Sociedