology have been published over the past 10 years in Portugal. The estimate of low back pain in the pre-

Table XI. Frequency of pediatric rheumatic diseases (studies characteristics and results)

First author, publication year, reference	Period of data collection	Collecting data method	Case definition	Study population	% males	Sample size	% participation	Age distribution	Estimates
Salgado M, 2004[21]	2001-2004	Clinical report consultation	*International League of Associations for Rheumatology* diagnostic criteria	Residents in Centro region of Portugal (children under 16 years old)	n/ap	n/ap	n/ap	n/ap	Yearly incidence rate (pediatric rheumatic diseases): 8.4 per 100 000 Yearly incidence rate (juvenile idiopathic arthritis): 4.3 per 100 000
Salgado M, 2004[21]	1988-2004	Clinical report consultation	*International League of Associations for Rheumatology* diagnostic criteria	Residents in Centro region of Portugal (children under 16 years old)	n/ap	n/ap	n/ap	n/ap	Prevalence in 2001 (pediatric rheumatic diseases): 56/100 000 children Prevalence in 2001 (juvenile idiopathic arthritis): 31/100 000 children

n/ap – Not applicable.

vious week found by Rabiais *et al* (2003)[33] was much higher than the point prevalence of low back pain in Spain estimated in 14.8% (95%CI: 12.2-17.4)[52].

To summarize and compare the results across these studies is difficult because of the heterogeneity of methods used. Particularly in this condition, studies showed substantial variation in case definition and distinct classification criteria, which affected the number of cases identified and probably explains apparent major differences in prevalence estimates of back pain[4]. Moreover, the results of studies focusing on symptoms are highly dependent on the formulation and wording of questions and this probably explains different patterns found in the prevalence of back pain when case definition and sampling frames are similar[48].

The lack of standardization and validation of the terminology and classification of back pain (frequency or duration of pain) also leads to confusion between prevalence and incidence estimates. In fact, as a consequence of the unstable and episodic nature and uncertainty of onset of back pain, the traditional epidemiological concept of incidence case definition is difficult to mainstream to this condition[4].

In 2003, *World Health Organization* has recommended the characterization of back pain as period prevalence measures, defining acute (less than sven days), sub-acute (more than seven days) and chronic pain (more than 42 days) [3]. However, we only identified three studies defining duration of pain episodes that could be classified according to this criteria[13,15,16].

Work-related musculoskeletal disorders

A broad range of studies on the prevalence of musculoskeletal diseases or complaints among different occupational activities have been published recently in Portuguese workers. The results of the *Fourth European Working Conditions Survey* reported Portugal as one of the European countries where a high prevalence of back pain and muscular pain in shoulders, neck and/or upper/lower limbs related to occupational activity was observed. Furthermore, the estimates for Portugal were higher than European average which were 24.7% for back pain and 22.8% for muscular pain in shoulders, neck and/or upper/lower limbs[38].

Comparing the results of the first cross-sec-

tional study on the prevalence of WRMDs within large Portuguese companies by Cunha-Miranda *et al* (2010)[19] with studies performed in other countries, clear differences were identified. The authors attributed these differences to presumable specificities of the Portuguese business sector or to differential clinical relevance given by Portuguese occupational physicians, or by patients themselves, compared to other countries[19].

There are limitations in directly comparing estimates between different occupational activities because, regarding WRMDs in particular, the differences in definitions and questionnaires used might be part of the explanation for the findings.

Osteoporosis and osteoporotic fracture

The burden of osteoporosis can be estimated indirectly through its single most relevant outcome, the incidence of fragility fractures. We identified four articles estimating the incidence of hip fracture[21,23,25,34], of which three used hospital records[21,23,25]. In fact, for these conditions which lead more or less inevitably to hospital admission, the total number of cases within a region and a time frame is relatively easy to obtain through hospital records[4].

In this review, the differences in estimates between the studies can be related to different selection criteria for patients' ages, and comparisons must be carefully made since the incidence of hip fractures is strongly age dependent[4].

Comparing the incidence of osteoporotic fractures obtained in Portugal with other European estimates, the overall incidence was higher than in Germany and lower than in Greece, Norway, Denmark and Finland. Comparing with Spain, the incidence in Portugal was lower in women and higher in men[23].

Lucas *et al* (2008) and Bernardo *et al* (2003) estimated osteoporosis prevalence using bone mineral density (BMD) measurement[22,24]. Implicit in this definition of osteoporosis is the relationship between BMD decay and rise in fracture risk. However, when we aim to assess the burden of osteoporosis the densitometry based estimate of prevalence has limited value and in the future, the burden of osteoporosis will probably be assessed through clinical risk factors for fracture[4].

Fibromyalgia

In an European survey estimating the prevalence of fibromyalgia in five countries, Branco *et al* (2010) identified no statistically significant differences in the prevalence in Portugal compared to other countries[27]. The main limitation of this study was the assessment of prevalence assuming positive-predictive values of LFESSQ-4 and LFESSQ-6 in the general population similar to those calculated in the rheumatology outpatient sample while the predictive value in the latter is probably substantially higher than in the former[27].

Rheumatoid arthritis

Costa *et al* (2004) estimated the prevalence of rheumatoid arthritis using self-reported information[13]. The validity of self-reported diagnosis of rheumatoid arthritis has been reported to be between 7 and 96%[49].

Several studies provided estimates on the prevalence of rheumatoid arthritis in defined populations and, although these studies have a number of methodological limitations, the remarkable finding is the uniformity of rheumatoid arthritis prevalence estimates in developed populations - approximately 0.3% to 1.0% of the adult population[4,53]. The prevalence of rheumatoid arthritis in the Portuguese population was higher than aforementioned but similar to figures obtained in other settings when the disease was assessed by self-report[46].

Spondyloarthritis

The prevalence of 0.6% for ankylosing spondylitis found in the Portuguese population by Bruges-Armas *et al* (2002)[29] was slightly higher than other estimates reported in different populations, varying from 0.036% to 0.10%[53], but similar to the prevalence of ankylosing spondylitis in Greece assessed recently [0.3% (95%CI: 0.3-0.9)][54].

Costa *et al* (2004) identified no cases of psoriatic arthritis in a sample of urban Portuguese adults[13]. A recent review described prevalence estimates for psoriatic arthritis varying from 1 case per 100 000 population, in Japan, to 420 cases per 100 000 population, in Italy[55].

Other systemic rheumatic diseases

The prevalence found by Costa *et al* (2004)[13] in a sample of the Portuguese population was not very different from estimates previously reported. One of these studies validated self-reported diagnoses of systemic lupus erythematosus, by reviewing available medical records, revealing a prevalence of 0.12%[56]. The validity of self-reported diagnosis of lupus has been estimated between 21% and 84%[49].

Pediatric rheumatic diseases

The majority of available studies on epidemiology of chronic arthritis in childhood is clinic-based and thus is susceptible to numerous biases[53]. The few existing population studies have reported an approximate prevalence of juvenile rheumatoid arthritis between 1 and 2 per 1 000 children, and an incidence between 11 and 14 per 100 000 children[53]. In the studies assessing the incidence of juvenile idiopathic arthritis published since 1995 the estimates ranged from 10 to 22.6 per 100 000 children[31]. Comparing these figures with the Portuguese estimates, according to Salgado *et al* (2004), it seems to exist a dispersion of the Portuguese patients (which may be examined by other medical specialties) or under diagnosis of cases[31].

Methodological issues in estimating the frequency of rheumatic diseases

To better assess the burden of rheumatic diseases in the population it is important to obtain accurate estimates of the current proportion of people suffering from these conditions as well as their time trends and geographic distribution.

The estimate of rheumatic diseases frequency represents a particularly complex methodological challenge. The difficulty in defining a case, the lack of clear distinction between the different disorders and the difficulty in case ascertainment are specific problems when undertaking rheumatic disease epidemiology. Moreover, many of the rheumatic diseases are so rare that the required sample size of the surveys to ensure accuracy are probably in excess of what is feasible or cost-effective[48].

The diversity of rheumatic diseases, regarding both etiology and frequency, argues for the importance of using sources of information collected at different levels of care. Therefore, while health surveys of the general population can provide valid and accurate estimates of the frequency of highly prevalent diseases, their accuracy is very limited when studying less frequent conditions, with worse prognosis, such as systemic rheumatic diseases. To characterize the frequency of these uncommon diseases it is more appropriate to collect data at differentiated levels of health care[48]. However, it is important to perceive that data collected at each level reflect the distribution of disease related factors, such as frequency and prognosis, but also the organization of the health system, collecting information systems, geographical distribution of the services, referral protocols and socio-demographic characteristics of the population. Moreover, as musculoskeletal conditions may have either an acute or a gradual onset and their outcomes vary from complete health recovery to chronic progressive course, incidence could be more relevant to measure frequency for some conditions whereas prevalence is the only measurement available for others[4].

The use of standardized criteria to identify cases of disease is critical to make meaningful comparisons between studies. Thus, since 2003, certain basic requirements were made by the Scientific Group on the Burden of Musculoskeletal Conditions of the *World Health Organization* to access data that can be compared across musculoskeletal conditions[4]. These requirements included the use of agreed definitions for each condition in all future studies; the use of agreed age bands for reporting data; the collection of data separated by gender and the development of guidelines for uniform data collection.

Also in 2003, the *Department of General Practice and Community Medicine of the University of Oslo* recommended indicators and sources of information which can be used across the European Community to measure and monitor the impact of musculoskeletal conditions, as unspecified musculoskeletal conditions (widespread and localized), rheumatoid arthritis, osteoarthritis, and osteoporosis, at a national and community level[7].

Methodological quality appraisal

Overall the methodological quality and reporting quality of the studies included in our review was heterogeneous. Few studies collected data from a representative sample of the population, used data-collection strategies that would minimize the risk of bias or described measures to address potential sources of bias.

Publication bias was not assessed in this review. Since these studies focus on prevalence or incidence estimates and not effect sizes, there is no reason to believe that they would be subject to publication bias.

Conclusion

There is a broad spectrum of health data generated by instruments of heterogeneous quality for this group of diseases. Theoretically, taken toge-

ther, these could allow to characterize, directly and indirectly, the burden of musculoskeletal conditions in the general population and on the Portuguese health system. However, we have identified important gaps in the knowledge about rheumatic disease epidemiology. The major gaps are related to the lack of studies estimating frequency of inflammatory arthropathies, such as gout and spondyloarthritis, and disabling pain syndromes that are not clearly defined.

In order to be able to develop preventive strategies and to measure the results of programs, such as the *National Program against Rheumatic Diseases*, it is necessary to have accurate baseline information on the present situation of rheumatic diseases occurrence. However, it is essential to take into account that, efficient and accurate frequency estimates should make use of multiple sampling frames, defined according to the frequency and the pathophysiology of each condition.

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FATIGUE IN RHEUMATOID ARTHRITIS: ASSOCIATION WITH SEVERITY OF PAIN, DISEASE ACTIVITY AND FUNCTIONAL STATUS.

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Abstract

Objective: Rheumatoid arthritis (RA) is an autoimmune disease characterized by chronic symmetric polyarthritis causing progressive joint destruction and disability. Major patient complaints are pain, disability and fatigue. The aim of this study is to assess fatigue and its association with disease-specific variables (severity of pain, disease activity, and functional status) in patients with RA.

Patients and Methods: A total of 160 RA patients were included in the study. Fatigue was measured by using Fatigue Symptom Inventory (FSI). The quadrivariate Disease Activity Score-28 (DAS28) was used for evaluating disease activity and Health Assessment Questionnaire (HAQ) for determining functional status. Severity of pain was measured by using 10 cm Visual Analog Scale-Pain (VAS-pain).

Results: Intensity items of FSI (most fatigue, least fatigue, average fatigue, current fatigue) were strongly correlated with DAS28, HAQ, and VAS pain (p=0.000). When the correlation coefficients were analyzed, current fatigue showed the highest correlation with VAS-pain (r: 0.96). This was followed by DAS28 and HAQ, respectively (r: 0.77 and 0.70) (p=0.000). Duration items of FSI (number of days fatigued, amount of time fatigued) were significantly correlated with DAS28, HAQ, and VAS pain (p=0.000). Also there were significant positive correlations between interference scale of FSI and DAS28, HAQ, and VAS-pain (r: 0.68, 0.61 and 0.67, respectively) (p=0.000). None of FSI subgroups showed statistically significant correlation with disease duration.

Conclusions: Fatigue is strongly associated with severity of pain, disease activity and functional status. Fatigue should be included in clinical practice and clinical trials as a RA outcome measure.

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Keywords: Rheumatoid Arthritis; Fatigue; Disease Activity; Functional Status.

Introduction

Fatigue is generally defined as a sense of persistent tiredness or exhaustion that is often distressing to the individual. It is one of the common complaints of Rheumatoid Arthritis (RA)[1]. Fatigue can be described as 'enduring, subjective sensation of generalized tiredness or exhaustion'. It is generally subscribed to disease-related factors such as inflammation, anemia and pain[2,3].

Fatigue is a subjective phenomenon and assessed by individual self-report. Various self-report measures have been developed to evaluate fatigue in chronic diseases. These measures range from one-item scales of intensity (i.e., visual analog scales) to multidimensional measures such as Multidimensional Fatigue Symptom Inventory (MFSI)[1].

The aim of this study is to evaluate correlation between fatigue and disease-specific variables (severity of pain, disease activity, and functional status) in patients with RA.

Patients and Methods

The study included a total of 160 RA patients, who were followed at the outpatient rheumatology clinic of physical medicine and rehabilitation department of Numune Training and Research Hospital which is a major referral center under Ministry of Health, located in Ankara, capital city of Turkey. All of the patients fulfilled the diagnostic criteria of the American College of Rheumatology (ACR)[4]. Patients' age, gender, number of swollen and tender joints, erythrocyte sedimentation rate (ESR) were recorded. The quadrivariate Disease Activity Score-28 (DAS28) was used for evaluating disease activity[5] and Health Assessment Questionnaire (HAQ)

for determining functional status[6]. 10 cm Visual Analog Scale-Pain (VAS-pain) was used to evaluate the level of pain[7]. Fatigue was assessed by using Turkish version of Fatigue Symptom Inventory (FSI) [Oksuz E., Malhan S., Tulunay F.C. Reliability and Validity of the Fatigue Symptom Inventory. In: Value in Health; Greece 2008 Nov; 11 (6), A426 – – SCI- (meeting abstract)]

FSI, first published in 1998, is a 14-item self-report measure designed to assess fatigue intensity (four items), duration (two items), its interference with quality of life (7 items), and the daily pattern of fatigue. Intensity is measured on separate 11--point scales (0=not at all fatigued; 10=extreme fatigue) that assess most, least, current fatigue and average fatigue in the previous week. Each of these is scored as an individual item. The interference items assess the extent to which fatigue interfered with a respondent's general activity level, ability to bathe and dress, work activity, ability to concentrate, relations with others, enjoyment of life and mood during the previous week using an 11 point rating scale (0 = no interference and 10 = extreme interference). These 7 items are averaged to obtain an interference scale score. Duration items (number of days fatigued, amount of time fatigued) assess fatigue frequency. It is measured as the number of the days (from 0 to 7 days) in the past week that respondents felt fatigued and the amount of each day on average respondents felt fatigued (0=none of the day, 10= the entire day). Each of these is scored as an individual item. The final item asks respondents to indicate their daily pattern of fatigue and so provides descriptive information about possible diurnal variation in the daily experience of fatigue (0=not at all fatigued, 1=worse in the morning, 2=worse in the afternoon, 3= worse in the evening, 4=no consistent daily pattern of fatigue). Final item provides information only and is not intended to be used as a quantitative scale [1, 8]. The items included in the FSI are shown in appendix I[8,9].

Statistical Analysis

Descriptive statistics [mean, median, SD (standard deviation), minimum, maximum and frequencies] were used for assessing the demographics and clinical parameters. Correlations between fatigue items and pain, disease activity, and functional status were evaluated with correlation analysis. The presence of correlation was examined with Pearson's correlation coefficient. A value of $P<0.05$ was considered statistically significant. All analyses were performed using Statistical Package for the Social Sciences-13.0 (SPSS-13.0) software.

Results

A total of 160 RA patients (132 females, 28 males) were included in the study. Mean age of patients was 53.16 ± 11.98 (24-79) years. Mean disease duration was 142.3 ± 98.88 (4-480) months. Of the patients 57.5% (92 patients) were fatigued in the morning, 20% (32 patients) were not at all fatigued, 6.25% (2 patients) were fatigued in the afternoon, and 1.25% (10 patients) were fatigued in the evening. 15% of them (24 patients) did not declare any consistency in the daily pattern of fatigue. Mean scores of DAS-28, HAQ, VAS-pain and FSI subgroups (intensity items, duration items, and interference scale), demographics and clinical data are summarized in Table I.

Intensity items (most fatigue, least fatigue, average fatigue, current fatigue) were strongly correlated with DAS28, HAQ, and VAS-pain (p=0.000). When the correlation coefficients were analyzed, current fatigue showed the highest correlation with VAS-pain (r: 0.96). DAS28 and HAQ followed it, respectively (r: 0.77, 0.70) (p=0.000) (Table II).

Duration items (number of days fatigued, amount of time fatigued) were strongly correlated with DAS28, HAQ, and VAS-pain (p=0.000) (Table II).

Also there were significant positive correlations between interference scale and DAS28, HAQ, and VAS-pain (r: 0.68, 0.61 and 0.67 respectively) (p=0.000) (Table II).

None of FSI subgroups showed statistically significant correlation with disease duration (Table II).

Discussion and Conclusions

To our knowledge this is the first study to demonstrate that fatigue levels are strongly correlated with three important items: severity of pain, functional status and disease activity. The strongest correlation was showed for current fatigue and VAS-pain. This association had been previously found in the study of Huyser et al., where fatigue was measured by using Piper Fatigue Self-Report Scale (PFS), however they did not find a strong association between fatigue and disease activity[10]. On the other

Table I. Demographic and Clinic Patient Data

	Minimum	Maximum	Mean	SD	Median
Age (year)	24.0	79.0	53.16	11.98	54.00
Disease duration (months)	4	480	142.3	98.88	120
Swollen joints	0	10	0.63	1.44	0
Tender joints	0	26	2.92	4.61	1
ESR	2	80	22.4	15.79	18
DAS28	0.49	7.58	3.37	1.37	3.08
HAQ	0	3.0	0.84	0.75	0.75
VAS-pain	0	10.0	4.16	2.66	4
Most fatigue	0	10	5.89	2.93	6
Least fatigue	0	10	2.2	2.55	1
Average fatigue	0	10	3.99	2.75	4
Current fatigue	0	10	4.3	2.72	4
Number of days fatigued	0	7	3.46	2.32	3
Amount of time fatigued	0	10	4.23	2.87	5
Interference scale	0	10	3.44	2.95	3.28

Most fatigue, least fatigue, average fatigue, current fatigue: FSI intensity items; Number of days fatigued, amount of time fatigued: FSI duration items; Interference scale: FSI Interference item; ESR: erythrocyte sedimentation rate; DAS28: Disease Activity Score; HAQ (Health Assessment Questionnaire): Functional Status Health Assessment Questionnaire;VAS pain:Visual Analog Scale-pain

Table II. The relation between FSI Scales and Other Parameters

		DAS28	HAQ	VAS-pain	Disease Duration
Most fatigue	r	0.62**	0.59**	0.66**	0.01
	p	0.000	0.000	0.000	0.9
Least fatigue	r	0.65**	0.64**	0.65**	0.04
	p	0.000	0.000	0.000	0.55
Average fatigue	r	0.69**	0.67**	0.71**	0.08
	p	0.000	0.000	0.000	0.92
Current fatigue	r	0.77**	0.70**	0.96**	-0.01
	p	0.000	0.000	0.000	0.86
Number of days fatigued	r	0.59**	0.60**	0.62**	-0.01
	p	0.000	0.000	0.000	0.93
Amount of time fatigued	r	0.72**	0.68**	0.72**	-0.2
	p	0.000	0.000	0.000	0.86
Interference scale	r	0.68**	0.61**	0.67**	0.01
	p	0.000	0.000	0.000	0.93

Most fatigue, least fatigue, average fatigue, current fatigue: FSI intensity items; Number of days fatigued, amount of time fatigued: FSI duration items; Interference scale: FSI Interference item; ESR: erythrocyte sedimentation rate; DAS28: Disease Activity Score; HAQ (Health Assessment Questionnaire): Functional Status Health Assessment Questionnaire;VAS pain:Visual Analog Scale-pain

hand, Raterman and Pollard reported strong associations between fatigue and disease activity, confirming our data. Raterman used two questionnaires [Checklist Individual Strength (CIS) and the Need for Recovery Scale (NFR)] for the measurement of several aspects of fatigue severity[11]. Nevertheless, in Pollard's study, the relationship between fatigue and pain was less significant and fatigue was accessed simply by using 100 mm VAS--fatigue, which did not permit to access the different aspects of fatigue in detail[12].

Fatigue is a multifactorial and a complex symptom and its assessment requires a multidimensional questionnaire that identifies more detailed

profile of fatigue. We evaluated fatigue by using FSI. FSI deals with various characteristics of fatigue including severity and frequency of fatigue and its perceived interference with quality of life in terms of general and normal work activities, ability to concentrate, enjoyment of life and mood. Furthermore, it states daily patterns of fatigue[8]. FSI is sensitive enough to detect changes over time, therefore it can be used as an outcome measure[13]. It was suggested as a useful instrument for assessment of fatigue[14].

In our study, pain was the first in rank among the variables that influenced fatigue. Similar relationships between fatigue and pain intensity were also reported by Riemsma, Tack and Hoogmoed[15,16,2].

We found that fatigue was significantly correlated with functional status. This result concords with the findings of Hoogmoed et al., and other studies which confirmed that fatigue has a negative impact on functional status in RA. Hoogmoed et al., evaluated fatigue by using CIS. They concluded that fatigue in RA was primarily related to pain and functional status[2]. It was found a similar correlation between fatigue and physical function in the study of Riemsma et al., where physical function was measured by using Arthritis Impact Measurement Scale-2 (AIMS-2)[15]. Likewise, Belza and Fifield noted that fatigue was associated with functional disability[17,18].

In the present study, no association was found between fatigue and disease duration. Pollard and Treharne found similar results, with no significant relationship between fatigue and disease duration[12,19]. Studies investigating the relationship between fatigue and disease duration in RA have contradictory results. Riemsma found that, among RA patients, fatigue positively correlated with disease duration[15]. Contrarily, Belza suggested that greater fatigue was associated with shorter disease duration[17].

Wolfe et al., found fatigue as correlated with almost all demographic and clinical variables, but in multivariate analyses the strongest independent predictors of fatigue were pain, sleep disturbance, depression, number of tender joints and functional disability[20].

To our knowledge, this study is the first to demonstrate daytime patterning of fatigue in RA patients. We found that fatigue was greater in the morning. More than half of the patients indicated that they felt fatigued in 3-4 hours after awakening and level of fatigue decreased during the day. This may be due to dysregulation of hormones. Sternberg et al., suggested that both inflammation and fatigue in RA might derive from dysregulation of the hypothalamic-pituitary- adrenal axis[21].

In all of these studies, fatigue was found as strongly associated with severity of pain. It was concluded that the pain was the strongest predictor of fatigue. The association between pain and fatigue in RA has not just been exactly known. It needs more studies for explaining this relationship.

It was reported a statistically significant correlation between fatigue and disease activity in most of the studies. Fatigue is a common symptom of RA, but it is not included in the disease activity core set measures and indices in RA. It should take place in clinical practice and trials as a RA outcome measure.

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APPENDIX I

The Fatigue Symptom Inventory (FSI)

1. Rate your level of fatigue on the day you felt **most** fatigued during the past week.
   0 1 2 3 4 5 6 7 8 9 10
   Not at all fatigued *Extreme fatigue*

2. Rate your level of fatigue on the day you felt **least** fatigued during the past week.
   0 1 2 3 4 5 6 7 8 9 10
   Not at all fatigued *Extreme fatigue*

3. Rate your level of fatigue on the **average** during the last week.
   0 1 2 3 4 5 6 7 8 9 10
   Not at all fatigued *Extreme fatigue*

4. Rate your level of fatigue **right now**.
   0 1 2 3 4 5 6 7 8 9 10
   Not at all fatigued *Extreme fatigue*

5. Rate how much in the past week, fatigue interfered with your **level of activity**.
   0 1 2 3 4 5 6 7 8 9 10
   No interference *Extreme interference*

6. Rate how much, in the past week fatigue interfered with your **ability to bathe and dress yourself**.
   0 1 2 3 4 5 6 7 8 9 10
   No interference *Extreme interference*

7. Rate how much, in the past week fatigue interfered with your **normal activity (includes both work outside the home and housework)**.
   0 1 2 3 4 5 6 7 8 9 10
   No interference *Extreme interference*

8. Rate how much, in the past week fatigue interfered with your **ability to concentrate**.
   0 1 2 3 4 5 6 7 8 9 10
   No interference *Extreme interference*

9. Rate how much, in the past week fatigue interfered with your **relations with other people**.
   0 1 2 3 4 5 6 7 8 9 10
   No interference *Extreme interference*

10. Rate how much, in the past week fatigue interfered with your **enjoyment of life**.
    0 1 2 3 4 5 6 7 8 9 10
    No interference *Extreme interference*

11. Rate how much, in the past week fatigue interfered with your **mood**.
    0 1 2 3 4 5 6 7 8 9 10
    No interference *Extreme interference*

12. Indicate **how many days**, in the past week, you felt fatigued for any part of the day.
    0 1 2 3 4 5 6 7 *days*

13. Rate **how much of the day**, on average, you felt fatigued in the past week.
    0 1 2 3 4 5 6 7 8 9 10
    None of the day *The entire day*

14. Indicate which of the following best describes the **daily pattern** of your fatigue in the past week
    0 1 2 3 4 5 6 7 8 9 10

0=not at all fatigued, 1=worse in the morning, 2=worse in the afternoon, 3= worse in the evening, 4=no consistent daily pattern of fatigue.

MARKERS OF PROGRESSION TO RHEUMATOID ARTHRITIS: DISCRIMINATIVE VALUE OF THE NEW ACR/EULAR RHEUMATOID ARTHRITIS CRITERIA IN A PORTUGUESE POPULATION WITH EARLY POLYARTHRITIS

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Abstract

Objectives: Our goal was to test the performance of the new American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) criteria for the classification of rheumatoid arthritis (RA) in a cohort of patients with very recent onset polyarthritis.

Patients: Untreated polyarthritis patients with less than 6 weeks of duration were enrolled. All patients were followed-up in order to establish a definitive diagnosis.

Results: Thirty-seven patients were included. During the follow up 57% of the patients evolved to RA. The median age of the RA-group patients was similar to the median age of the non-RA group (median (IQR) 47 (31-58.5) *vs* 43 (34-69) years, p=0.74). At the initial visit the DAS 28 in the RA group was significantly higher than in the non-RA group, as well as the visual analogue scale (VAS), the HAQ and the number of swollen joints. Among the 21 RA patients, 43% presented RF and 28.6% presented anti-citrullinated protein antibody (ACPA) in the first visit. RF and ACPA were not detectable in any of the patients who did not evolve to RA. According to the new ACR/EULAR criteria, the mean total score of the RA group at baseline was significantly higher than the non-RA group (median (IQR) 6 (4.5-8) *vs* 4.5 (2.2-6), *p=0.007*).

Conclusion: In our cohort high DAS28, swollen joint count, VAS and HAQ and the presence of RF or ACPA were eventually associated with the evolution into RA. The new ACR/EULAR criteria for the classification of RA seem to perform well in very early RA.

Keywords: Rheumatoid Arthritis; Very Early Polyarthritis; ACR/EULAR Classification criteria.

Introduction

Up to 30% to 50% of the patients attending a rheumatology clinic present arthritis of recent onset[1]. The definition of early arthritis is not precisely clear and, consequently, recent-onset arthritis cohorts differ in disease duration at entry (between 4 weeks and 24 months)[2-5]. Moreover, recent-onset arthritis exhibits considerable clinical and prognostic variability, as it may progress to established rheumatoid arthritis (RA), evolve to other inflammatory arthropathies, remain undifferentiated or, in opposite, it may also enter spontaneous remission. To achieve the best possible outcome, patients with early arthritis must be identified and treated aggressively[6-11]. In fact, European League Against Rheumatism (EULAR) recently recommended that patients presenting with arthritis of more than one joint should be referred to and observed by a rheumatologist, ideally within 6 weeks after the onset of symptoms[12]. Due to the current lack of reliable methods of differentiating between RA and other inflammatory joint diseases during the first weeks of symptoms[13], the diagnosis of these early arthritis patients is often uncertain in clinical practice[14].

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It is well known that the 1987 American College of Rheumatology (ACR) classification criteria for RA[15], which were developed based on patients with established RA, are weak predictors for the development of RA in early polyarthritis patients[16]. Thus, a taskforce constituted by rheumatologists from Europe and North America developed new classification criteria for RA that allows earlier identification of cases, focusing in variables that predict evolution to a chronic arthritis. The final goal was the early beginning of an adequate treatment to prevent progression of the disease[17]. Another relevant point was that the criteria were aimed to be useful and understandable for primary care physician's referral and not just for specialists.

The new criteria for the classification of RA[17] focus on some parameters that were absent from the previous criteria, such as anti-citrullinated protein antibody (ACPA) testing. The criteria are mainly based on 4 topics: number and localization of joints affected, disease duration, acute phase response (erythrocyte sedimentation rate (ESR) and C reactive protein (CRP)), and presence and level of rheumatoid factor (RF) and ACPA. These criteria were developed based on 6 European cohorts: Netherlands (Amsterdam and Rotterdam), Austria, France, United Kingdom (Manchester) and Norway, and validated in 3 additional populations (Leeds, Leiden and Toronto). As described, the large majority of the cohorts were originated from North Europe, and three even came from the same country (Netherlands). As the authors emphasized these criteria need to be tested in other populations. Moreover publications applying the criteria are useful for its divulgation and increase worldwide use. It is also necessary to test them in cohorts with different inclusion criteria. In this study we applied the new RA classification criteria to a Portuguese untreated polyarthritis cohort with less than 6 weeks of disease duration, representing the characteristics of a Southern European population.

The goal of our work was to test the performance of the new ACR/EULAR criteria for the classification of RA in a cohort of patients with a very recent onset polyarthritis (less than 6 weeks of arthritis).

Patients and Methods

Patients presenting with more than 4 tender and/ /or swollen joints with less than 6 weeks of disease duration coming from the Emergency Room and from the Rheumatology outpatient clinic of Santa Maria Hospital were consecutively enrolled in this study during a period of 5 years (2005-2009). They were not exposed previously to corticosteroids or disease modifying anti rheumatic drugs (DMARDs). All the patients with very early arthritis were prospectively followed during the study period, in order to establish a definitive clinical diagnosis. The minimum follow-up time for each patient was 10 months.

Patients were excluded if the disease presentation was monoarthritis or oligoarthritis, if disease duration exceeded 6 weeks at the recruitment date and if they were already medicated with corticosteroids or DMARDs.

A protocol was applied (PMAR)[18], including demographic and clinical data, the number of swollen and tender joints using the 66/68 joint assessment, the visual analogue scale (VAS) of global health as assessed by the patient and ESR to calculate the disease activity score of 28 joints (DAS28).

The health assessment questionnaire (HAQ)[19] was also completed at the first visit. A blood sample was collected to assess laboratorial parameters, namely ESR, RF and ACPA levels, before any treatment was started. During follow up, patients were divided in two groups, according to the final diagnosis: RA (defined both by the clinician opinion and by the 1987 ACR criteria) *vs* non-RA group. After the initial visit (first visit), patients were observed 4-6 weeks after starting low dose prednisone (5-10 mg) (2nd visit) and, if applicable, 4 months after reaching the minimum effective dose of MTX (3rd visit) Patient's management was done in accordance with the standard practice. At the end of the study period all the included patients were submitted to a final clinical evaluation (final visit).

This study was approved by the local Ethics committee and all patients gave written informed consent to participate. The follow-up was performed in accordance with the Helsinki declaration.

Statistical analysis

The continuous variables were described as median and interquartile range, whereas categorical variables were presented as frequencies. Univariate analysis and statistical differences between continuous RA and non-RA variables groups were determined by the non-parametric Mann-Whit-

Table I. Baseline differences between patients who latter evolved to RA (RA-group), comparing to who did not (non-RA group)

Parameter	RA	Non-RA	p-value
n	21	16	
DAS28	6.2 (5.2-7.3)	5.1 (4.3-6.1)	0.018*
VAS	60 (50-89.5)	46 (30-60)	0.045*
Swollen joints	8 (3-20)	2 (0-9.7)	0.024*
Tender joints	10 (4.5-20)	5.5 (4-17.7)	0.191
Total involved joints	12 (8-19)	11 (4-18)	0.580
CRP	2.74 (1.7-4.3)	2.1 (0.1-4.8)	0.810
ESR	37 (26.5-63.5)	25 (19.5-60)	0.419
HAQ	1.9 (1-2)	0.87 (0.25-1)	0.020*

*p-value <0.05 in univariate analysis performed using Mann-Whitney test; n: number of patients; DAS28: Disease Activity Score 28; VAS: Visual Analogue Scale; ESR: Erythrocyte sedimentation rate; HAQ: Health Assessment Questionnaire; RA: Rheumatoid arthritis. Values are expressed as median and interquartile range: median (IQR).

ney test. Generalized linear model (GLM) for repeated measures was used to detect differences between the follow-up visits within the RA group. Contingency tables with discrete variables were analysed by the Fisher's exact test. Sensitivity and specificity using the cut-off criteria of 6 and of 7 points in our population was calculated. All the analysis was done using GraphPad Prism (GraphPad, San Diego, CA). Differences were considered statistically significant for $p<0.05$.

Results

Thirty-seven patients with untreated early polyarthritis with less than 6 weeks duration were included. The mean age of the group was 48 ± 18 years [median: 47, inter-quartile range (IQR) 32-62 years], and 68% (25 out of 37) were females. All the patients were Caucasian from European origin. The mean follow-up time was 33.2 ± 11.2 (10-48) months. During the follow up period most of the patients evolved to RA (twenty-one individuals, 57%) (Table I). The remaining patients evolved to other diseases as can be detailed in Table II.

RA *vs* NON-RA PATIENTS

The median age of the patients who evolved to RA (the RA-group) was similar to the median age of the patients who developed other diagnosis (non-RA group) [median (IQR) 47 (31-58.5) *vs* 43 (34-69) years, respectively, *p=0.74*].

Table II. Diagnosis of the patients included in the non-RA group

Diagnosis	Number of patients
Self-limited arthritis	5
Gouty arthritis	3
Paraneoplasic arthritis	2
Systemic lupus erythematosus	2
Psoriatic arthritis	2
Polymialgia rheumatica	1
HIV-related arthritis	1
Total	16

The majority of patients in the RA group were females (81%), as opposed to the non-RA group (50% females) (*p=0.077*).

The global initial mean DAS 28 was 5.8±1.4. At the initial visit the median DAS 28 in patients who have latter evolved to RA was significantly higher than in the non-RA patients [median (IQR) 6.2 (5.2-7.3) *vs* 5.1 (4.3-6.1), respectively; *p=0.018*] (Table I). VAS was also higher in the RA group [median (IQR) 60 (50-89.5) *vs* 46 (30-60), respectively; *p=0.045*], as well as the number of swollen joints [median (IQR) 8 (3-20) *vs* 2 (0-9.7); *p=0.024*], when compared to the non-RA group.

We did not find significant differences in the number of tender joints in both groups [median (IQR) 10 (4.5-20) *vs* 5.5 (4-17.7), respectively; *p=0.19*]. The involvement of hands and wrists (pain or swelling of finger joints or wrists) was also similar in the RA and non-RA groups (*data not shown*).

Among the 21 RA patients, 21 were evaluated for RF and 17 for ACPA in the first visit. Of these, 9 (43%) presented RF and 6 (28.6%) presented ACPA in the serum. Importantly, RF and ACPA were not detectable in any of the patients who did not evolve to RA (*p=0.0019* and *p= 0.0177*, respectively).

The initial ESR values did not differ significantly between RA and non-RA groups [median (IQR) 37 (26.5-63.5) *vs* 25 (19.5-60), *p=0.419*] (Table I).

At baseline ESR was normal (<20 mm/h) in 20% patients.

At the first visit, the RA group had a higher functional impairment when compared to the non-RA group, as it was shown by the HAQ values [median

(IQR) 1,87 (1-2) *vs* 0.87 (0.25-1), respectively; *p*=0.020] (Table I).

EARLY RA-group EVALUATION

In the RA cohort, at the initial visit the median (IQR) DAS 28 was 6.2 (5.2-7.3). We found no differences in DAS 28 between patients with or without detectable serum RF [median (IQR) 6.2 (4.8-6.6) *vs* 6.7 (4.9-7.8), respectively; *p*=0.436], and between ACPA positive or negative patients [median (IQR) 5.7 (3.8-6.8) *vs* 6.7 (4.9-7.8), respectively; *p*=0.313]. We also compared the mean value of HAQ of these groups, however no differences were found between RF positive and RF negative patients [median (IQR) 1.6 (1.1-1.8) *vs* 1.2 (0.75-1.8), respectively; *p*=0.495], or when comparing ACPA positive and ACPA negative patients [median (IQR) 2.0 (1.5-2.0) *vs* 1.6 (0.8-2.0), respectively; *p*=0.333].

The DAS28 after starting prednisone (2nd visit) was significantly lower than that at the initial visit [median (IQR) 3.8 (3.1-5.7) *vs* 6.1 (5.2-7.3), respectively; *p=0.0008*]. Between the initial visit and the visit after starting prednisone treatment, five patients had an EULAR good response, five patients had an EULAR moderate response and eight patients did not reach an EULAR response[20].

After 4 months of a stable dose of MTX (3rd visit) the mean DAS28 was significantly lower when comparing to DAS28 before starting MTX treatment [median (IQR) 2.6 (1.9-4.3) *vs* 3.8 (3.1-5.7); *p=0.021*] (**Figure 1**) and only 3 patients maintained a DAS28 >3.2. An EULAR good response (20) occurred after starting MTX treatment in eight patients, in two patients a moderate response occurred and two patients had no EULAR response. The 3 patients that still had a DAS28>3.2 received combination therapy with sulphasalazine and hydroxychloroquine, with further reduction of DAS28 below 3.2. In the 4th visit, after a mean follow up of 33 months, the mean DAS28 was of 2.84 ± 1.39. The majority of our RA patients responded with a moderate or good EULAR response to low dose corticosteroids and MTX (in monotherapy or combined DMARD therapy). At the final visit, the mean DAS28 was significantly lower when compared to baseline evaluation [median (IQR) 2.6 (1.9-3.2) *vs* 6.2 (5.2-7.3), respectively; *p=0.0003*]. The mean DAS28 reduction between all the visits was always statistically significant.

The presence of RF or ACPA did not influence the final DAS28: we found no difference when comparing RF positive and RF negative patients [median (IQR) 2.9 (1.9-4.2) *vs* 2.5 (1.9-2.8), respectively; *p*=0.464], or when comparing ACPA positive and ACPA negative patients [median (IQR) 2.4 (1.8--3.6) *vs* 2.6 (2.3-3.1), respectively; *p*=0.859].

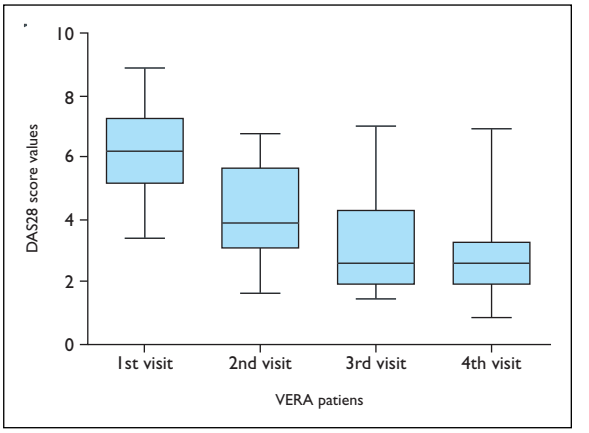

Figure 1. Median values of DAS28 in early RA cohort at the different time-points evaluated

Legend – DAS28: Baseline (1st visit), 4-6 weeks after starting prednisone (2nd visit), 4 months after MTX (3rd visit) and at the final evaluation (4th visit) after a mean follow up of 33 months of the RA-group of patients. At the final visit, the mean DAS28 was significantly lower when compared to baseline evaluation (p=0.0004). The mean DAS28 reduction between all the visits was always statistically significant.

Discriminative value of the new ACR/EULAR Criteria for the classification of rheumatoid arthritis in a very early arthritis population

The new ACR/EULAR criteria for the classification of RA are mainly based on 4 items: number and localization of affected joints, disease duration, levels of acute phase reactants (ESR and CRP), and presence and title of RF and ACPA.

As previously observed the total number of involved joints (tender and/or swollen joints) was not significantly higher in the RA group [median (IQR) 12 (8-19) *vs* 11 (4-18), *p=0.58*) when compared with the non RA group. Taking into consideration the median joint counts, the two groups scored 5 in the joint involvement category and individually there were 12 (57.1%) patients scoring 5 in the RA group and 8 (50%) patients reaching the same score in the non RA group.

All patients had zero points in the "disease duration" category of the criteria, as all included pa-

Table III. Performance characteristics for different cut-points of 6 and 7 in our cohort

Total score	RA	Non-RA		RA	Non-RA
≥ 6 points	15 (71.4%)	7 (43.8%)	≥7 points	14 (66.7%)	0 (0%)
< 6 points	6 (28.6%)	9 (56.2%)	<7 points	7 (33.3%)	16 (100%)
RR	1.7			3.3	
Sensitivity(%)	71			67	
Specificity(%)	56			100	
PPV (%)	68			100	
NPV (%)	60			69	

RA: Rheumatoid arthritis, RR: relative risk of evolving to RA, Sensitivity: measures the proportion of actual positives which are correctly identified as such (e.g. the percentage of RA patients who are correctly identified as having RA), Specificity: measures the proportion of negatives which are correctly identified (e.g. the percentage of non-RA patients who are correctly identified as not having RA), PPV: positive predictive value (proportion of patients with positive test results who are correctly diagnosed as RA), NPV: negative predictive value (proportion of patients with negative test results who are correctly diagnosed as non-RA).

tients had less than 6 weeks of disease duration (one of the inclusion criteria).

The analysis of the acute phase reactants showed that the initial ESR values did not differ significantly between RA and non-RA patients [median (IQR) 37 (26.5-63.5) *vs* 25 (19.5-60), *p=0.419*] as well as the initial CRP values [median (IQR) 2.74 (1.7-4.3) *vs* 2.1 (0.1-4.8), p=0.810, respectively], thus the two groups scored 1 in this parameter. At an individual basis 19 (90.5%) patients scored 1 in the RA group and 12 (75%) patients attained the same score in the non RA group.

Regarding the presence and title of RF and ACPA, the mean score in this item was significantly different between the groups (1.05 ± 1,28 in the RA group *vs* 0 ± 0 in the non-RA group, *p<0.05*). Of notice, RF and ACPA were not detectable in any of the patients who did not evolve to RA. Therefore, the non-RA group score zero and 9 (43%) of the patients in the RA group scored at least 2 [4 (19%) patients scored 3].

Globally, according to the new RA classification criteria, the median total score of the RA group at baseline was significantly higher than the non-RA group [median (IQR) 6 (4.5-8) points in the RA group *vs* 4.5 (2.2-6) points in the non-RA group, *p=0.007*]. Only 6 (28.6%) of the 21 RA's patients had baseline scores lower than 6 comparing to 9 (56.3%) of the 16 patients that did not evolve to RA. Interestingly, the highest score reached in the non--RA patients was 6 points, the cut off point to classify patients as having RA. These results prompted us to test a cut off point of 7 (Table III) in order to improve the specificity of the criteria in our very early arthritis population. As expected, the relative risk of evolving to RA in patients who have 7 or more points is higher than with the original cut off point of 6 (1.7 *vs* 3.3, respectively). The specificity and positive predictive value improve dramatically to 100% when applying the cut point 7 in our cohort, without a significant decrease in the sensitivity of the criteria (71% to 67%, respectively).

Discussion

In a cohort of untreated polyarthritis patients with less than 6 weeks of evolution we have assessed the performance of the new ACR/EULAR RA classification criteria. We have identified baseline RF and ACPA positivity, the initial disease activity and functional impairment as predictors of evolution to RA. In addition, our data suggest that in this particular setting of a very early polyarthritis cohort, a cut off of 7 points increases the specificity without significantly affecting the sensitivity of the new ACR/EULAR classification criteria.

In order to understand which factors influence the persistence of arthritis, it is crucial to study patients very early in their disease course, preferentially without any exposure to treatments. However, studies enrolling this type of patients are hindered by delay on referral from the general practitioners or delay in reaching a rheumatology clinic, and in most of the cases cohorts include patients exceeding 6 weeks of disease duration. The herein work recruited only untreated polyarthritis patients with less than 6 weeks of disease duration,

which enriched the interest of this analysis but restricted the number of patients included.

The proportion of patients that evolved to RA in our cohort was about 60%, much higher than it was expected according to the published literature of European early arthritis clinics[2,4,5], which describes progression to RA in about 33.3% of the patients presenting with early arthritis. However, we have to emphasize that most of those cohorts also included patients presenting with mono and oligoarthritis, increasing the probability of developing other diseases. This might had also an effect on another observation, in fact, we were expecting that initial involvement of hands and wrists would be significantly higher in RA patients, but this was not the case. Again, this involvement may be more important in differentiating RA from non-RA patients when lower limbs oligoarthritis and monoarthritis cases are included.

In our very early polyarthritis cohort the comparison of the patients that evolved to RA *vs* those that were latter classified as having other conditions revealed that RF and ACPA were highly specific but had a low sensitivity to very early RA. In our study the presence of both antibodies (RF and ACPA) conferred a high risk of progression to RA. In addition, patients that evolve to RA tend to present a more severe onset of the disease when compared to non-RA patients, as it is shown by the higher baseline values of DAS28, swollen joints, VAS and HAQ.

The application of the new ACR/EULAR criteria for classification of RA to our population showed that patients evolving to RA presented a significantly higher score than patients who evolved to other diseases. Moreover, the application of the new criteria in our cohort identified the majority of patients that evolved to RA: 15 (71.4%) of the 21 RA's patients had scores higher or equal to 6 comparing to 7 (43.7%) of the 16 patients that did not evolve to RA. However, in our population, about 30% of patients who progressed to RA did not meet the new criteria for RA in the first evaluation, a higher proportion than would be expected. Of notice, all patients included in the study had arthritis with less than 6 weeks of duration (one of the study inclusion criteria). This restriction on disease duration lowers by one point the total score of every patient included in our cohort. The effect of treatment on acute phase reactants and on joint counts precluded further application of the criteria at latter time points.

The new ACR/EULAR RA classification criteria have determined the cut off point of 6, to classify patients as definite RA in order to maximise the sensitivity of the criteria. In our cohort of patients with less than 6 weeks of disease duration, all of the non-RA patients had 6 points or less, which motivated our intention to test a higher cut-point (7 points) in order to improve the specificity of the criteria in our population. Applying the new cut point to our cohort, we found this cut point of 7 to be much more specific for patients evolving to RA, comparing to the original cut off point of 6 (Table III): none of the patients that did not progress to RA had a score equal or higher than 7, comparing to 7 (43.8%) non-RA patients who scored 6. Despite a dramatic effect on the specificity, the sensitivity of the criteria with the new cut off point of 7 was similar when compared to the original cut off point of 6 (67% *vs* 71%, respectively), which means that in our very early arthritis population the cut off point of 7 highly improves specificity without compromising the original sensitivity of the criteria. Our sample size hinders the generalization of this finding, but these results indicate that the cut off point of 7 might be used in polyarthritis patients with less than 6 weeks of disease duration.

The aim of the working group of the new RA classification criteria was to provide a standardized approach for discriminating, from a population of individuals presenting with arthritis, the subgroup with the highest probability of persistence and joint damage, who may benefit from DMARD intervention. In fact the high criteria performance in addition to a very good outcome of the patients classified as RA in our cohort consubstantiate this strategy.

In conclusion, we have shown that in a cohort of polyarthritis patients with less than 6 weeks of disease duration a high DAS28 score, a high number of swollen joints, a low functional status assessed by HAQ and the presence of RF or ACPA are eventually associated with the evolution to RA. In this cohort, 71.4% of the patients that latter progressed to RA, when initially assessed (with less than 6 weeks of symptoms), scored the 6 points needed to be classified as RA. Thus, the new ACR/EULAR criteria for the classification of RA showed, even in very early arthritis, a good sensitivity for the identification of patients that are likely to evolve to RA. However, the specificity was rather low as 43.7% of the patients that evolved to non-RA conditions also scored 6 points. By raising

the cut off point, in this very early arthritis cohort to 7, it was possible to increase specificity while keeping sensitivity.

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PATIENTS' SATISFACTION WITH THE RHEUMATOLOGY DAY CARE UNIT

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Abstract

Background: Patients receiving biological therapies are regularly evaluated and monitored at rheumatology day care units (RDCU). Despite patients' satisfaction with the delivered care and the relationship between the patient and the multidisciplinary team being acknowledged as important aspects to ensure adherence to therapy, factors associated with them have not been investigated so far.

Objectives: To evaluate patients' satisfaction with the functioning of the RDCU and to identify the factors associated with the level of satisfaction.

Methods: An anonymous questionnaire was administered to all patients with rheumatoid arthritis (RA) or spondyloarthritis treated with biological drugs and followed at the RDCU at Hospital Garcia de Orta, Almada, Portugal. Satisfaction was measured using a visual analogue scale (0-100, 0 meaning completely unsatisfied, 100 meaning completely satisfied). Further information was collected on socio-demographic variables, physical conditions of the RDCU, waiting time, satisfaction with the role of medical, nursing and administrative staff (satisfaction level with their friendliness, question answering, care delivery, privacy during consultation, clarity in the information given, which was then transformed into a composite score, 0-20). Factors associated with satisfaction were studied by univariable followed by multiple linear regression to adjust for potential confounders.

Results: In total, 150 patients were included in the study (mean age 50.6 ± 13.7 years, 64% female, 62% RA, mean disease duration 10.6 ± 6.1 years). The majority of patients attended the RDCU for more than three years and 57% received subcutaneous therapy. The mean level of satisfaction with the RDCU was 81.9 ± 17.9. Multivariable analysis showed that intravenous therapy (β 6.13, 95% confidence interval – CI 0.71-11.55), physician score (β 2.28, 95%CI 1.20-3.35) and increasing levels of satisfaction with the room temperature (β 5.64, 95%CI 3.06-8.21) and waiting time (β 25.53, 95%CI 8.17-42.89, for a very good vs non-acceptable waiting time) were positively associated with the level of satisfaction, while the nursing score was inversely associated.

Conclusions: Patients were overall very satisfied with the functioning of the RDCU. Waiting time, satisfaction with the physician role, room temperature and intravenous therapy were the main factors positively associated with the level of satisfaction.

Keywords: Patient Satisfaction; Day care; Biological Therapy; Portugal.

Introduction

Patients' satisfaction has been widely investigated in health care research. Many authors consider patients' satisfaction as an indicator of quality of care from the patients' perspective[1-4] and it is increasingly considered an important component of comprehensive chronic disease management[5]. The importance of patients' satisfaction as a measure of quality is based in two main principles: 1) patients are an essential source of information on how a health care service works; 2) patients' perspective is increasingly being valued when planning and evaluating services[1,6,7].

The assessment of patients' satisfaction through satisfaction surveys is nowadays the preferred method for valuing the perspective of patients about the health care provided[8]. Findings from several studies established the importance of the relationship between satisfaction and both the physical environment and the interpersonal components of a health unit[9,8]. Empathy and assurance with the health care team, which mainly represent interpersonal communication, were identified as having a strong influence on the patients' willingness to come back to the hospital[9]. This, in turn,

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may also represent a better adherence to the treatment plan and disease monitoring, particularly important in chronic conditions.

In the last decade there has been a paradigm shift in the approach to chronic inflammatory rheumatic diseases, in part thanks to a better understanding on the etiopathogenic mechanisms of the diseases, but also the emergence of new and more efficacious drugs. With the widespread use of biological drugs in various inflammatory rheumatic diseases, including rheumatoid arthritis (RA) and spondylarthritis (SpA), rheumatology departments have adapted to this reality, being it essential to ensure high levels of quality in the care delivered. Patients treated with biological drugs are evaluated in a standardized way in dedicated clinics, usually in the environment of a RDCU. At Hospital Garcia de Orta, in Almada, the RDCU is an integrated outpatient unit at the Department of Rheumatology, where every day patients with chronic systemic diseases are followed, in particular RA, SpA (including ankylosing spondylitis, psoriatic arthritis and undifferentiated spondylarthritis), juvenile idiopathic arthritis, Behçet's disease, systemic lupus erythematosus, progressive systemic sclerosis, Sjögren syndrome, systemic vasculitis or idiopathic inflammatory myopathy treated with biotechnological drugs. The biological therapies, administered subcutaneous (SC) or intravenously (IV), are expensive drugs with some well-known risks that justify close monitoring and rigorous evaluation of the risks and benefits. All patients taking these drugs, either administered IV (Infliximab, Rituximab, Abatacept, Tocilizumab), or SC (Etanercept, Adalimumab, Anakinra), are regularly monitored at the RDCU. When patients are stable, the clinical and laboratory evaluations are carried out every 12-16 weeks.

The quality of health services provided by multidisciplinary teams and the patient's relationship and empathy with those, are essential issues to increase the security and the patient's compliance to therapy, which are a key to therapeutic success[10-12]. For these reasons, it is important to know the level of the patients' satisfaction, both with to the physical aspects of our RDCU, but also with the provision of health care by the various elements of the health team, in particular physicians, nurses and administrative staff.

The purpose of this study was to evaluate the level of patients' satisfaction with the functioning of the RDCU and to investigate the factors associated with this level of satisfaction.

Methods

Study Population

We conducted a cross-sectional study that included patients with RA and SpA, treated with biological drugs and regularly followed at the RDCU at HGO. All patients with the above-mentioned diseases and assessed at the RDCU during the first semester of 2010 were invited to participate and no further eligibility criteria were applied. The 150 patients who participated in the study were assessed using an anonymous questionnaire.

Patients' satisfaction with the rheumatology day care unit

The overall patients' satisfaction regarding the RDCU was assessed using a visual analogue scale from 0 (completely unsatisfied) to 100 (completely satisfied). We evaluated various dimensions of patients' satisfaction with regard to the physical conditions of the RDCU (room's size, decoration and temperature) and to the role of the physician, nursing and administrative staff, using Likert scales (ranging from 0 to 4, from unsatisfied to very satisfied). The delivery of care by physicians and nurses was evaluated with respect to their friendliness and attention, response to questions, way how provided care was delivered, privacy during care and clarity of the information provided. The administrative service was classified for the kindness, availability/attention, speed/efficiency and clarity of the information provided. For each professional, we calculated an overall score reflecting the level of patients' satisfaction with the performance of the health professional. In the case of the level of patients' satisfaction with the rheumatologist's performance, this score was designated as physician score (ranging from 0, patient unsatisfied with the performance of the physician in all five evaluated dimensions to 20, patient very satisfied with the performance of the physician in the five dimensions evaluated). The nursing score was constructed similarly, ranging between the same values. The administrative score, also built in a similar way, ranged from 0-16, reflecting the four dimensions evaluated.

Factors possibly associated with patients' satisfaction with the rheumatology day care unit

We also evaluated demographic and clinical factors

possibly associated with the level of patients' satisfaction with the RDCU. Demographic factors assessed were age, gender, marital status, number and relationship to the people with whom the patient lived and educational level. With regard to clinical factors, we collected information on the rheumatic disease diagnosed, disease duration, type of biological drug used, follow-up time at RDCU and disease activity. The disease activity was assessed by the Disease Activity Score with 28-joint assessment (DAS28)[13], in the case of RA, and the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)[14], in the case of SpA.

Patients were also asked about some aspects related to the RDCU that could be associated with their level of satisfaction, including the distance from home to the RDCU, travel method, accompanying in the visit to the RDCU, ease of access to the RDCU from the main entrance of the hospital, waiting time and adequacy of the physical environment for the purpose of the RDCU. The waiting time was rated from 0 to 3, where 0 corresponded to "not acceptable", 1 "reasonable", 2 "good" and 3 "very good". The RDCU team recommends to patients to contact the RDCU by telephone, in case of doubt or appearance of any new event, so that an urgent evaluation can be considered. In this context, patients were asked whether they were aware of this possible telephone contact, as well as their previous experience with contact to the RDCU in an urgent situation, in case they had any.

Statistical Analysis

First, a descriptive statistical analysis was undertaken, in which the categorical variables are expressed as frequencies and the continuous variables in the form of mean ± standard deviation.

The administrative score was converted to vary from 0 to 20, to be more easily comparable to the results obtained for the physicians' and nurses' scores.

In order to identify factors associated with the level of the overall patients' satisfaction with the RDCU, univariable linear regression analyses were undertaken between the level of the overall patients' satisfaction (0-100) and the demographic, clinical and physical factors related to the RDCU previously described.

Factors with a p-value < 0.1 were subsequently included in a model of multiple linear regression analysis (backwards method) until the best final model was obtained and which is presented. Statistical analysis was performed using Stata SE version 11 and a significance level of 5% was assumed.

Results

The study included 150 patients, with a mean age of 50.3 ± 13.7 years, being 64% female (Table I). Sixty-two percent of the patients had a diagnosis of RA, the remaining had SpA (ankylosing spondylitis/undifferentiated spondylarthritis). The average rheumatic disease duration was 10.6 ± 7.9 years. Considering only the patients with RA, the mean disease duration was 10.3 ± 7.0 years and 11.2 ± 9.1 years for the patients with SpA.

Most patients were followed at the RDCU for more than five years, and 43% of the patients were on intravenous therapy (Infliximab, Rituximab, Abatacept or Tocilizumab), while the remaining were treated with subcutaneous therapy (Adalimumab, Etanercept or Anakinra).

Most patients (46%) lived at a distance from the hospital lower than 15 Kms, 31% at a distance of over 25 Kms, the vast majority of the patients (75%) travelled to the hospital by car and 65% on their own (Table II).

Table I. General characteristics of the population

	Mean ± SD or % (n = 150)
Age (years)	50.3 ± 13.7
Gender (% female)	64
Marital status (% married)	73
Educational level (%)	
• read and write only	3
• 4th grade	30
• 9th grade	18
• 12th grade	19
• graduation	21
Follow-up time in RDCU ≥ 3 years (%)	62
RA (%)	62
Rheumatic disease duration (years)	10.6 ± 7.9
IV therapy (%)	43
DAS 28 (n=93)	3.75 ± 1.39
BASDAI (n=57)	2.38 ± 1.33

SD – standard deviation; RA – rheumatoid arthritis; IV – intravenous; DAS28 – disease activity score with 28-joint assessment; BASDAI – Bath Ankylosing Spondylitis Disease Activity Score

Table II. Characterization of aspects of the RDCU

	Mean ± SD or % (n = 150)
Distance home – hospital (%)	
• 1-15 km	46
• 15-25 km	19
• >25 km	31
Easy access to the RDCU (%) (yes/no)	85
Patients' satisfaction with the waiting time (%)	
• not acceptable	2
• reasonable	27
• good	42
• very good	29
Room appropriate for the RDCU (%) (yes/no)	84
Patients' satisfaction with the room size (%)	
• satisfied	26
• reasonably satisfied	24
• very satisfied	22
Patients' satisfaction with the room decoration (%)	
• satisfied	43
• reasonably satisfied	26
• very satisfied	24
Patients' satisfaction with the room temperature (%)	
• satisfied	41
• reasonably satisfied	20
• very satisfied	35
Knowledge of possible telephone contact in case of urgency (%) (yes/no)	92
Efficiency of telephone contact in case of urgency (%) (yes/no)	99
Previous access to the RDCU in an urgent situation (%) (yes/no)	35
Easy access to the RDCU in urgent situation (%) (yes/no)	98

RDCU – rheumatology day care unit; SD – standard deviation

When asked about ease of access to RDCU from the entrance of the hospital, 85% confirmed it was easily accessible. Of the 23 patients (15%) who reported a not easy to access to the RDCU from the entrance of the hospital, the reasons given were in 39% the difficulty in parking the car, in 30% a long waiting time for the lifts and in 30% the long distance between the RDCU and main entrance.

The waiting time was considered good by 42% of the patients; 29% found it very good and 27% reasonable; 2% found it not acceptable.

When asked about the adequacy of the RDCU room for its purpose, 84% of the patients agreed it was adequate. The level of satisfaction with the room size was fairly satisfactory for 24% of the patients and very satisfactory for 22%. As for the decoration of the room, 43% of the patients were satisfied, 26% fairly satisfied and 24% very satisfied. Regarding the room temperature, 41% showed satisfaction, 20% were fairly satisfied and 35% very satisfied.

One hundred and thirty-eight patients (92%) admitted having knowledge of the possible telephone contact to the RDCU in case of urgency, and 99% of the patients confirmed that when they needed help, the telephone contact with the RDCU did solve their problems. We also wanted to know if patients had used the RDCU in case of an urgent situation and 52 patients (35%) said yes. Of those patients, 98% reported to be easily attended at the RDCU in these situations.

The average overall patients' satisfaction level with the RDCU, considering all its functioning, was 81.91 ± 17.91, on a scale from 0 to 100, where 0 meant completely unsatisfied and 100 completely satisfied.

The levels of patients' satisfaction with the different dimensions in delivery of care by the physician, nursing and administrative staff are in Tables III, IV and V. The mean physician score was 16.53 ± 4.27 and the nursing score was 17.70 ± 3.54. The administrative score obtained the mean value of 16.71 ± 4.86. The privacy of patients during their consultation, either with the physician or nurse, was the aspect evaluated as the least satisfactory for patients: only about 40% of the patients were very satisfied with this aspect, comparing with a frequency of above 70% for the other aspects evaluated. The various aspects of delivery of care with respect to the nursing team were identified as very satisfactory, with more than 85% of the patients being very satisfied. With respect to the performance of the administrative staff, the speed and efficiency in the service was the least satisfactory aspect.

The disease activity of patients with RA, assessed using the DAS28, had an average score of 3.75 ± 1.39. Sixty-two of the 93 patients (67%) had a DAS28 equal or superior to 3.2, so they had active

Table III. Physician Score

	Unsatisfied	Little satisfied	Satisfied	Fairly satisfied	Very satisfied
Friendliness and attention	0%	1%	13%	8%	78%
Response to questions	0%	1%	14%	13%	71%
Way how provided care was delivered	0%	1%	13%	6%	80%
Privacy during care	6%	15%	19%	25%	35%
Clarity of the information provided	1%	0%	16%	12%	70%

Table IV. Nursing Score

	Unsatisfied	Little satisfied	Satisfied	Fairly satisfied	Very satisfied
Friendliness and attention	0%	0%	7%	2%	91%
Response to questions	0%	0%	8%	6%	86%
Way how provided care was delivered	0%	0%	6%	1%	92%
Privacy during care	5%	13%	16%	22%	44%
Clarity of the information provided	0%	0%	9%	5%	86%

Table V. Administrative Score

	Unsatisfied	Little satisfied	Satisfied	Fairly satisfied	Very satisfied
Kindness	0%	1%	15%	15%	69%
Availability/attention	1%	1%	17%	15%	67%
Speed/efficiency	0%	1%	19%	21%	59%
Clarity of the information provided	0%	1%	19%	14%	66%

disease. Thirty-one of the 93 patients evaluated with the DAS28 (33%) had low disease activity (DAS28 < 3.2), and of these, 17 (17 of 93 patients = 18.3%) met criteria for remission (DAS28 < 2.6).

Disease activity of patients with SpA was assessed by the BASDAI and had an average score of 2.38 ± 1.33. Six of the 57 evaluated patients (11%) with BASDAI had active disease (BASDAI>4).

Factors associated with the level of patient satisfaction with the RDCU

The factors that were associated with patients' level of satisfaction were identified by a univariable linear regression analysis, followed by multivariable regression (Table VI). The best final model, adjusted for gender, age and main diagnosis, identified the use of intravenous treatment (β 6.13, 95% CI 0.71 – 11.55), the satisfaction with the room temperature (β 5.64, 95% CI 3.06 – 8.21), the satisfaction with the physician performance (β 2.28, 95% CI 1.20 – 3.35) and the evaluation of the waiting time as factors with a positive association with the level of satisfaction.

Taking the patients that evaluated the waiting time as not acceptable as a reference, the patients who considered the waiting time very good had a global level of satisfaction 25 times higher (β 25.53, 95% CI 8.17 – 42.89), while the patients who considered the waiting time as good had a satisfaction level 24 times higher (β 24.04, 95% CI 7.50 – 40.59).

There was an inverse relationship between the overall patients' satisfaction and the nursing score (β -1.71, 95% CI -2.91 – -0.50). There was no statistically significant association (either in the univariable regression) between the overall level of satisfaction and the following variables: disease

Table VI. Univariable and multivariable linear analysis

Variables	Univariable Analysis β (95% CI)	Multivariable Analysis β (95% CI)
Gender (female vs male)	-6.76 (-12.74; -0.79)	0.42 (-5.56; 6.39)
RA (yes/no)	-6.80 (-12.68; -0.92)	-2.50 (-8.70; 3.71)
Age (years)	-0.04 (-0.25; 0.18)	-0.05 (-0.23; 0.14)
IV therapy (yes/no)	9.81 (4.15; 15.46)	6.13 (0.71; 11.55)
Satisfaction with the room temperature (0-4)	8.56 (5.90; 11.22)	5.64 (3.06; 8.21)
Physician score (0-20)	1.85 (1.20; 2.51)	2.28 (1.20; 3.35)
Nurse score (0-20)	1.11 (0.22; 1.99)	-1.71 (-2.91; -0.50)
Reasonable vs not acceptable waiting time	28.09 (9.11; 47.07)	19.21 (2.65; 35.78)
Good vs not acceptable waiting time	35.35 (16.61; 54.09)	24.04 (7.50; 40.59)
Very good vs not acceptable waiting time	45.34 (26.41; 64.27)	25.53 (8.17; 42.89)
Satisfaction with the room size (0-4)	5.10 (2.92; 7.25)	*
Satisfaction with the room decoration (0-4)	7.24 (4.40; 10.09)	*
Administrative score (0-20)	0.85 (0.24; 1.46)	*
Travel to the RDCU by car vs walking	27.89 (7.27; 48.51)	*
Travel to the RDCU by bus vs walking	23.04 (1.47; 44.61)	*
Travel to the RDCU by train vs walking	26.22 (2.74; 49.70)	*

* The variable was not selected during the multivariable analysis (p ≥0.05)
CI – confidence intervals; IV – intravenous; RA – rheumatoid arthritis; RDCU – rheumatology day care unit.

duration, marital status, educational level, number of people with whom the patient lived, ease of access to the RDCU, satisfaction with the adequacy of the room, knowledge about the possibility of telephone contact with RDCU in an urgent situation, the follow-up time at the RDCU, the distance from home to RDCU, the travel to the RDCU with a companion and the disease activity (DAS28 and BASDAI).

The multivariable linear regression analysis was repeated, including in the model the individual variables that were part of the physician and the nursing scores, and the results were similar, with the same variables in the final model (except for intravenous therapy) and the regression coefficients being in the same order of magnitude (results not shown). From the individual variables from the physician and nursing scores, the only one that remained in the final model was the satisfaction with the friendliness of the doctor (β 12.95, 95% CI 9.54 – 16.37, in the univariable analysis and β 2.28, 95% CI 1.20 - 3.35, in the multivariable analysis).

Discussion

Overall, patients are very satisfied with the functioning of the RDCU. The average level of satisfaction was 81.91 ± 17.91, on a scale from 0 to 100, where 0 meant completely unsatisfied and 100 completely satisfied.

The main factors which have been shown to be associated with the overall level of patients' satisfaction were: the waiting time, global satisfaction with the medical delivery of care, intravenous therapy and the temperature of the room, all with a positive association with the level of patients' satisfaction. Satisfaction with the nursing care showed an inverse relationship with the level of overall satisfaction.

The results of this study are consistent with the literature, though sparse in this area. Cleary and McNeil[15] identified the characteristics of health care providers or organizations that result in personal care as factors associated with higher levels of satisfaction. No other similar studies analyzing factors associated with patients' satisfaction with respect to their treatment were found.

The results of several studies have shown the importance of the interpersonal component of the delivery of care on patients' satisfaction[16,17]. A similar result was obtained in our study, with regard to overall medical assistance and more specifically to the most valued by patients: the physician's friend-

liness and this was the only item, among the different ones evaluated on the delivery of care by health professionals, with a statistically significant association with the overall patients' level of satisfaction.

With respect to patients' satisfaction with the performance of the nursing staff, we obtained an inverse association with the level of overall patients' satisfaction. As a possible explanation, we consider the fact that this health professional does not yet have a recognized significant impact on the assessment and treatment of rheumatic patients, such as the physician's expertise actually has. This result enhances the fact that, in Portugal, there is still a long way to go. There is much room for improvement in the nursing training and skills development for the treatment of rheumatic patients and for the assertion of the specialized nurse role so that this health professional is truly recognized in their working environment and their contribution has a positive impact on the approach to the patient.

Eijk-Hustings *et al.*[18], on behalf of the European League Against Rheumatism (EULAR) nursing task force, developed ten recommendations for the role of the rheumatology nurse in the management of patients with chronic inflammatory arthritis. These recommendations may provide a basis for emphasising and optimising nursing care in order to contribute to a more standardised level of professional nursing across Europe. These recommendations underline the nurses' role to be an interface between the patient and other members of the multidisciplinary team. As a result of the availability of new treatment options and organisational developments, the role of the nurse has undergone significant changes over the last decades. However, there are still striking difference between and within countries, mainly due to differences in legal regulations, educational background of the nurses, and funding issues related to overall health care provision[18].

One of the items most valued by patients was the waiting time. It is understood that the time spent by patients in their hospital visits is necessary to be spent on other activities and it is not pleasant for the patient to have to wait. In this regard, one of the concrete proposals resulting from this project consists precisely in the attempt to optimize the organization of the RDCU, in order to reduce the waiting time of patients.

In order to plan specific measures in an attempt to maximize the patients' level of satisfaction with the RDCU, it would be important to identify not only factors which were associated with the overall level of satisfaction, but essentially factors with a causal relationship. In this sense, studies with a longitudinal design could assess this particular point. The identification of factors with a possible causal relationship with the overall level of satisfaction would enable the planning of specific measures to improve this aspect, so important for the patient and the success of the therapy, a key objective for all professionals involved in treating these patients. Later, it would also be interesting to follow prospectively patients and investigate the different outcomes of patients with different levels of satisfaction with the care delivered.

Conclusion

Overall, patients are very satisfied with the functioning of the RDCU. Patients more satisfied with the waiting time for evaluation at the RDCU, under intravenous therapy and more satisfied with the room temperature and with the delivery of care by the rheumatologist revealed a higher level of overall satisfaction. Satisfaction with the performance by nurses was inversely associated with the overall level of satisfaction, which probably reflects a failure to recognize the important role of nurses in the management of chronic rheumatic diseases.

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PORTUGUESE GUIDELINES FOR THE USE OF BIOLOGICAL AGENTS IN RHEUMATOID ARTHRITIS – OCTOBER 2011 UPDATE

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Abstract

The authors present the revised version of the Portuguese Society of Rheumatology (SPR) guidelines for the treatment of Rheumatoid Arthritis (RA) with biological therapies. In these guidelines the criteria for introduction and maintenance of biological agents are discussed as well as the contraindications and procedures in the case of non-responders. Biological treatment (with a tumour necrosis factor antagonist, abatacept or tocilizumab) should be considered in RA patients with a disease activity score 28 (DAS 28) equal to or greater than 3.2 despite treatment with at least 20mg-weekly-dose of methotrexate (MTX) for at least 3 months or, if such treatment is not possible, after 3 months of other conventional disease modifying drug or combination therapy. A DAS 28 score between 2.6 and 3.2 with a significant functional or radiological deterioration under treatment with conventional regimens could also constitute an indication for biological treatment. The treatment goal should be remission or, if that is not achievable, at least a low disease activity, defined by a DAS28 lower than 3.2, without significative functional or radiological worsening.

The response criteria, at the end of the first 3 months of treatment, are a decrease of at least 0.6 in the DAS28 score. After 6 months of treatment response criteria is defined as a decrease greater than 1.2 in the DAS28 score. Non-responders, in accordance to the Rheumatologist's clinical opinion, should try a switch to another biological agent (tumour necrosis factor antagonist, abatacept, rituximab or tocilizumab).

Keywords: Rheumatoid Arthritis; Biological Therapies; Guidelines.

Introduction

In 2003, the Rheumatoid Arthritis Study Group (GEAR – Grupo de Estudos de Artrite Reumatóide) of the Portuguese Society of Rheumatology (SPR – Sociedade Portuguesa de Reumatologia) published the first version of the guidelines for the use of biological therapies in rheumatoid arthritis (RA) in Acta Reumatológica Portuguesa (ARP)[1].

These guidelines have been regularly updated as new evidence is published and the experience on their use increases.

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The monitoring of RA patients in Portugal is performed according to a national protocol of follow-up. The adopted model is based on the systematic use of a RA patient follow-up form, which includes a core set of variables, approved by the GEAR as well as by all national Rheumatology Department Directors. This follow-up protocol includes the data proposed initially in 2001 and reviewed in 2007[2]. This protocol has been included now in a national registry of rheumatic patients (Reuma.pt)[3]. The criteria used in these guidelines are based on the standardized use of validated assessment tools: the disease activity score 28 (DAS 28)[4,5], the health assessment questionnaire (HAQ)[6] and the radiological assessment of Sharp score modified by van der Heijde (SvdH)[7]. Although these recommendations contain some original concepts, their general structure follows the pattern of other international recommendations[8].

Guidelines for the use of biological therapies in RA patients

The guidelines intend to propose national recommendations, approved by SPR members, for the use of biological therapies in RA. The guidelines' aims are:

- To improve the quality of clinical practice in the field of Rheumatology;
- To guarantee a rational use of biological therapies approved for use in RA patients with inadequate response to conventional disease modifying anti-rheumatic drugs (DMARDs) or that are inadequate responders to at least one TNF antagonist, in accordance with the indications approved by the European Medicines Agency (Table I).

Criteria for introduction of biological agents

1. Patients who fail or have an inadequate response to conventional disease modifying antirheumatic drugs (DMARDs) are eligible for treatment with biological therapies. «Inadequate response or treatment failure» is defined when a patient, treated with conventional DMARDs over a period of time deemed adequate in these guidelines, present one of the following situations:
   - DAS ≥ 3.2 or
   - 2.6 ≤ DAS < 3.2 and worsening of HAQ≥0.22 (6/6M)[9] or worsening x-ray scores: Larsen≥6/ /SvdH ≥5 (12/12M)[10]

   All patients selected for treatment with biological therapies should be included in Reuma.pt[3].
2. Biological agents are recommended for patients with an inadequate response to MTX used in a stable dose of at least 20 mg/week (orally or parenterically), for at least 3 months. In this situation, the rheumatologist may either proceed directly to biological therapy (particularly in patients with severe prognostic markers) or may consider further treatment with another con-

Table I. Biological therapies approved for Rheumatoid Arthritis

	Inadequate response to conventional DMARDs	Inadequate response to at least one TNF antagonist
In association with MTX	abatacept adalimumab anakinra certolizumab etanercept golimumab infliximab tocilizumab	abatacept rituximab tocilizumab
In monotherapy	adalimumab etanercept certolizumab tocilizumab	tocilizumab

DMARD – Disease Modifying Antirheumatic Drugs.

ventional DMARD or association of conventional DMARDs during at least 3 months before starting a biological agent (chiefly in patients without a severe prognosis).
3. In case of intolerance, toxicity or refusal (signed statement) to take MTX, the patient may be considered eligible for treatment with a biological agent if there is an inadequate response (according to the above provided definition) after a period of at least 3 months of treatment with a stable dose of another conventional DMARD or an association of conventional DMARDs. If MTX cannot be included in the treatment regime, the patient will be eligible for treatment with biological therapies that do not require simultaneous use of MTX.

Treatment Objective

Remission is a realistic goal and a major therapeutic target in RA patients under treatment with biologicals. In clinical practice, remission can be defined in two distinct levels:
1. Remission based on a DAS28 < 2.6.
2. A more stringent goal for remission can be considered: a tender joint count (in 28), swollen joint count (in 28), CRP (in mg/dl) and patient global assessment (0-10 scale) scoring all ≤1 or Simplified Disease Activity Index (SDAI) ≤ 3.3[11].

If DAS28 < 2.6 is not achievable, 2.6 ≤ DAS28 < 3.2 in two successive assessments without significative worsening of the HAQ score assessed each 6 months and/or x-ray progression evaluated every 12 months is considered acceptable**.**

Criteria for maintenance of biological therapy

1. The first decision is taken 3 months after the introduction of biological therapy, supported by the opinion of the Rheumatologist:
   - Maintenance of biological treatment if responder, e.g., if there is an improvement of at least 0.6 in the DAS28 score.
2. Subsequent decision 6 months after the introduction of biological therapy, supported by the opinion of the Rheumatologist:
   - Maintenance of biological treatment if there is an improvement greater than 1.2 in the DAS28 score.

Procedure in case of inadequate response to a biological agent

If the patient fails or has an incomplete response to a first-line biological treatment the Rheumatologist, according to the current evidence, may proceed to switch to a second biological agent: TNF antagonist, abatacept, rituximab or tocilizumab.

Failure to response to one TNF antagonist does not preclude response to another. Patients have been switched successfully from one TNF antagonist to another. Observational studies suggest that non-responding patients are less likely to respond to a second TNF antagonist. Patients who have not tolerated one TNF antagonist may respond to a second one but are also less likely to tolerate a second TNF antagonist. Globally, after a second TNF antagonist failure the probability of response to a third TNF antagonist is low[12].

Procedure in case of sustained long-term remission under a biological agent

If the patient experiences remission for at least 12 months, the Rheumatologist can consider tapering biological DMARDs (expanding the interval between doses or reducing the dose), especially if this treatment is combined with a conventional DMARD[13].

Tuberculosis screening before introduction of biological therapies

The Portuguese Society of Rheumatology (SPR) and the Portuguese Society of Pneumology (SPP – Sociedade Portuguesa de Pneumologia) have developed recommendations on the diagnosis and treatment of latent tuberculosis (LTB) and active tuberculosis (ATB) in patients with inflammatory joint diseases (IJD), namely RA, psoriatic arthritis and ankylosing spondylitis, treated with biologicals, which are periodically updated and available at the SPR, SPP and Direcção-Geral da Saúde websites[14].

«Absolute» contraindications for the use of biologicals

- Active infection (some exceptions can be considered and this issue is detailed in the practical guide for prescribing biological published by SPR[15]);

- Concurrent administration of live vaccines;
- Recent history (<5 years) of malignancy (except in the case of basal cell cancer);
- Congestive heart failure (NYHA class III-IV);
- History of demyelinating disease.

Pregnancy and the use of biologicals

1. Biological therapy should not be started in pregnant or breastfeeding women.
2. If pregnancy occurs under treatment, biological therapy should be stopped.

This issue is detailed in the practical guide for prescribing biological published by SPR[15] and reviewed in a recently published systematic literature review[16].

Criteria for temporary suspension / postponement of introduction of biologicals

1. Active infection;
2. Recurrent infection or high risk for infections
3. Major surgery planned

This issue is detailed in the practical guide for prescribing biological published by SPR[15] and in a recent review[17].

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GUIA PRÁTICO DE UTILIZAÇÃO DE TERAPÊUTICAS BIOTECNOLÓGICAS NA ARTRITE REUMATÓIDE – ACTUALIZAÇÃO DE DEZEMBRO 2011

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Resumo

Os autores revêem os aspectos práticos de utilização de terapêuticas biológicas nos doentes com artrite reumatóide, emitindo pareceres sobre aspectos de segurança antes e depois do início da terapêutica e comentando as melhores opções estratégicas para optimizar a eficácia.

Palavras-chave: Guia Prático; Terapêuticas Biológicas; Segurança; Eficácia.

Abstract

The authors review the practical aspects of biological therapy use for rheumatoid arthritis patients, commenting safety issues before and after treatment initiation and the best treatment strategies to optimize efficacy.

Keywords: Practical Guide; Biological Therapy; Safety; Efficacy.

Introdução

A evolução do conhecimento da fisiopatologia da artrite reumatóide (AR) permitiu identificar protagonistas fundamentais nesta doença. Estes avanços possibilitaram conceber terapêuticas dirigidas contra alvos específicos nos mecanismos celulares e moleculares de controlo da resposta imunitária e inflamatória. Estas terapêuticas estão em clara fase de expansão. Em 1999 começámos a utilizar, na prática clínica, os primeiros antagonistas do factor de necrose tumoral (TNF) e pouco mais de dez anos depois temos disponíveis para utilização 5 inibidores desta molécula (infliximab, etanercept, adalimumab, certolizumab e golimumab), um antagonista da interleucina (IL)-1 (anakinra), um depletor dos linfócitos B (rituximab), um modulador da co-estimulação dos linfócitos T (abatacept) e um bloqueador do receptor da IL-6 (tocilizumab). Para além disso, estão em várias fases de desenvolvimento muitas outras moléculas que interferem com a sinalização intracelular das células imunitárias, modulam a função dos linfócitos B e inibem diversos receptores ou ligandos relevantes na resposta imunitária. A AR tem funcionado como o protótipo das doenças reumáticas inflamatórias, onde se têm ensaiado novas terapêuticas biotecnológicas eventualmente aplicáveis, mais tarde, noutras doenças, como o Lúpus Eritematoso Sistémico, a Artrite Psoriática, a Espondilite Anquilosante, a Doença de Still, a Artrite Idiopática Juvenil ou as Vasculites Sistémicas.

Tendo em conta a experiência acumulada nos últimos 10 anos no uso de terapêuticas biotecno-

*ambos os autores contribuiram de igual forma para a realização deste trabalho

lógicas na AR, o Grupo de Estudos de Artrite Reumatóide (GEAR) da Sociedade Portuguesa de Reumatologia elaborou em 2009 um guia prático de utilização destes fármacos centrado nas questões de segurança e de optimização da utilização dos vários fármacos então disponíveis[1]. Este trabalho resultou da análise crítica da prática clínica dos Serviços de Reumatologia Portugueses, dos resumos das características do medicamento dos fármacos biotecnológicos aprovados pela Agência Europeia de Medicamentos[2-10], das recomendações Portuguesas para o uso de Biológicos[11] e das recomendações práticas para o uso de antagonistas do TNF emitidas pela Sociedade Francesa de Reumatologia[12,13]. No dia 12 de Maio de 2011, o grupo reuniu-se tendo sido discutido as últimas evidências publicadas na literatura, com particular ênfase dada à discussão do último consenso internacional sobre o uso do rituximab na artrite reumatóide[14] e da última actualização do documento das recomendações práticas da utilização do tocilizumab da Sociedade Francesa de Reumatologia[15].

Segurança das Terapêuticas Biotecnológicas na Artrite Reumatóide

Aspectos Gerais

Os ensaios clínicos fornecem informação fundamental sobre a eficácia e segurança dos vários fármacos biotecnológicos. No entanto, excluem frequentemente situações clínicas comuns, pelo que, a monitorização contínua dos doentes na prática médica diária, com a recolha e análise dos dados de farmacovigilância, é um complemento imprescindível dessa informação. Só assim é possível identificar reacções adversas pouco frequentes ou particulares de determinado grupo populacional e avaliar adequadamente os seus benefícios e riscos a longo prazo. Não sendo desprovidos de efeitos secundários, os fármacos biotecnológicos apresentam uma favorável relação risco/benefício no tratamento da AR moderada a grave, quando utilizados dentro das indicações correctas e monitorizados de forma adequada[16]. O acompanhamento de doentes sob terapêutica biotecnológica pressupõe uma vigilância constante de complicações infecciosas, particularmente de tuberculose. As reacções alérgicas, incluindo reacções anafiláticas graves, podem ocorrer com todos os fármacos biotecnológicos e estão adicionalmente descritas reacções de auto imunidade. A vigilância a longo prazo da incidência de neoplasias em utilizadores de fármacos biotecnológicos deve ser mantida. A segurança a longo prazo dos retratamentos com rituximab, nomeadamente as implicações práticas da redução de imunoglobulinas, que pode ocorrer em alguns doentes, não está completamente esclarecida[17]. A resposta a vacinas administradas após o início destes fármacos poderá estar diminuída, particularmente no caso do rituximab[14].

Para que seja possível manter uma vigilância adequada sobre todos estes aspectos a monitorização dos doentes sob terapêutica biológica deverá ser registada na base de dados nacional Reuma.pt[18].

Procedimentos recomendados antes do início de terapêutica biotecnológica

Para aumentar a segurança de utilização do infliximab, etanercept, adalimumab, certolizumab, golimumab, abatacept, anakinra, rituximab e tocilizumab, constituem procedimentos de rotina, antes do início deste tipo de fármacos, um exame físico detalhado para identificação de focos infecciosos, sinais de insuficiência cardíaca, neoplasia ou de outras situações clínicas que contra-indiquem o uso destes fármacos; a realização de exames complementares que incluem, no mínimo, hemograma, marcadores de função renal e de função hepática, análise sumária da urina, parâmetros inflamatórios (velocidade de sedimentação e proteína C reactiva), serologias dos vírus VHB [Ag Hbs, anticorpo (ac) anti-Hbc, ac anti-Hbs], VHC (ac anti-VHC), VIH (ac anti-VIH1 e VIH2), radiografia do tórax e prova tuberculínica. Embora no caso do rituximab não seja teoricamente necessário efectuar a prova tuberculínica, este procedimento deve ser considerado em todos os doentes com AR que iniciam qualquer tipo de fármaco imunossupressor, porque estes indivíduos têm um risco acrescido de reactivação de tuberculose. Desta forma, sugere-se o cumprimento das recomendações da Sociedade Portuguesa de Reumatologia (SPR) e da Sociedade Portuguesa de Pneumologia (SPP) para prevenção de tuberculose em todos os doentes que iniciam este tipo de terapêuticas[19]. Alguns Centros de Reumatologia procedem à avaliação de anticorpos anti-nucleares (ANA) e, se justificado, anti-dsDNA. Para além disso, é defensável efectuar mais alguns procedimentos de segurança antes do início destes fármacos, que deverão assegurar que o doente tem as peças dentárias adequadamente tratadas,

não tem sinusite activa e não tem infecções urinárias ou respiratórias de repetição (o que poderá implicar em casos seleccionados avaliação imagiológica adicional e consulta especializada).

Vacinas

Todos os doentes candidatos a terapêutica biológica devem ter o plano nacional de vacinação actualizado.

A vacina anti-pneumocócica e a vacina da gripe também deverão ser consideradas antes do início destes fármacos[20]. A vacina da gripe deverá ser actualizada anualmente. Sugere-se ainda a realização da vacina anti-pneumocócica de 5 em 5 anos. As vacinas vivas (BCG, febre amarela, varicela, sarampo-parotidite epidémica-rubéola) estão contra-indicadas durante a terapêutica com agentes biotecnológicos.

Perante a necessidade de administrar a vacina da febre amarela, deve-se suspender o fármaco biotecnológico 5 semividas antes e reiniciar 3 semanas após a vacinação[12].

Aspectos específicos da administração de Rituximab

No caso específico do rituximab, antes do início da terapêutica, deverá proceder-se ao doseamento de imunoglobulinas e, para além da actualização do plano nacional de vacinação, ponderar realizar também a vacina anti-Haemophilus (pelo menos um mês antes do início da terapêutica). A quantificação das populações linfocitárias de linfócitos B não revelou ter utilidade clínica. Antes de todas as administrações deste fármaco deve ser feita pré-medicação endovenosa com 100 mg de metilprednisolona. Embora constitua prática corrente, não existe evidência na literatura que sustente a administração sistemática de anti-histamínico (2 mg de clemastina) e paracetamol oral (500 a 1000 mg), No seguimento dos doentes tratados com rituximab deverá ser repetido o doseamento de imunoglobulinas antes dos retratamentos, dado o risco elevado de infecções graves nos doentes com hipogamaglobulinémia (particularmente níveis baixos de IgG). Não existem recomendações que indiquem o intervalo de tempo em que o doseamento de imunoglobulinas deve ser repetido, nem o valor abaixo do qual não deve ser administrado rituximab[14]. O rituximab está aprovado em combinação com o metotrexato. Contudo, nos doentes que não tolerem a terapêutica com metotrexato, pode ser usada com segurança a leflunomida[14].

Aspectos específicos da administração de Tocilizumab

No caso específico do tocilizumab, salienta-se adicionalmente que o fármaco não deverá ser iniciado em doentes com contagens de neutrófilos inferiores a 0,5 x 10^9/l, plaquetas inferiores a 50 x 10^3/µl ou transaminases superiores a 5 x o limite superior do normal (LSN) e deve ser iniciado com precaução em doentes com contagens de neutrófilos inferiores a 2 x 10^9/l, plaquetas inferiores a 100 x 10^3/µl ou transaminases superiores a 1,5 x o LSN. Estes parâmetros laboratoriais devem ser vigiados de acordo com a prática clínica de cada centro, que poderá implicar avaliação mensal, nos primeiros 3 meses de utilização do fármaco, ou trimestral. Se antes da infusão o valor de neutrófilos for inferior a 0,5 x 10^9/l ou o de plaquetas inferiores a 50 x 10^3/µl ou as transaminases forem superiores a 5 x LSN o fármaco deve ser descontinuado. Se antes da infusão o valor de neutrófilos for de 0,5 a 1 x 10^9/l ou o de plaquetas de 50 a 100 x 10^3/µl ou as transaminases forem 3 a 5 x LSN o fármaco deve ser suspenso e reiniciado na dose de 4mg/Kg após os neutrófilos serem superiores a 1 x 10^9/l ou as plaquetas superiores a 100 x 10^3/µl ou as transaminases inferiores a 3 x LSN (eventualmente aumentado para 8mg/Kg de acordo com a eficácia e toxicidade, não sendo aconselhadas doses superiores a 800 mg). Se os aumentos das transaminases se situarem entre 1,5 a 3 x LSN a dose do metotrexato deve ser reduzida. Se o aumento persistir deverá ser reduzida a dose de tocilizumab para 4mg/Kg ou interromper até normalização das transaminases. A interferência do tocilizumab com a proteína C reactiva e com os neutrófilos (eliminando a febre durante os episódios infecciosos) pode dificultar a detecção de uma infecção, pelo que todos os sintomas e sinais sugestivos de infecção devem ser valorizados. O tocilizumab altera o perfil lipídico, pelo que é recomendável a sua vigilância e caso justificado deve ser feita intervenção terapêutica apropriada, dando preferência a estatinas que não sejam metabolizadas pela via CYP 450 (p.e. fluvastatina, pravastatina e rosuvastatina)[8,15].

Reacção de Hipersensibilidade

Em caso de reacção alérgica a qualquer dos fármacos biotecnológicos, sugere-se a sua interrupção, administração de anti-histamínicos e/ou corticóides[1,21]. Embora se possa continuar a administração destes fármacos, quando as reacções alérgicas não são graves, efectuando terapêutica preventiva com

anti-histamínicos e corticóides, a disponibilidade de outras opções terapêuticas sugere que a atitude mais prudente seja a interrupção definitiva após a reacção alérgica e a mudança para outro fármaco.

Cirurgias

Os doentes tratados cronicamente com fármacos biotecnológicos que necessitem de efectuar cirurgias programadas deverão interromper previamente a terapêutica em curso com uma antecedência mínima que depende da semi-vida do fármaco: 2 semanas para o etanercept e certolizumab, 4 semanas para o infliximab e adalimumab, 8 semanas para o abatacept e 24 semanas para o rituximab. Embora exista menos experiência com o tocilizumab, recomenda-se como intervalo de tempo mínimo entre a última perfusão e uma cirurgia pelo menos 4 semanas. A experiência sobre a segurança do tratamento com golimumab em doentes que tenham sido submetidos a procedimentos cirúrgicos é limitada. Se estiver planeada uma intervenção cirúrgica, deve ser considerada a longa semi-vida do medicamento (12 ± 3 dias)[2,3,5-10].

Para todos estes fármacos, no caso de cirurgias de urgência deverá ser assumido um maior risco infeccioso e nos tratamentos dentários invasivos deverá ser realizada profilaxia antibiótica[12].

Infecções

Após a ocorrência de uma infecção grave, o fármaco biotecnológico não deve ser iniciado enquanto não existir resolução completa da infecção. Na ausência de sinais infecciosos, o tratamento pode recomeçar, sob vigilância, cerca de 8 dias após a paragem do tratamento anti-infeccioso. Se houver reaparecimento da sintomatologia infecciosa, considerar a suspensão definitiva do tratamento[12]. No caso específico do tocilizumab salienta-se que este suprime a elevação da PCR.

Gravidez e aleitamento

Não existe evidência de que qualquer das terapêuticas biotecnológicas em curso seja teratogénica. No entanto, os Resumos das Características do Medicamento (RCM) destes fármacos recomendam intervalos de segurança entre a última administração e a concepção: abatacept 14 semanas, adalimumab e certolizumab 20 semanas, infliximab e tocilizumab 24 semanas (6 meses) e rituximab 12 meses (não há referência a este aspecto no RCM do etanercept e não existe informação disponível sobre a utilização de golimumab e anakinra em mulheres grávidas)[2-10,12]. Na prática clínica, baseando-nos na experiência prévia de registos de doentes, estes intervalos podem ser encurtados: etanercept e infliximab 8 semanas, adalimumab e tocilizumab 12 semanas, rituximab 24 semanas. Estes fármacos devem ainda ser evitados nas mulheres que estejam a amamentar[15,22,23].

É necessária uma contracepção eficaz durante o tratamento com fármacos biotecnológicos. Não há necessidade de interrupção deste tipo de terapêutica nos homens que desejam ser pais.

Optimização da utilização das várias opções terapêuticas de Biotecnologia na Artrite Reumatóide

A disponibilidade de várias opções terapêuticas e a hipótese de inclusão de doentes em ensaios clínicos de novos fármacos potencialmente úteis para os doentes refractários cria uma responsabilidade acrescida sobre a necessidade de atingirmos remissão ou a mínima actividade de doença possível para cada doente, caso esse objectivo não seja alcançável. Como primeira linha terapêutica, estão disponíveis, neste momento, 5 antagonistas do TNF, o abatacept e o tocilizumab[24]. A evidência disponível neste momento sugere que os doentes que não têm resposta a um antagonista do TNF podem ser tratados com outro antagonista do TNF ou com um fármaco com um mecanismo de acção diferente, nomeadamente abatacept, rituximab ou tocilizumab[25-30]. No entanto, após a falência de um segundo antagonista do TNF, a probabilidade de resposta a um terceiro fármaco desta classe é mínima[31]. A decisão de escolha entre o abatacept, rituximab ou tocilizumab após a utilização de um antagonista do TNF não é clara. No caso específico do rituximab verificou-se que a eficácia clínica é superior nos doentes com factores reumatóides e/ou anticorpos anti-péptido citrulinado detectáveis no soro[32].

Embora não existam regras precisas para definir com segurança os tempos mínimos para a mudança entre fármacos biotecnológicos, sugere-se que o tempo mínimo para introdução de um novo fármaco biotecnológico após utilização do etanercept seja de 3 semanas, após abatacept, adalimumab, certolizumab, golimumab e infliximab de 8 semanas, após rituximab para um antagonista do TNF de 16 semanas e após rituximab para outros fármacos biotecnológicos de 24 semanas. Os retratamentos com rituximab devem ser realizados logo que ocorra reactivação da doença e não devem ser

feitos com intervalos inferiores a 24 semanas. Deve ser considerado o retratamento semestral com o objectivo de manter uma baixa actividade da doença (DAS28 < 3,2). O tempo mínimo de paragem do tocilizumab antes de iniciar outro fármaco não é neste momento claro[2-10]. Contudo, segundo um documento de consenso da Sociedade Francesa de Reumatologia, o início do anti-TNF pode ser efectuado 4 semanas após a última perfusão de tocilizumab[12].

O uso do anakinra como segunda opção terapêutica tem efeitos muito limitados e só deve ser considerado em doentes que falhem todas as opções terapêuticas. É, no entanto, a primeira opção terapêutica para a Doença de Still refractária à terapêutica convencional[33,34].

Monoterapia e/ou associação com Metotrexato

Fármacos biotecnológicos aprovados como 1ª linha terapêutica

Os agentes biotecnológicos aprovados como 1ª linha em combinação com o metotrexato são: anakinra, golimumab, infliximab e abatacept. Os agentes aprovados como 1ª linha em monoterapia ou em associação com o metotrexato são: adalimumab, etanercept, certolizumab e tocilizumab[35].

Doentes refractários aos antagonistas do TNF

Nos doentes refractários aos agentes anti-TNF, o abatacept e o rituximab estão aprovados em combinação com o metotrexato. O tocilizumab pode ser administrado isoladamente ou em combinação com o metotrexato, de acordo com decisão do médico[35].

Recomendações Práticas

1. Procedimentos de segurança prévios ao primeiro tratamento com qualquer fármaco biotecnológico:
   a. Cumprimento das recomendações SPR/SPP para prevenção de tuberculose;
   b. Serologias VIH, VHC, VHB;
   c. ANA;
   d. Avaliação da existência de infecções activas e/ou recorrentes nomeadamente das peças dentárias, vias urinárias, vias respiratórias e seios perinasais;
   e. Actualização do Plano Nacional de Vacinação e considerar vacinação anti-pneumocócica e anti-gripal.
2. Procedimentos de segurança adicionais específicos do tratamento com rituximab:
   a. Doseamento das imunoglobulinas.
3. Cuidados de segurança adicionais específicos do primeiro tratamento com tocilizumab:
   a. Não deverá ser iniciado em doentes com contagens de neutrófilos inferiores a 0,5 x 10^9/l, plaquetas inferiores a 50 x 10^3/µl ou transaminases superiores a 5 x o limite superior do normal (LSN) e deve ser iniciado com precaução em doentes com contagens de neutrófilos inferiores a 2 x 10^9/l, plaquetas inferiores a 100 x 10^3/µl ou transaminases superiores a 1,5 x o LSN.
4. Procedimentos de segurança durante o tratamento com qualquer fármaco biotecnológico:
   a. Em caso de reacção alérgica prescrever anti-histamínico e corticóides e suspender a terapêutica, ponderando a mudança para outro fármaco biotecnológico.
   b. Suspender terapêutica antes de cirurgias programadas: etanercept e certolizumab 2 semanas; infliximab, adalimumab e tocilizumab 4 semanas; abatacept 8 semanas, rituximab 24 semanas.
   c. Suspender terapêutica antes de gravidez programada: etanercept e infliximab 8 semanas; adalimumab e tocilizumab 12 semanas; abatacept 14 semanas; certolizumab 20 semanas; rituximab 24 semanas.
   d. Antes de retratar com rituximab cumprir tempo mínimo de 24 semanas sobre tratamento anterior e dosear imunoglobulinas.
   e. Os doentes medicados com infliximab, que suspenderem a terapêutica por um período igual ou superior a 12 semanas, deverão fazer pré-medicação com 100 mg de hidrocortisona EV, nas 3 primeiras administrações após a reintrodução do infliximab.
5. Procedimentos nos doentes com ausência de resposta ao fármaco biotecnológico em curso (ao fim de 3 a 6 meses de administração):
   a. Verificar se a dose de metotrexato está optimizada; confirmar a compliance do doente à terapêutica.
   b. Se se mantiver a ausência de resposta no caso do infliximab poderá ser aumentada a frequência para 6 em 6 semanas e/ou aumentar a dose para 5mg/Kg;
   c. No caso de não resposta apesar destas medidas propor a mudança para outro fármaco antagonista do TNF ou abatacept, rituximab ou tocilizumab.
   d. No caso de paragem de um antagonista do

TNF por efeito adverso poderá ser proposta a mudança para outro antagonista do TNF ou para outro agente biológico com um mecanismo de acção diferente.

e. Tempo de suspensão de uma terapêutica antes da mudança para um segundo fármaco biotecnológico: etanercept 3 semanas; abatacept, adalimumab, certolizumab, golimumab e infliximab 8 semanas; rituximab 16 semanas para anti-TNF e 24 semanas para outros fármacos biotecnológicos; tocilizumab: 4 semanas para anti-TNF, embora o tempo mínimo de paragem do tocilizumab antes de iniciar terapêutica com outro grupo de fármacos biológicos (que não os anti-TNF) não seja neste momento claro.

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4. Resumo das características do medicamento Kineret, anakinra.
5. Resumo das características do medicamento Enbrel, etanercept.
6. Resumo das características do medicamento Remicade, infliximab.
7. Resumo das características do medicamento Mabtera, rituximab.
8. Resumo das características do medicamento Roactemra tocilizumab.
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REGRESSÃO ESPONTÂNEA DE HÉRNIA DISCAL LOMBAR SINTOMÁTICA

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Resumo

A patologia discal herniária é muito frequente, levando por vezes à incapacidade dos doentes, e em razoável número de casos à cirurgia. Este trabalho reporta um caso clínico de um doente com uma hérnia discal sintomática de grandes dimensões, que sofreu reabsorção espontânea, não sendo necessário recorrer a tratamento cirúrgico. O caso é documentado com base em RM da coluna lombar seriadas, concordantes com a melhoria clínica do doente.

Palavras-Chave: Coluna Vertebral; Hérnia Discal; Regressão Espontânea.

Abstract

Lumbar disc herniation is very common, sometimes leading to disability of the patient, and in a significant number of cases can only be solved with surgery. This paper reports a case with a large symptomatic disc herniation, which suffered spontaneous regression, and no surgery was necessary. The case is documented on serial MRI, consistent with the clinical improvement of the patient.

Keywords: Spine; Disc Herniation; Spontaneous Regression.

Introdução

A hérnia discal lombar, mais frequente em L4-L5 e L5-S1, consiste na herniação do núcleo pulposo para o canal vertebral, podendo comprimir uma ou mais raízes nervosas provocando dor com irradiação ao membro inferior e alterações sensitivo/motoras. Esta sintomatologia surge, quer pela compressão directa, quer pela irritação química provocada pela substância de degradação do núcleo pulposo sobre as raízes nervosas[1].

Apesar do tratamento cirúrgico na abordagem desta patologia ser prática comum há mais de 60 anos, ainda hoje permanecem algumas dúvidas acerca do melhor tratamento do doente com patologia discal lombar. O tratamento conservador apresenta-se como alternativa à cirurgia, com remissão completa ou parcial da sintomatologia dolorosa e neurológica em alguns doentes, inclusive com redução do tamanho da hérnia[2].

Em 1985, Teplick e Haskin publicaram pela primeira vez um caso clínico confirmado por imagem (TAC) de regressão espontânea de hérnia discal. Desde essa altura vários casos dispersos têm sido descritos[3].

Os autores apresentam um caso acompanhado durante 3 meses e controlado por RM, com resolução espontânea.

Caso Clínico

Homem de 34 anos, sem antecedentes patológicos relevantes, inicia quadro de instalação súbita de lombociatalgia direita severa, em pontada, com irradiação até ao pé, associado a parestesias no território de S1, "com sensação de choque eléctrico". O quadro clínico surgiu na sequência de esforço físico intenso durante a actividade profissional (ao levantar um objecto pesado), mantendo-se por cerca de 4 meses. A dor estava presente em repouso, agravando com esforços e com o ortostatismo. Durante esse período o doente manteve-se sempre apirético, com bom estado geral e sem queixas relativas a outros aparelhos e sistemas, tendo sido orientado para consulta de Ortopedia. No exame

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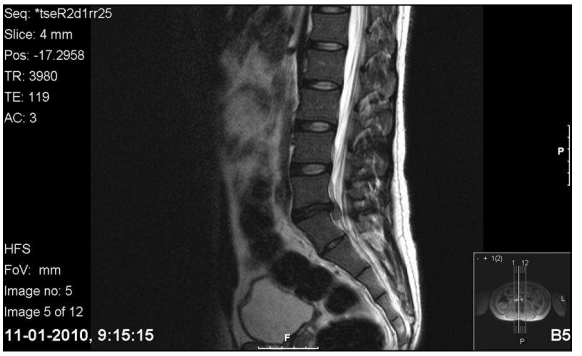

Figura 1. RM inicial (corte sagital) evidenciando volumosa hérnia discal L5-S1

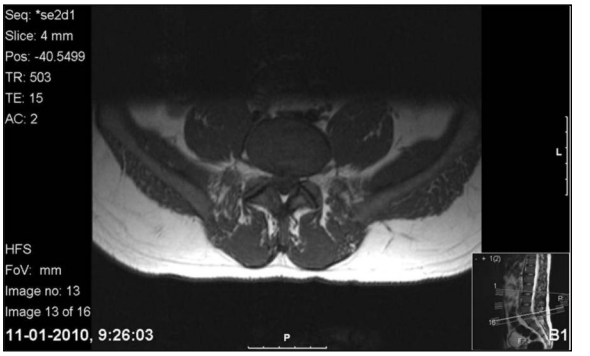

Figura 2. RM inicial (corte transversal), onde é visível compressão da raiz S1 direita.

neurológico inicial apresentava, a nível do membro inferior direito, sinal de Lasègue positivo, hipostesia táctil do território de S1 e diminuição da força muscular de flexão plantar do hallux (grau IV/V) com dificuldade em caminhar «em pontas» associada. Sem alterações dos reflexos rotulianos e aquilianos bilateralmente.

Suspeitando de se tratar de uma hérnia discal traumática a nível lombar, solicitou-se RM da coluna lombar, que revelou diminuição da altura com desidratação do disco intervertebral, hérnia posterior extrusada centro-lateral direita, migrada caudalmente a ocupar o recesso lateral, causando compressão da raiz S1 direita (Figuras 1 e 2).

Confirmada a suspeita clínica, prescindiu-se da electromiografia tendo-se iniciado de imediato tratamento conservador com analgesia, relaxante muscular e uso de cinta com apoio lombar, com remissão gradual do quadro clínico. Ao fim de 3 meses o doente encontrava-se assintomático, altura em que efectuou nova RM onde era evidente regressão quase completa da hérnia discal migrada (Figuras 3 e 4). Um ano depois, o doente encontra-se sem dor ou défices musculares, apenas com ligeira parestesia ao nível do bordo lateral do pé direito, em franca regressão.

Discussão

As hérnias discais lombares afectam 2% da população. Destes, menos de 10% apresentam sintomatologia após 3 meses que justifiquem intervenção cirúrgica. Em alguns destes casos, a ruptura abrupta do anel fibroso ocorre com extrusão de material do núcleo pulposo, com formação de um sequestro volumoso e clinicamente sintomático[1]. No entanto, mesmo nestes casos, a sua regressão espontânea encontra-se descrita na literatura, tendo mesmo vindo a aumentar o número de casos descritos com o aumento disseminado do uso da RM, embora apenas em casos isolados e sem explicação definitiva do mecanismo[4-6]. Três teorias

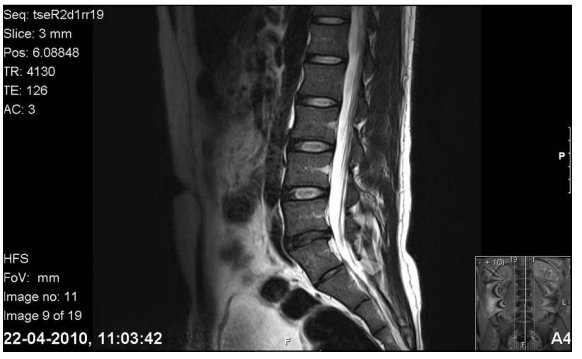

Figura 3. RM de controlo, passados 3 meses de tratamento conservador, mostrando regressão quase completa da hérnia discal

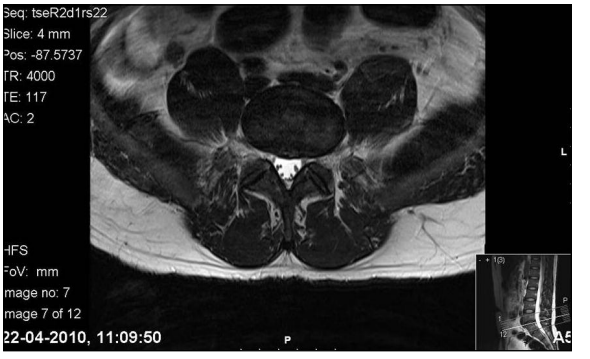

Figura 4. RM de controlo (corte transversal), em T2, evidenciando recesso lateral direito livre de hérnia

foram apresentadas tentando explicar este fenómeno. A 1ª envolve a reabsorção de tecidos, na qual vários investigadores defendem que esta acontece por degradação enzimática e fagocitose, durante a reacção inflamatória e da neo-vascularização. A 2ª teoria defende que o fragmento desaparece por progressiva desidratação, degeneração e encolhimento do mesmo, sendo esta teoria suportada pela evidência da diminuição de sinal em RM seriadas. A 3ª teoria refere ser simplesmente uma variação da tensão do ligamento longitudinal posterior como responsável[4-6].

As extrusões maciças de material do núcleo pulposo podem ser gravemente sintomáticas. Numa primeira abordagem deve ser privilegiado o tratamento conservador nos casos em que não se verifiquem alterações neurológicas agudas. Desses, segundo The Weber Study, cerca de 25% acaba por ser operado ao fim de 1 ano, devido à não remissão dos sintomas ou progressão dos mesmos[7,8]. Um outro estudo publicado refere que, dos pacientes tratados inicialmente de forma conservadora, 15% acabam por ser operados ao fim de 3 meses[7,9]. Saal e Saal demonstraram que o tratamento conservador nos casos de radiculopatia secundária a hérnia discal é eficaz e apresenta resultados bons a excelentes em 90% dos casos[7,10]. Com o tratamento conservador, estima-se que poderá haver regressão espontânea superior a 50% da massa de disco herniado entre o 3º e o 12º mês[11].

Assim sendo, os cirurgiões de coluna devem considerar sempre a possibilidade de regressão da hérnia discal em episódios agudos, antes de optarem pela cirurgia, nos casos que não preenchem critérios de emergência cirúrgica [4-6].

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UM CASO DE ACROPARESTESIAS, ASTENIA E FEBRE. UMA NOVA MUTAÇÃO EM DOENÇA DE FABRY

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Resumo

A doença de Fabry é uma doença metabólica hereditária ligada ao cromossoma X, devida à deficiência em alfa-galactosidase A lisossómica, com acumulação de glicosfingolípidos, principalmente globotriaosilceramida (GL-3), a nível celular. O envolvimento multiorgânico ocorre progressivamente, conduzindo a graves manifestações e à morte precoce.

Apresentamos o caso de um homem de 20 anos, enviado à consulta de Reumatologia por um quadro de sintomas inespecíficos com a duração de anos, que consistiam em parestesias e dores mal localizadas nas mãos, bem como crises de febre elevada e fraqueza muscular generalizada, autolimitadas. Apesar de negar a existência de alterações cutâneas, à observação tinha um *rash* centrípeto de pápulas punctiformes eritematosas, diagnosticado como angioqueratomas, e o doseamento sérico da enzima alfa-galactosidase A confirmou a suspeita de doença de Fabry. A avaliação posterior revelou a presença de córnea verticilata e sequelas de enfartes lacunares cerebrais.

Os autores pretendem salientar a importância do exame objectivo nestes casos de doentes com sintomas inespecíficos arrastados, sem diagnóstico estabelecido, com repercussão no seu estado funcional, e para a importância da colaboração entre médicos de várias especialidades nestes casos. Salientamos também que a mutação em causa não estava ainda descrita.

Palavras-chave: Doença de Fabry; Acroparestesias; Alfa-galactosidase A.

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Abstract

Fabry's disease is an X-linked hereditary metabolic storage disorder, due to the deficiency in lysosomal alpha-galactosidase A, with the consequent glycosphingolipids accumulation, primarily globotriaosylceramide, at cellular level. Multiorganic involvement occurs progressively, leading to severe manifestations and even premature mortality.

We describe a case of a 20 year-old man who was sent to Rheumatology because of inespecific symptoms that lasted for years, namely acroparesthesias and diffuse hand pain and autolimited flares of high fever and general muscular weakness. Despite denying cutaneous findings, a remarkable purplish-red rash of slightly raised angiectases in the lower trunk was present. This rash was diagnosed as angiokeratomas, and blood measurement of alpha-galactosidase A confirmed the suspicion of Fabry's disease. He was referred to a "rare disease" consultation, where the evaluation revealed the presence of other characteristic findings, such as cornea verticilata and cerebral lacunar infarction sequelae.

The authors want to remark the importance of physical examination in these cases of inespecific long-lasting symptoms, with no diagnosis and with functional impairment, and the importance of multidisciplinary evaluation and collaboration. We also highlight that this mutation was not as yet described.

Keywords: Fabry's disease; Acroparesthesias; Alpha-galactosidase A

Introdução

Descrita em 1898 por dois Dermatologistas, o alemão Johann Fabry e o inglês William Anderson, a doença de Fabry é uma doença metabólica hereditária devida a uma mutação no gene da alfa galac-

tosidase localizada no braço longo do cromossoma X. Estão descritas mais de 400 mutações. A mutação leva à deficiência em alfa-galactosidase A lisossómica, com a consequente acumulação de glicosfingolípidos, principalmente globotriaosilceramida (GL-3), a nível celular, nomeadamente no epitélio, glomérulos e túbulos renais, miocárdio, fibrócitos valvulares, neurónios dos gânglios da raiz dorsal e do sistema nervoso autonómico, endotélio e músculo liso. O envolvimento multiorgânico ocorre progressivamente, conduzindo a graves manifestações e à morte precoce. Os homens manifestam precocemente a doença. As mulheres, que, face a uma doença hereditária ligada ao cromossoma X eram classificadas como portadoras, têm (apesar do espectro variável e manifestações mais tardias) um percurso da doença que pode assumir a mesma gravidade que nos homens[1]. Na criança e no adulto jovem, as queixas são muito inespecíficas, pelo que raramente o diagnóstico é feito nesta fase, se não houver antecedentes familiares conhecidos. São comuns, numa fase inicial, as parestesias crónicas, episódios de dor (chamadas crises de Fabry), a intolerância ao calor por anidrose e os episódios recorrentes de febre e o aparecimento de angioqueratomas. Na ausência de tratamento, a esperança de vida é geralmente reduzida em 20 anos nos homens e 15 anos nas mulheres. Muitos doentes têm diagnósticos incorrectos, resultantes do recurso a múltiplas consultas de diferentes especialidades[2]. Estima-se que o tempo médio decorrido entre o início dos sintomas e o estabelecimento do diagnóstico seja de cerca de 12 anos. A idade média do aparecimento das complicações e da morte são mais tardias nas mulheres do que nos homens. As mulheres podem manifestar todos os sintomas clássicos, mas a doença pode ser diagnosticada em mulheres com atingimento isolado de órgão. O diagnóstico deve ser baseado na análise de DNA, em vez da actividade enzimática, em mulheres com uma história familiar positiva ou com sintomas sugestivos da doença. O tratamento consiste na substituição enzimática prolongada através da administração endovenosa periódica de uma forma recombinante humana da alfa-galactosidase A.

Caso Clínico

Descreve-se o caso de um homem de 20 anos, de raça branca, solteiro, operador de *call center*, observado na consulta de Reumatologia em Maio de 2010 por dores de ritmo mecânico, mal definidas, nas mãos e joelhos, iniciadas alguns anos antes, acompanhadas de parestesias nas mãos. Referia ainda episódios autolimitados de febre elevada (até 40°C), durante os quais tinha astenia intensa, com necessidade de ser transportado ao colo para se deslocar em curtos espaços, e absentismo laboral associado. Neste contexto, tinha sido diagnosticada febre reumática dois anos antes, e estava medicado com injecções mensais de penicilina. Negava episódios de tumefacção articular e também alterações cutâneas. Perante este diagnóstico e os sintomas discordantes, a nova médica de família enviou-o à consulta de Reumatologia. Tinha sido medicado com tramadol e deflazacort, sem melhoria. Referia sintomas depressivos com alguma gravidade, decorrentes do facto de não ter um diagnóstico nem tratamento satisfatório para os seus sintomas. Na consulta, o exame objectivo articular era normal, não tendo sido detectadas tumefacções nem deformações, e a mobilidade axial e periférica eram normais. A auscultação era normal, não sendo audíveis sopros cardíacos. Tinha edemas ligeiros e indolores dos tornozelos e um *rash* eritematoso punctiforme, que atingia o tronco e membros, predominando no abdómen e região pélvica (Figura 1). Tinha ainda *naevus* irregulares no dorso. Foi por esse motivo enviado à consulta de Dermatologia, onde a hipótese de diagnóstico considerada mais provável foi a de angioqueratomas, o que a biópsia de pele confirmou. As análises laboratoriais não revelaram alterações, nomeadamente da função renal nem

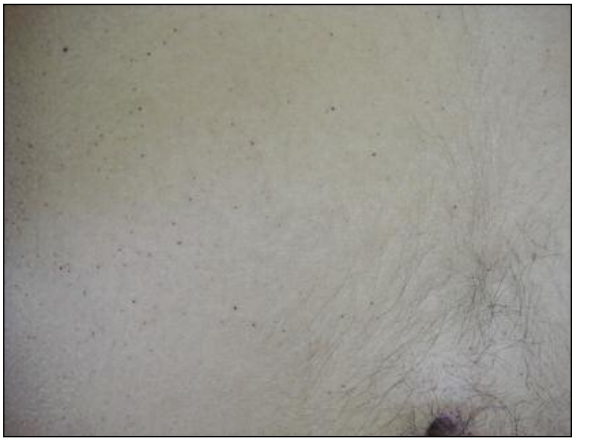

Figura 1. Figura 1. Angioqueratomas, com maior densidade peri-umbilical

proteinúria anormal, nem a presença de anticorpos anti-nucleares nem anti-CCP. O ecocardiograma revelou uma ligeira insuficiência tricúspide, pulmonar e mitral, com uma pressão sistólica na artéria pulmonar (PSAP) estimada em 32 mmHg, sem outras alterações. Assim, o diagnóstico apontado foi o de doença de Fabry. O doseamento sérico da enzima alfa-galactosidase A num centro de genética médica mostrou a quase inexistência da enzima, e o doseamento urinário de GL-3 confirmou o diagnóstico. Foi então enviado a uma consulta de doenças raras, onde todo o estudo complementar de avaliação inicial foi efectuado, permitindo diagnosticar algumas das manifestações e consequências da doença: córnea verticilata e sequelas de pequenos acidentes vasculares cerebrais lacunares. O estudo de regiões do gene GLA permitiu detectar a presença, em hemizigotia, da mutação c.154T>G (p.C52G). Esta mutação não está ainda descrita na literatura nem nas principais bases de dados genéticos. A mesma mutação foi encontrada na mãe deste doente. Aguarda autorização para o início da terapêutica de substituição enzimática.

Discussão

A prevalência da doença de Fabry é classicamente estimada em 1 em 117.000 nados vivos, sendo 1 em cerca de 50.000 do sexo masculino, o que a torna uma doença rara[3]. Contudo, a realidade poderá ser muito diferente, como o demonstra um estudo de rastreio em recém-nascidos realizados em Itália, onde mutações genéticas desta doença foram detectadas em 1 em 3.100 recém-nascidos do sexo masculino[4]. Representa a segunda mais frequente doença lisossómica de armazenamento nos humanos, estando porém sub-diagnosticada. Em Portugal são conhecidos actualmente cerca de 60 a 70 casos, embora a única publicação encontrada sobre prevalência da doença aponte para 4 casos diagnosticados entre 1982 e 2001, no Porto, entre 353 doenças de armazenamento lisossómico diagnosticadas neste período[5]. Os angioqueratomas surgem geralmente durante a adolescência e são o sinal mais visível da doença, já que o diagnóstico pode ser indiciado quando é detectada a característica erupção cutânea papular punctiforme, de cor avermelhada ou violácea, mais evidente na porção inferior do tronco e nos membros inferiores. As parestesias dolorosas ocorrem devido à lesão dos nervos periféricos. Entre a terceira e a quarta décadas de vida, surgem os sintomas relacionados com o comprometimento sistémico progressivo, que conduzem à morte por enfarte agudo do miocárdio, acidente vascular cerebral ou falência renal. O rastreio de homens em clínicas de hemodiálise, acidentes vasculares cardíacos e cerebrais detectou a doença, que não estava diagnosticada, em 0,25% a 1% dos em hemodiálise[6-11], 3 a 4% dos com hipertrofia ventricular esquerda ou miocardiopatia hipertrófica[12,13] e em 5% daqueles com AVC criptogénicos[14].

A insuficiência renal crónica é uma manifestação proeminente da doença de Fabry, e a causa principal de morte prematura no fenotipo clássico. As manifestações iniciais incluem diminuição do filtrado glomerular, proteinúria[15] e tubulopatia, por acumulação de GL-3, sobretudo nos homens.

As primeiras alterações cardíacas são o encurtamento do intervalo PR, bradicardia em repouso, insuficiência valvular ligeira e disfunção diastólica. Há diminuição da variabilidade RR e as arritmias com alterações da condução[16] levam com frequência à necessidade de implantação de marcapasso. Os doentes devem ser monitorizados com electrocardiograma e ecocardiograma.

Os primeiros sintomas neurológicos são as acroparestesias episódicas, com início precoce, relacionadas com o atingimento de pequenas fibras do sistema nervoso periférico, e devem ser diferenciadas de outras causas de dor neuropática periférica em indivíduos jovens[17]. Crises esporádicas de dor ou episódios graves de dor neuropática fulminante podem durar desde minutos a várias semanas e ser acompanhados de fadiga, febre e artralgias. Estas crises podem ser despoletadas por actividade física, exposição a frio ou calor, febre ou stresse. Também são manifestações precoces a hipo ou anidrose e a baixa tolerância ao exercício, também reportadas em mulheres[18]. O peso das complicações no sistema nervoso central (SNC) aumenta com a idade e todos os doentes com mais de 54 anos já tiveram atingimento cerebrovascular. O acidente vascular cerebral (AVC) é 20 vezes mais frequente nestes doentes do que na população geral. Ocorre em idades precoces, sendo uma causa significativa de AVC criptogénico, e passa muitas vezes despercebido[19]. Um estudo prospectivo português obteve uma prevalência estimada de 2,4% mutações relacionadas com a doença de Fabry em indivíduos até 55 anos com o primeiro AVC[20]. A demência pode ocorrer como conse-

quência da leucomalácea difusa, AVC múltiplos ou por deposição de lípidos nos neurónios do hipocampo e lobo frontal. A investigação deve incluir a ressonância magnética (RM) do SNC, ou mesmo angio-ressonância[18]. A RM revela, geralmente, lesões localizadas na substância branca[21].

As manifestações gasterenterológicas podem incluir a dor abdominal post-prandial com aumento do peristaltismo e diarreia, náuseas e vómitos e saciedade precoce, geralmente com início na adolescência ou até antes dos 10 anos, cursando com deficiente progressão estatoponderal. É muitas vezes necessário fazer o diagnóstico diferencial com a síndrome do cólon irritável, pela inespecificidade dos sintomas.

As manifestações dermatológicas incluem as lesões vasculares cutâneas (angioqueratomas) e a anidrose ou hipohidrose. Os angioqueratomas são causados por enfraquecimento da parede capilar e ectasia vascular na epiderme e na derme, são um dos primeiros sinais clínicos, ocorrem em ambos os sexos e geralmente surgem entre os 5 e os 13 anos. Inicialmente são angiectasias pequenas, minimamente papulares, eritemato-purpúricas e não desaparecem com a pressão, aumentando em número e tamanho com a idade. Atingem sobretudo as coxas, o dorso, as nádegas, pénis e escroto, bem como a mucosa oral e a conjuntiva. As lesões genitais são mais susceptíveis às tromboses e hemorragias. O resultado do tratamento com várias técnicas de laser não foi encorajador e não evitou o aparecimento de novas lesões[18], mas um relato português refere muito bom resultado numa mulher com luz intensa pulsada[22].

As manifestações na córnea estão reportadas em mais de 90% dos doentes, sendo mais conhecido o padrão de estrias espirais pálidas no epitélio corneano – córnea verticilata. Esta lesão raramente ou mesmo nunca é causa de sintomas visuais, embora possa haver uma história de dificuldade na visão em condições de ofuscamento. As lesões conjuntivais vasculares mais frequentes são os aneurismas saculares, que geralmente não causam desconforto nem são causa de hemorragia.

Como já foi referido, as artralgias ou periartralgias de ritmo inespecífico podem fazer parte do quadro inicial de sintomas desta doença, por vezes acompanhadas de febre e calafrios, mas sem tumefacção articular nem eritema[23].

No caso deste doente, com 20 anos quando foi observado pela primeira vez na consulta de Reumatologia e de Dermatologia, os sintomas tinham tido início alguns anos antes, sendo bastante inespecíficos, apesar de episodicamente incapacitantes, por crises de acroparestesias, febre e astenia intensas, responsáveis por sintomas depressivos e absentismo laboral. Quando interrogado na primeira consulta, com a hipótese de doença de Still, sobre a existência de alterações cutâneas, nomeadamente durante as crises de febre, negou. Dado que a suspeita do diagnóstico surgiu na consulta de Dermatologia após a observação dos angioqueratomas, pelos quais aí tinha sido enviado, salienta-se a importância do exame objectivo cuidadoso e detalhado, particularmente nestes doentes com sintomas arrastados e inespecíficos e sem diagnóstico. As doenças de armazenamento lisossómico, pela idade do início dos sintomas, podem conduzir não raras vezes ao diagnóstico de febre reumática ou de artrite idiopática juvenil[24], atrasando o diagnóstico correcto e levando ao início de medicação não isenta de efeitos adversos e sem eficácia nesta doença[23], como tinha sido o caso deste doente. A presença ocasional de factor reumatóide pode também ajudar a fundamentar o diagnóstico errado. É muito importante salientar que as dores referidas pelos doentes com doença de Fabry não correspondem a artrite nem se verifica tumefacção articular, o que pode ajudar a excluir os diagnósticos anteriores. Também salientamos a importância da colaboração entre os médicos de diferentes especialidades, que foi a condição essencial para o estabelecimento do diagnóstico e para o início do seguimento numa consulta de «doenças raras», com vista à avaliação inicial, à monitorização do estado clínico e ao início do tratamento. O estudo genético deste caso permitiu a identificação de uma mutação até agora desconhecida.

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ASSOCIATION OF SYSTEMIC-ONSET JUVENILE IDIOPATHIC ARTHRITIS AND CELIAC DISEASE – A CASE REPORT

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Abstract

Introduction: In a 28-year period, 5,508 patients were followed at our Paediatric Rheumatology Division and 712 (13%) patients had juvenile idiopathic arthritis (JIA) (ILAR criteria). One (0.14%) of them had association with celiac disease (CD), with predominance of gastrointestinal manifestations and this case was described herein.

Case report: A 10-years-old female patient was hospitalized with persistent fever, weight loss, asthenia, anorexia and an evanescent pink macular rash. After one week, she presented arthritis of left knee and ankle with duration of 75 days. The initial laboratory exams revealed anemia and elevation of inflammatory markers. Immunological tests were positive for anti-endomysial antibodies IgA and anti-thyroglobulin antibody. The diagnosis of systemic JIA was established and indomethacin (2.0 mg/ /kg/day) was started with improvement of arthritis. The patient evolved with vomiting, diarrhea and abdominal pain and upper gastrointestinal barium study showed areas of small bowel dilatation and thickening of folds, suggestive of malabsorption syndrome. Colonoscopy was normal and small intestinal biopsy was compatible with CD.

Discussion: We reported a case of a rare association of early diagnosis of systemic JIA occurring simultaneously with CD. This study reinforces the importance of taking into account the possible association of organ-specific autoimmune diseases during JIA course.

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Keywords: Systemic Onset Juvenile Idiopathic Arthritis; Celiac Disease; Children.

Introduction

Systemic-onset juvenile idiopathic arthritis (SoJIA) is a chronic inflammatory disease of unknown etiology characterized by chronic arthritis, fever and often associated with other signs and symptoms, such as: skin rash, hepatosplenomegaly, pleuritis and pericarditis[1,2]. Eventually these patients may also present gastrointestinal involvement, such as abdominal pain and mesenteric lymphadenopathy[2].

Of note, celiac disease (CD) is an autoimmune enteropathy illness characterized by the presence of at least four of the following criteria: clinical manifestations (diarrhea, stunting and/or iron deficiency anemia), presence of celiac disease IgA class antibodies, HLA-DQ2 or DQ8 genotype, small intestine biopsy compatible with celiac enteropathy, and response to gluten-free diet[3].

Arthritis, involving both the peripheral and axial skeletal, might be an early extra-intestinal manifestations of CD[4]. Additionally, CD has also been rarely described in patients with chronic arthritis, such as JIA, mainly in oligoarticular and polyarticular subtypes[5,6]. To our information, only two cases of CD were reported in SoJIA patients during follow-up of disease[5,7].

From January 1983 to December 2010, 5.508 patients were followed at the Paediatric Rheumatology Unit of Instituto da Criança da Faculdade de Medicina da Universidade de São Paulo and 712 (13%) patients fulfilled the International League of Associations for Rheumatism (ILAR) classification criteria for JIA[1]. One of these (0.14%) patients had a concomitant diagnosis of SoJIA and CD, and this case was described herein.

Case Report

A 10-years-old female patient was hospitalized in our University Hospital with persistent high fever (39-40ºC) for 25 consecutive days associated with an evanescent erythematous rash, weight loss (9 kg in 25 days), asthenia and anorexia. No epidemiology for Lyme disease, brucellosis and tuberculosis was reported. After one week of hospitalization, she presented hepatomegaly, chronic arthritis of left knee and ankle for a period of 75 days. The initial laboratory exams revealed hemoglobin 9.3 g/dL, hematocrit 28.5%, white blood cell count 6,700/mm^3 (73% neutrophils, 18% lymphocytes, 2% eosinophils and 7% monocyte), platelet count 492,000/mm^3, thyroid stimulating hormone (TSH) 1.82 µU/mL (normal range 0.6-5.4 µU/mL) and free thyroxine 1.36 ng/dL (normal range 0.7--1.5 ng/dL). Erythrocyte sedimentation rate was 61 mm/1st hour and C-reactive protein 121 mg/L (normal < 5). She had normal cardiac examination according to pediatric cardiologist evaluation. The thoracic radiography and echocardiography were normal. The bone marrow aspiration was normal. Serologic tests, such as: hepatitis virus A, hepatitis virus B, hepatitis virus C, Epstein-Barr virus (EBV), cytomegalovirus (CMV), human immunodeficiency virus (HIV), toxoplasmosis and rubella, were all negative. Antistreptolysin o (ASLO) titer was 132 UI/mL and immunological tests were negative for the following serum antibodies: antinuclear antibody (ANA), anti-double-stranded DNA (anti-ds DNA), anti-Sm, anti-Ro, anti-La and anti-peroxidase (anti-TPO). Serum IgG was 1735 mg/dL (normal range 970-1710 mg/dL), IgM was 141 mg/dL (normal range 53-145 mg/dL) and IgA was 56 mg/dL (normal range 45-234 mg/dL). Therefore, the diagnosis of SoJIA was established according to the ILAR classification criteria[1] and indomethacin (2.0 mg/kg/day) was introduced with improvement of chronic arthritis after hospitalization, with persistence of fever, rash and hepatomegaly. At 10 years and 3 months of age, she presented vomiting, diarrhea and severe abdominal pain that worsened after food ingestion, and was re-admitted. At that hospitalization, upper gastrointestinal barium study showed small bowel dilatation and thickening of folds, suggestive of malabsorption syndrome. Abdominal ultrasound was normal**.** The abdominal computed tomography scan evidenced mild distension of small bowel. Upper endoscopy and colonoscopy were normal. Immunoglobulin A (IgA) class anti-endomysial antibody (IgA-EMA) by indirect immunofluorescence was 1/40 (normal < 1/10). Remarkably, the endoscopic small bowel biopsy showed chronic duodenitis and jejunitis with dense cellular infiltrate in the lamina propria, villous atrophy, crypt hyperplasia and elevated intraepithelial lymphocytes (IELS), compatible with CD (Figure 1). A gluten--free diet was introduced with improvement of diarrhea, and the CD diagnosis was established[3]. In order to ensure the adherence to a complete removal of gluten from the diet, the patient remained hospitalized, however 29 days after CD diagnosis the patient evolved with sepsis by *Serratia sp* and died of septic shock.

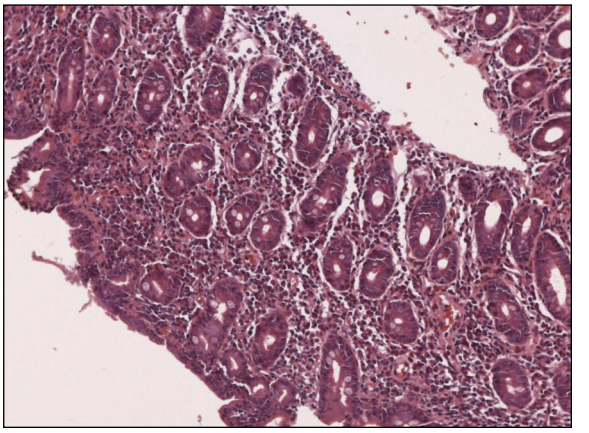

Figure 1. Endoscopic biopsy of jejune showed dense cellular infiltrate in the lamina propria, villous atrophy, crypt hyperplasia and elevated intraepithelial lymphocytes (IELS), compatible with celiac disease.

Discussion

We described a case of concomitant diagnosis of these two autoimmune diseases (SoJIA and CD) with a fatal outcome. These diagnoses were rarely observed in a large tertiary of pediatric hospital in Brazil.

CD is an immunologically based enteropathy characterized by sensitivity to gluten in genetically predisposed subjects[3,5]. Notably, similar mechanisms elicited by environmental triggers may induce the concomitant occurrence of multiple organ-specific autoimmune diseases in CD patients, such as type I diabetes mellitus, Graves' disease and Hashimoto's thyroiditis[6,8].

Likewise, systemic autoimmune diseases, such

as JIA, may also be associated with this autoimmune enteropathy[5-10]. In fact, CD was previously reported in 2.5% to 6.5% of JIA children[5,7,11,12]. Of note, the most frequent JIA subtypes associated with CD were oligoarticular and polyarticular[5,6] and very rarely patients had SoJIA[5]. Notably, our patient presented classical features of SoJIA, including diary high fever during more than 2 weeks, chronic arthritis, evanescent rheumatoid rash and hepatomegaly together with the general symptoms, such as anorexia and weight loss, that in few months would evolve to typical gastrointestinal symptoms of CD. Differently to the present report, Alpigiani *et al.* had demonstrated CD diagnosis 3.5 and 4.6 years after JIA onset[11], however the subtypes of these patients were not described.

Remarkably, CD frequently remains asymptomatic for years but may be associated with an increased risk of a second autoimmune disease[5]. Of note, the CD diagnosis requires at least four of the following criteria: presence of typical symptoms of celiac disease, positivity of serum celiac disease autoantibodies (IgA-EMA and/or anti-tissue transglutaminase) at high titer, HLA-DQ2 or DQ8 genotypes, celiac enteropathy at the small intestinal biopsy and response to the GFD[3], as identified in our present case.

Differential diagnosis must be done with a variety of infections affecting small bowel mucosa. Furthermore, autoimmune enteropathy, secondary to the production of autoantibodies against enterocytes, is usually characterized by histologic findings of villous flattening and crypt hyperplasia, similarly to CD. Crohn disease may also be excluded, once it affects the upper gastrointestinal tract in up to 30% to 50% of cases. In addition, primary immunodeficiencies, such as common variable immunodeficiency, may be associated with autoimmune diseases such as JIA and CD[13]. Of note, the patient reported herein died of septic shock by *Serratia* sp. infection and presented lymphopenia lower than 1500 cells/uL, however Immunophenotyping of lymphocytes were not performed.

Our patient was prone to intestinal mucosal lesion associated to CD. In fact, *Serratia* bacteremia originates mainly from bloodstream, respiratory, gastrointestinal and urinary tract. Previous studies demonstrated hospital-acquired septic shock by *Serratia* in 14.8% and mortality rates related to *Serratia* bacteremia of 25% to 58%[14].

CD treatment is based on a gluten-free diet, which can reduce articular and intestinal manifestations[5,6,11]. To our knowledge, the use of non-steroidal anti-inflammatory drugs, such as indomethacin, has no influence to the course of CD, as observed in our case.

In conclusion, we reported a case of early diagnosis of SoJIA occurring simultaneously with CD. This study reinforces the importance of taking into account the possible association of organ-specific autoimmune diseases during JIA course.

Acknowledgment

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SYSTEMIC SCLEROSIS, A RARE CASE

Elsa Sousa*, Paula Valente*, Mafalda Santos*

Abstract

Systemic sclerosis (SS) is a rare severe autoimmune disease involving the connective tissue. The pathophysiology is not clearly understood. It is characterized by a remarkable clinical heterogeneity, and virtually all organs can be affected. Concerning diagnosis, the presence of antinuclear antibodies (ANA) can be found in more than 90% of patients, but the diagnosis is made gathering clinical manifestations, autoimmune panel, nailfold capillaroscopy and in some cases biopsy of the organ involved. The disease course is also weakly understood, although some serological patterns can be distinguished. Current therapeutic options target few aspects of pathologic mechanism and clinical management remains a challenge.

The authors presented a rare case of a SS ANA negative, which demonstrates the diagnostic challenge of this disease.

Keywords: Systemic sclerosis; Antinuclear Antibodies; Myopericarditis.

Introdution

Systemic sclerosis is a rare, severe autoimmune disease involving the connective tissue of the skin and internal organs[1].

The pathophysiology is not totally understood, although it seems that there are abnormalities in at least three types of cells: fibroblasts, cells of the immune system (T and B lymphocytes) and endothelial cells[2]. The disease hallmark is an overproduction and accumulation of collagen and other extracellular matrix proteins, resulting in thickening of skin and fibrosis of affected organs (gastrointestinal tract, lung, heart and kidney)[3]. Reflecting current concepts, on a given heterogeneous genetic background (involving, in particular, genes of immune system and the connective tissue), one or several unknown factors induce an inflammatory response, which spreads and induces an activation of the immune and vascular system. Profibrotic signals cooperatively activate fibroblasts of the affected tissues, which under repeated hypoxic stress and the influence of fibrogenic mediators lose their original organ-derived phenotype and transdifferentiate in the direction of a bone/cartilage like differentiation. Increased deposition of altered proteins contributes to perpetuation of the hypoxic state[3].

SS is a rare disease and epidemiologic data varies greatly according to geographic location and disease definition[4], with estimated annual prevalence between 3 and 24 per 100000 inhabitants, higher in North America and Australia compared to Europe and Japan[1]. SS occurs more frequently in women than men (4:1), although this ratio is more pronounced in younger patients than in patients over 50 years[4]. The type of SS, as well as autoantibodies markers varies by geographic region and racial group, giving a strong indication that host and environmental factors (exposure to silica, organic solvents and heavy metals) play a role in pathogenesis and expression[1,4,5].

The ten-year cumulative survival has improved significantly from 54% in the 1970s to over 70% in the 2000s, and pulmonary fibrosis and pulmonary arterial hypertension are the two main causes of death[1]. Concerning the risk factors which influence mortality, diffuse cutaneous form, cardiac, pulmonary or renal involvements are considered independent risk factors[1].

Case Report

Female patient, 39 years old, working in frozen-food industry, with familiar history of rheumatoid arthritis (sister), who initiated 3 months before cutaneous thickness, digital edema with Raynaud s

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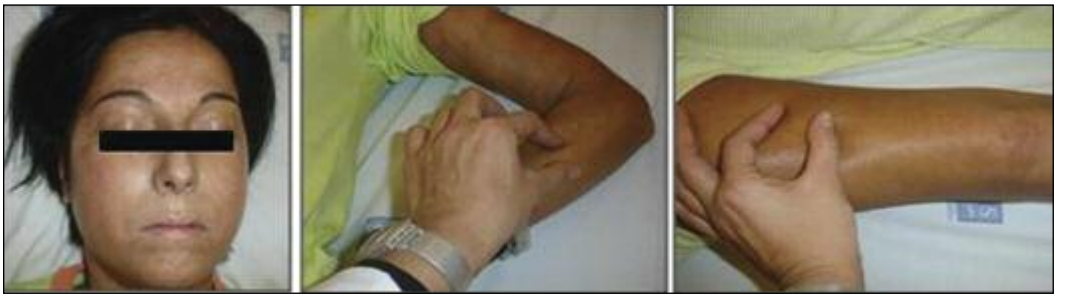

Figure 1. Skin thickness: face and limbs.

phenomena, complicated by digital ulcer of the third finger of her right hand (aggravated by her job). She also referred symmetrical inflammatory polyarthralgias, namely in the wrists, hands, knees and ankles. At physical examination, she had diffuse cutaneous thickness (Figure 1) in the face, trunk and on upper and lower limbs (both proximal and distal); there was no sign of active arthritis and a scar was observed in third finger (right hand). In initial study there was no evidence of systemic inflammatory syndrome and the immunological study [namely ANA by enzyme immunoassay (EIA), anti-Scl 70, anti-centromere, anti-Jo, anti-dsDNA] was negative. The chest X-ray was normal, but pulmonary function tests showed reduced diffusing capacity for CO (78% of predicted DLCO). The high resolution CT scan was normal. The nailfold capillaroscopy was inconclusive due to severe Raynaud s phenomena in all fingers (granular flow and one enlarged capillary). Concluding, this patient had a suggestive clinical picture of systemic sclerosis, without characteristic serologic or capillaroscopic markers, and so without a clear diagnose. She maintained in follow up, with symptomatic treatment (namely calcium channel antagonist, acetylsalicylic acid and physical precautions).

About 10 months later, she started with fever (maximum 38°C) and non-productive cough during 48h and was treated with acetaminophen. This auto-limited clinical presentation evoluted with progressive dyspnea, orthopnea and generalized oedema. She was admitted in the Emergency Department with acute heart failure (HF) presenting ansarca, increased jugular venous pressure, hypotension, pulmonary sounds suggesting bilateral pleural effusion and pulmonary congestion, and digital ischemia signs (Figure 2). In complementary exams we found: elevation of specific myocardial biomarkers as well as elevated liver enzymes; low-voltage QRS complexes in EKG (the previous was normal); echocardiogram showed concentrically hypertrophy of left ventricle with infiltrative aspect of epicardium, pericardial effusion with thickness of visceral layer, as well as severe decrease function, no signs suggesting pulmonary hypertension; and, chest CT reveled bilateral pleural effusion, discrete hepatomegaly (congestive aspect), no signs of pulmonary hypertension or embolism. The patient progressed to cardiogenic shock, with multiorgan failure. The presence of acute left HF without pulmonary hypertension in a female patient with cutaneous thickness but no serologic autoimmune abnormalities was a diagnostic challenge. Two hypothesis were considered: infectious cardiac disease and cardiac involvement by autoimmune seronegative disease. In fact, the analytic study for main agents associated with myopericarditis (Table I) was negative, as well as new immunological study (Table II). Aggressive measures were taken, covering both hypothesis: steroids (1mg/kg/day of prednisone, associated with renin-angiotensin-aldosterone inhibitor for renal protection), hypocoagulation and HF therapeutic including dobutamine. Forty-eight hours later, there was sustained clinical improvement with complete resolution of HF signs. All echocardiographic changes disappeared within

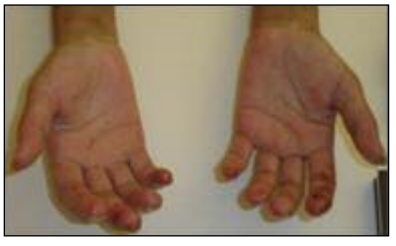

Figure 2. Skin thickness and digital ischemia, suggesting vasculopathy

Table I. Virology study

Human immunodeficiency virus	negative
Hepatitis C virus	negative
Hepatitis B virus	negative
Adenovírus IgM	negative
Adenovírus IgG	weak positive
Echovírus	negative
Parvovírus B19	negative
Coxsackievirus A	negative
Coxsackievirus B IgM	negative
Coxsackievirus B IgG	weak positive

Table II. Immunologic study

ANA (U/mL)	negative
Anti-ds DNA Ab (U/mL)	negative
Anti RNP Ab (U/mL)	negative
Anti SCL 70 Ab (U/mL)	negative
Anti Centromere Ab (U/mL)	negative
Anti Jo Ab (U/mL)	negative
Anti- β2glycoprotein Ab IgG/IgM	negative
Anti-Cardiolipin Ab (U/mL)	negative
Immunoglobulinne (A,D,G,M)	normal

the first month, so to clarify cardiac involvement a MRI was performed and did not show abnormalities in myocardial structure. The diagnosis accepted was probable myopericarditis in a patient with suspected SS, and she was discharged with steroid therapy (at decreasing doses) and treatment for Raynaud s phenomena. Concerning digital ischemic signs, low molecular weight heparin in therapeutic dose was continued until full recovery. In outpatient clinic, a skin biopsy (Figure 3) was performed, which confirmed the systemic sclerosis diagnose. All HF therapeutic approach was suspended without symptomatic complains, as well as hypocoagulation.

After steroid suspension, she developed joint complaints with functional disability and methotrexate was initiated. There was a clear improvement regarding joint complaints and also ameliorated skin thickness, including limbs, trunk and face (Figure 4). To demonstrate the improvement during treatment the 17 sites Modified Rodnan Skin test was preformed, with a total score of 45 (out of 51) in admission to an up to date present total score of 31 (out of 51). During one year follow up, the immunological study was once again negative, the gastrointestinal study was normal, there was normalization of DLCO and the echocardiogram was normal. Repeated nailfold capillaroscopy revealed an early sclerodermic pattern. Currently, she maintains outclinic follow up, with symptomatic therapy for Raynaud s phenomena (calcium blocker antagonists, anti-oxidants and transdermal nitrates), methotrexate (20mg/week) and antiplatelet therapy.

Discussion

Systemic sclerosis is characterized by a remarkable heterogeneity of the disease course and affected organs in the individual patient[3]. It is usually subclassified as limited or diffuse depending on the extent of skin involvement. The distinction between this two forms varies, although most authorities concur that diffuse SS has truncal and acral involvement, while changes distal to metacarpophalangeal and metatarsophalangeal joints are consistent with limited SS. Typically, patients with

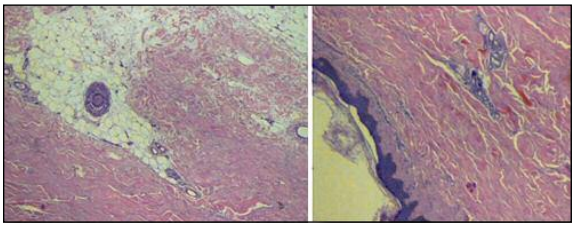

Figure 3. Normal epidermis, dermis markedly thickened by deposition of collagen, markedly sclera-hyaline particularly involving hypodermic adipose tissue. Rare glandular annexes. No vacuities or amyloid deposition

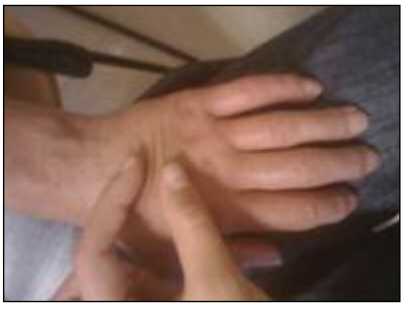

Figure 4. Skin thickness improved after MTX introduction

limited SS have more insidious disease onset, describing Raynaud s phenomenon for some years prior to onset of sclerodactyly. In the diffuse form the skin thickening tends to more closely coincide with the onset of Raynaud s phenomenon and there is a more acute course involving internal organs within 5 years[4]. In this case, the clinical picture was consistent with the diffuse form, as the symptoms evolutes only during one year, first with Raynaud and then cutaneous thickness.

Virtually all organs can be affected. The lung involvement, particularly important in mortality risk, can develop as interstitial lung disease or vascular pulmonary disease (pulmonary hypertension). Although less frequent, with the introduction of angiotensin-converting enzyme inhibitor, the scleroderma renal crisis is still a threat when corticosteroids are used. Gastrointestinal involvement with dysmotility, is frequent and indolent. Cardiac involvement may occur in less than 50% of the patients; the most common cardiac manifestations are those secondary to pulmonary hypertension, but it can include primary cardiac tissue involvement by myocardial fibrosis and contraction band necrosis, which can lead to cardiomyopathy with heart failure as well as varying degrees of heart block or rhythm abnormalities[6]. The heterogeneity plays an extraordinary challenge to the diagnostic and management of these patients. This case is an example. When the patient was admitted, there was no doubt about skin, digital vasculophathy and joint involvement. The issue was on cardiac versus pulmonary involvement. In this case, there was a life threatening situation which justifies the clinical options covering all diagnostic hypothesis.

Concerning diagnosis, the presence of ANA can be found in more than 90% of patients[4,6,7,8]. Anti-centromere antibodies (ACA) and anti-topoisomerase I antibodies (anti-topo I, formerly Scl-70) are the classic autoantibodies associated with SS. ACA are associated with limited SS involvement and isolated pulmonary hypertension as well as a favorable prognosis. Anti-topo I are associated with diffuse skin involvement and pulmonary fibrosis, correlated with a poor prognosis and SS-related mortality. Additionally, anti-RNA polymerase antibodies are associated with diffuse cutaneous disease and renal involvement. Anti-nucleolar antibodies define multiple subgroups of patients with SS, and of these, anti-Th/To antibodies and anti-PM-Scl antibodies are associated with limited cutaneous SS, whereas anti-U3RNP antibodies are associated with diffuse cutaneous SS. In addition, anti-Th/To and anti-U3RNP can be predictors for a less favorable prognosis. Other autoantibodies are less frequently reported: anti-Ku antibodies, anti-U1RNP antibodies, anti-human upstream-binding factor, and anti-U11/U12 antibodies[7]. Although a battery of laboratory tests are available for ANA detection, indirect immunofluorescence antinuclear antibody test (IF-ANA) and EIA/enzyme linked immunosorbent assay (ELISA) are commonly used in day-to-day practice. IF-ANA, with high sensitivity and specificity, detects ANA by adhere to reagent test cells (substrate), forming distinct fluorescence patterns that are associated with certain autoimmune diseases (reporting three parameters: pattern of fluorescence, substrate used and the titer of a positive test). There are two types of EIA or ELISA methods currently used for ANA testing (one called generic assay which detects ANA of broad specificity similar to IF-ANA and other is antigen specific assay that detects ANA and reacts with a single autoantigen); these tests, both highly specific and sensitive, became the most widely used method not only for routine screening but also for detection of specific ANA[12]. The method used in this case report was EIA, with a sensitivity and specificity estimated by the manufacturer of 96%.

Nailfold video-capillaroscopy (NVC) shows a variety of morphological changes, including enlarged capillaries, bushy capillary formations, microhaemorrhages and a variable loss of capillaries with or without avascular areas[6]. The diagnosis is made gathering clinical manifestation, autoimmune panel, NVC, and in some cases, biopsy of the organ involved. SS differential diagnosis was based on the exclusion of diseases showing similar changes namely: physical trauma, chemical exposure (vinyl chrolide, silica, organic solvents), drugs (arsenic, toxic oil syndrome, bleomicin), other autoimmune diseases (cryoglobulinemia, lupus, rheumatoid arthritis), eosinophilic syndromes (eosinophilic fasciitis, eosinophilia myalgia syndrome), metabolic disorders (scleromyxedema, diabetes related scleroderma, paraproteinemias and amyloidosis) or paraneoplasic syndromes[5,6]. This clinical case belongs to the rare group of patients without serologic autoimmune markers, namely ANA. This fact became the diagnosis approach more difficult and the skin biopsy the key exam.

Several treatments have been proposed over the past decades, and so far, no single effective SS treat-

ment exists[9]. Mehtotrexate, cyclophosphamide, calcium channel blockers, angiotensin converting enzyme inhibitors, prostacyclin analogues, D-penicillamine are the most widely study treatments[9]. The European League Against Rheumatism guidelines recommend assessing the patient for organ systems involved and, on this basis, suggest using cyclophosphamide for lung disease and either cyclophosphamide or methotrexate for skin disease[10,11]. More recently, the approach with endothelin receptor antagonists and phosphodiesterase-5 inhibitors for pulmonary arterial hypertension and peripherical vascular disease was introduced. Waiting for solid data are stem cell transplantation, intravenous gamma globulins, mycophenolate mophetil, fluoxetine, pirfenidone, relaxin, halofunginone, anti-TNF antibodies and tyrosine kinase inhibitors. Current therapeutic options target few aspects of pathologic mechanism, but clinical management remains a challenge[9]. In this clinical case, MTX was started with very good results particularly in skin thickness, joint complains and pulmonary changes.

Conclusion

Diffuse systemic sclerosis is a rare disease. Serum negative ANA is even a more rare case. This clinical case is part of this particular group of patients, and exemplifies the diagnostic challenge as well as treatment management.

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ADULT-ONSET STILL'S DISEASE MISDIAGNOSED AS PNEUMONIA: TWO CASE REPORTS

Han-xiang Nie*, Xu-hong Ding*, Yi Huang*, Su-ping Hu*

Abstract

Adult-onset Still's disease (AOSD) is an uncommon inflammatory condition of unknown origin and pathogenesis. Pulmonary involvement is rare and includes pleuritis and transient radiological infiltrations. We report two cases of AOSD characterized by lung involvement at presentation. Both were misdiagnosed as pneumonia with para-pneumonic effusion. We also discuss the difficulties in diagnosis of AOSD with pulmonary infiltration.

Keywords: Adult-onset Still's Disease; Pneumonia; Misdiagnosis.

Introduction

Adult-onset Still's disease (AOSD) is a rare systemic inflammatory disorder with no specific histological features and with unknown origin, characterized by high-spiking fever, an evanescent rash, arthritis, and multiorgan involvement[1]. AOSD is an exclusion diagnosis based on clinical signs and laboratory findings[1]. It is common for AOSD patients to have symptoms involving other organs such as liver, kidney, bone marrow and less often the lungs. Pulmonary involvement includes pleuritis, pleural effusion and transient pulmonary infiltrations[2]. We herein report the clinical case of two patients, whose initial complaints were fever, cough, chest pain, pulmonary infiltrations and pleural effusion, who were misdiagnosed as suffering of pneumonia with para-pneumonic effusion.

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Case Report

Case I

In 2007, a 39-year-old woman presented to her doctor with cough, chest pain and fever. These symptoms had existed for 1 week after four days of sore throat. Chest pain existed in her posterior bilateral sides, which was felt during deep inspiration and cough. The patient had productive cough but no rash and weight loss. Laboratory test revealed that blood leukocyte count was 14,710/mm^3 with a differential count of 86.3% neutrophils. The patient had been extensively examined for infectious disease. The patient had no history of smoking and no lymph nodes. Neoplasm and tuberculosis were considered and excluded. Before admitted into our hospital, she had been treated with intravenous cefoperazone-sulbactam (4.5 g/day) for four days without any improvement of her symptoms. The patient presented breathlessness from the exertion and then was hospitalized. Her family history and previous medical history were unremarkable. On physical examination, the patient's temperature was 39.1ºC, and her heart rate was 116 bpm; blood pressure, 90/60 mmHg; respiratory frequency, 18 breaths/min. Physical examination found dullness on percussion over lung bases and absent breath sounds. The rest of the physical examination was unremarkable.

Laboratory studies were notable and the results were summarized in Table I. Renal function test and D-Dimer were normal. Urine analysis, tuberculin skin test, HIV serology and tumor markers were all negative. Three hemocultures were negative for microorganisms. Antinuclear antigen (ANA), rheumatic factor (RF), antistreptolysin O (ASO) and anti-neutrophil cytoplasmic antibody (ANCA) were negative as well. Bone marrow examination showed inflammatory changes. Serologic tests for Influenza virus A and B, Parainfluenza virus of type 1, 2 and 3, Respiratory syncytial virus, Epstein-Barr virus, Cytomegalovirus, *Klebsiella pneu-*

Table I. Routine laboratory findings for Case 1

	Pre-treatment	Post-treatment	Normal values
ESR (mm/hr)	89	60	Female: 0-20 Male: 0-15
CRP (mg/L)	192	18.9	0-8
Hemoglobin (g/dL)	8.8	11.3	12-17
Leukocyte (/mm3)	15,900	9,040	3,800-10,000
Neutrophils (%)	84.8	74.5	40-72
Platelets (/mm3)	299,000	178,000	100,000-320,000
ALT (IU/L)	62.3	14.2	0-40
AST (IU/L)	42.0	19.5	0-40
LDH (IU/L)	421.6	106	109-245
Serum ferritin (ng/mL)	13,146.58	613.7	Female: <322 Male: <219

ESR: erythrocyte sedimentation rate; CRP: C reactive protein; ALT: alanine aminotransferase; AST: asparate aminotransferase; LDH: lactate dehydrogenase

moniae, Mycoplasma pneumoniae and *Legionella pneumophila* were negative. An abdominopelvic ultrasonograph and echocardiogram showed normal results. ECG showed sinus tachycardia. Chest X-ray showed pleural effusion in bilateral side (Figure 1). Pleural fluid was an exudate, with pleural fluid/serum protein, 0.61; pleural fluid/serum LDH, 0.59; pleural fluid LDH, 248 IU/L. Bacteriological pleural fluid culture was also negative. After pleural effusion was aspirated, a computed tomography (CT) scan of chest showed bilateral lower lobe infiltration (Figure 2). The patient was first diagnosed as pneumonia with a para-pneumonic effusion, and intravenous imipenem and cilastain sodium (3 g/day) and fusidic acid (1.5 g/day) were administered. Three days later, the patient presented with arthralgia in her knees, wrists and elbows.

Seven days later, the patient had no improvement in her symptoms and signs. According to Yamaguchi criteria[3], the patient was finally diagnosed as AOSD, and methylprednisolone (1 mg/kg body weight, 40 mg/day) was initiated. Her symptoms improved markedly in 5 days. Chest CT scan showed normal assessment in 6 days (Figure 3). Laboratory examinations after fourteen days of treatment were listed in Table I. All laboratory findings including serum ferritin levels were normal after two months of treatment. The dose of methylprednisolone was decreased progressively and

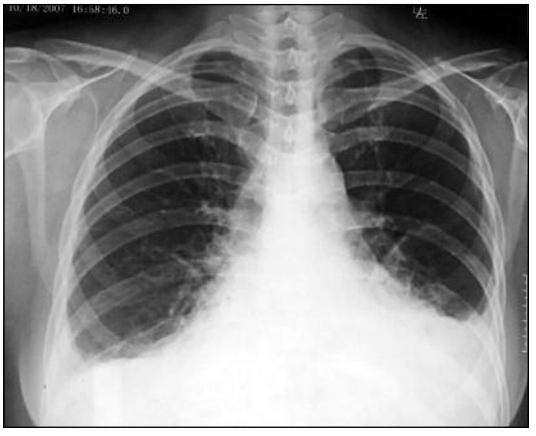

Figure 1. Chest X-ray showing pleural effusion in bilateral side

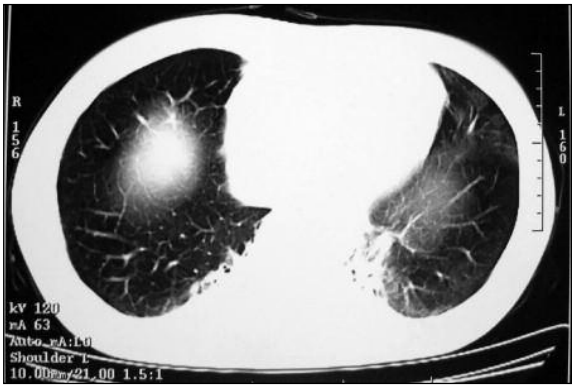

Figure 2. Computed tomography scan of chest showing bilateral lower lobe infiltration after pleural effusion was aspirated

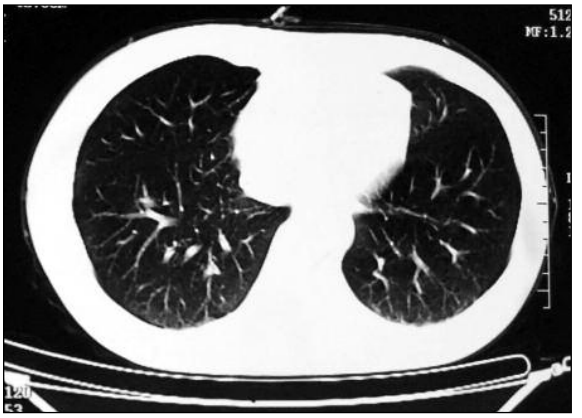

Figure 3. Six days after methylprednisolone treatment, computed tomography scan of chest was normal

withdrawn in six months. The patient's symptoms and signs were stable during the one-year follow--up period. She has fully recovered and no medication is currently prescribed.

Case II

In 2010, a 21-year-old man complained of fever, sore throat, nonproductive cough for 10 days. The spiking fever was over 39ºC. Laboratory findings were summarized in Table II. A chest CT scan showed normal results. He was first diagnosed as sepsis in another hospital and intravenous ceftazidime (4 g/day) and levofloxacin (0.5 g/day) were administered. A week later, there was not any relief of his symptoms and the patient complained of chest pain in his left side, which was felt during inspiration and cough. He was referred to our hospital. His family history and previous medical history were unremarkable. On physical examination, the patient's temperature was 39.2ºC, heart rate was 112 bpm; blood pressure, 120/75 mmHg; respiratory frequency, 21 breaths/min. His pharynx was mildly erythematosus. The remaining physical examination was unremarkable.

The renal function test and D-Dimer were normal. Urine analysis, tuberculin skin test, HIV serology and tumor markers were all negative. Three hemocultures were negative for microorganisms. ANA, RF, ASO and ANCA were negative as well. Bone marrow examination showed inflammatory changes. Serologic tests for Influenza virus A and B, Parainfluenza of type 1, 2 and 3, Respiratory syncytial virus, Epstein-Barr virus, Cytomegalovirus, *Klebsiella pneumoniae*, *Mycoplasma pneumoniae* and *Legionella pneumophila* were negative. An abdominopelvic ultrasonograph and echocardiogram showed normal results. ECG showed sinus tachycardia. The chest CT scan in our hospital showed a left lower lobe infiltration with small pleural effusion in bilateral sides (Figure 4). He was diagnosed as pneumonia with a para-pneumonic effusion, and intravenous imipenem and cilastain sodium (3 g/day) were administered. Two days later, the patient presented a macular rash, concomitant with fever on his trunk and arms, which

Table II. Routine laboratory findings for Case II

	Pre-treatment	Post-treatment	Normal values
ESR (mm/hr)	160	43	Female: 0-20 Male: 0-15
CRP (mg/L)	198.9	67.7	0-8
Hemoglobin (g/dL)	12.8	12.9	12-17
Leukocyte (/mm3)	26,900	17,300	3,800-10,000
Neutrophils (%)	90.1	95.1	40-72
Platelets (/mm3)	413,000	290,000	100,000-320,000
Plasma procalcitonin (mg/L)	0.1	0.22	0-0.1
ALT (IU/L)	76	12	0-40
AST (IU/L)	45	37	0-40
LDH (IU/L)	401	189	109-245
Serum ferritin (ng/mL)	33,159.69	455.45	Female: <322 Male: <219

ESR: erythrocyte sedimentation rate; CRP: C reactive protein; ALT: alanine aminotransferase; AST: asparate aminotransferase; LDH: lactate dehydrogenase

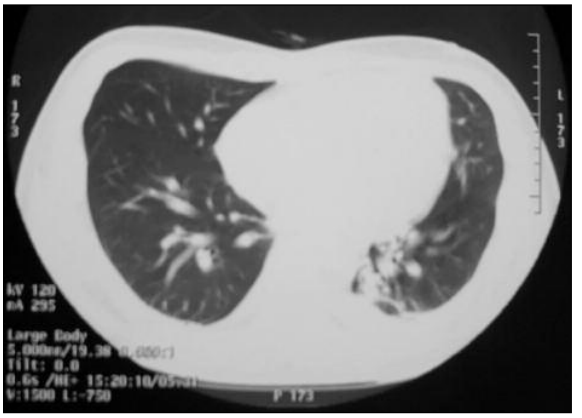

Figure 4. Computed tomography scan of chest showing a left lower lobe infiltration with small pleural effusion in bilateral side

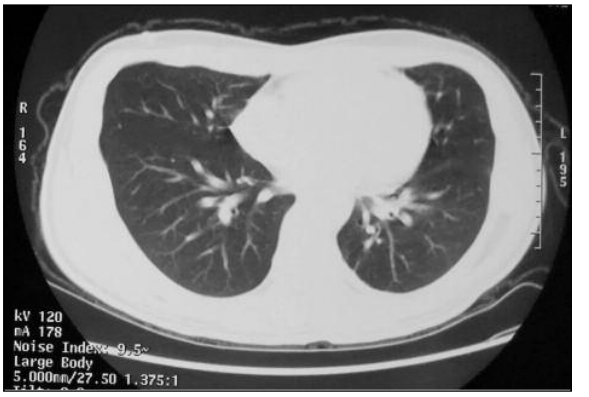

Figure 5. Ten days after methylprednisolone treatment, computed tomography scan of chest was normal

was interpreted as allergic reaction, and antibiotic treatment was changed to intravenous moxifloxacin therapy (400 mg/day) and linezolid (1.2 g/ /day).

Seven days later, the patient had no improvement with medication for pneumonia. According to Yamaguchi criteria[3], the patient was diagnosed as AOSD, and methylprednisolone (80 mg/day) was initiated. His symptoms improved markedly in 1 week. A subsequent chest CT scan showed normal results after ten days of treatment (Figure 5). Laboratory examinations after ten days of treatment were summarized in Table II. Methylprednisolone dose was progressively tapered. The patient has recovered and no medication is currently prescribed.

Discussion

AOSD is a rare condition of unknown etiology usually presenting with high hectic spiking fever accompanied by systemic symptoms[1]. There are no specific laboratory tests for AOSD and the diagnosis is established after exclusion of infections, malignancies and other autoimmune diseases according to the Yamaguchi's criteria[3,4]. Pulmonary involvement in AOSD is rare and even more as first and single AOSD manifestation[2]. Therefore, the association between pulmonary involvement and AOSD is prone to be ignored. The most two common forms of pulmonary involvement are pleural effusion (12-53%) and transient pulmonary infiltrations (6-27%)[2]. Unilateral or bilateral pleuritis or pleurisy (12-53%) with inflammatory pleural fluid has been reported[5]. Interstitial lung disease and fibrosis have been reported with rapid improvement under corticosteroids or nonsteroidal anti-inflammatory drugs[6]. Life-threatening pulmonary complications, such as respiratory distress syndrome and diffuse alveolar hemorrhage, were occasionally reported[7,8]. Spirometry showed a restrictive lung function with low diffusion of CO[9]. Chest X-rays have shown pleural thickening or effusions, pulmonary infiltrations or atelectasis[10,11]. Pulmonary involvement in AOSD seems to be related to pro-inflammtory cytokines, especially IL--18[12].

Our patients first presented with fever, cough, chest pain and lobe infiltration accompanied by pleural effusion. Leukocyte count with a differential count of neutrophils, erythrocyte sedimentation rate (ESR) and C reactive protein (CRP) were found to be markedly elevated in our patients. The patients had been extensively investigated for infectious disease. They were first misdiagnosed as pneumonia with a para-pneumonic effusion. However, the most probable infectious causes were investigated and none was determined. Antimicrobial treatment was unresponsive. Meanwhile, the range of pulmonary infiltration was so small that it might not cause large amount of pleural effusion or even bilateral pleural effusion. Therefore, a noninfectious disease was highly suspected.

The diagnosis of AOSD is difficult in some cases due to the absence of specific serological and pathological findings. The Yamaguchi's criteria are the most widely adopted standards and were shown to be the most sensitive ones (93.5%)[13]. High

levels of serum ferritin seem to be characteristic of AOSD and over 80% of patients present hyperferritinemia[14]. Our patients were diagnosed as AOSD according to the Yamaguchi's criteria[3]. Meanwhile, our patients had extremely elevated serum ferritin level. Therefore, the likelihood of AOSD was high whether other causes, such as infections, malignancies and other autoimmune diseases, were excluded. Moreover, responding to glucocorticosteroid treatment was an important piece of evidence to establish the diagnosis[15].

In conclusion, AOSD is characterized by nonspecific clinical features, which are difficult to be differentiated from many other infectious and noninfectious disorders. When pulmonary infiltration occurs, AOSD is very easily misdiagnosed as pneumonia[16]. Therefore, it is important to consider the diagnosis of AOSD when pulmonary infiltration is involved.

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RECURRENT SYMPHYSITIS PUBIS

JF de Carvalho*, RA Brandão-Neto**, C Faillace*

A 49-year-old woman experienced pain on her pubis since 1988 during her first pregnancy with improvement after delivery by cesarean section. After ten years, in 1998, during her second pregnancy she experienced the same symptom on the same region and also on the medial face of her thighs. After delivery, she experienced healing of this condition. In 2006, she was submitted to abdominal plastic surgery. In 2007, she had recurrence of pubalgia mainly on walking and regular physical training during adduction of lower limbs. She denied any symptom in other joints and pain at rest. Visual analogical scale (VAS) pain was 80 mm. Physical examination demonstrated pain on adduction of her thighs and provoked pain by pubis palpation. No other abnormality was detected. Sacroiliac and waist joints were normal. X-ray image showed irregularities and subcortical cysts of pubis symphysis (Figure 1) and magnetic resonance imaging demonstrated degenerative alterations on symphysis pubis, characterized by irregularities, subcortical cysts, bone marrow edema and margin osteophytes (Figure 2). Bone scintigraphy showed symphysitis pubis (Figure 3). Laboratory tests showed C-reactive protein of 0.42 mg/L, erythrocyte sedimentation rate 9 mm/1st hour, normal blood cell count and protein electrophoresis, and negative rheumatoid factor and antinuclear antibodies. A diagnosis of symphysitis pubis was made and she was treated with naproxen 1g/day, bethametasone and physical therapy. She experienced great improvement of her clinical condition (VAS 0) during the treatment course. However, recurrence of pain after non-steroidal antiinflammatory drugs (NSAID) interruption was observed (VAS 70).

Symphysitis pubis or osteitis pubis was firstly described in 1923 and it is a rare painful noninfectious inflammatory disorder of the symphysis pubis involving the pubic bone, symphysis and surrounding structures[1].

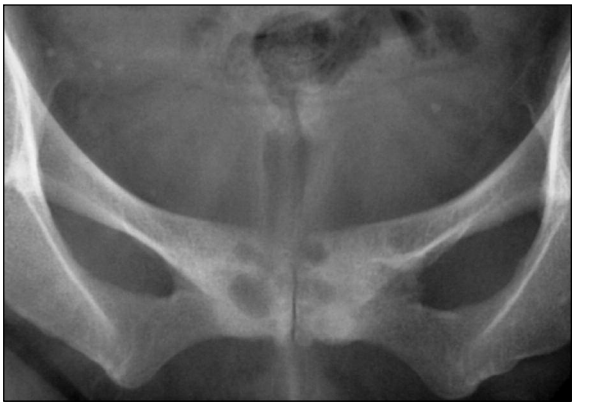

Figure 1. X-ray showing irregularities and subcortical cysts of pubis symphysis

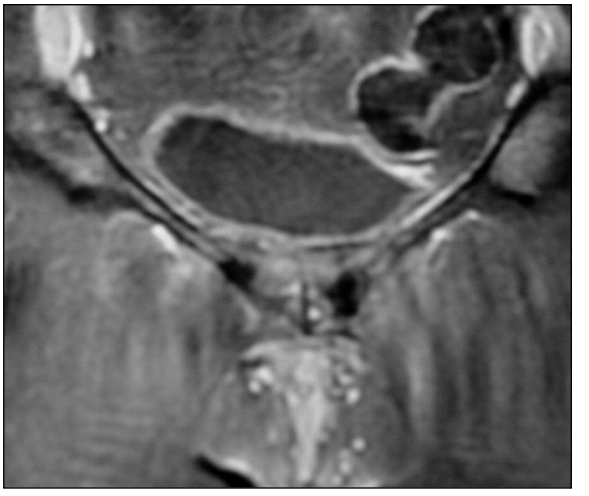

Figure 2. Magnetic resonance imaging T2 signal demonstrating irregularities, subcortical cysts, bone marrow edema of symphysis pubis

Osteitis pubis is commonly linked to several conditions, such as urological and gynecological surgery[2], obstetric complications[3], infections, intense physical training and spondyloarthritis[4]. Our patient had some predisposing conditions such as gynecologic and plastic surgeries. Although, symphysitis only started during the

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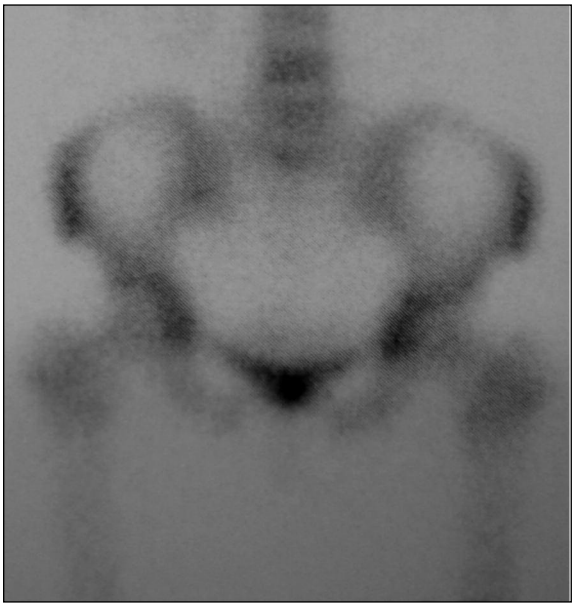

Figure 3. Bone scintigraphy showing hyper-captation of radionuclide characterizing symphysitis pubis

pregnancy and before cesarian section.
Successful results have been reported with both NSAID and glucocorticoid[5].

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- **Article published online (insert DOI)**

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Name(s) and initials of author(s) of chapter. Chapter title. In: Name(s) and initial(s) of editor(s). Book title. City: Name of publisher, year of publication: page(s).

Ex: Stewart AF. Hypercalcemia resulting from medications. In: Favus MD, ed Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism. New York: Raven Press, 1991: 177-178.

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Name(s) and initials of author(s). Book title. City: Name of publisher, year of publication: page(s).

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Ex: Programa Nacional de Luta Contra a Tuberculose. Sistema de Vigilância (SVIG-TB). Direcção-Geral da Saúde – Divisão de Doenças Transmissíveis, Março de 2005. http://www.dgsaude.pt/upload/membro.id/ficheiros/i006875.pdf. Accessed in January 25th 2008.

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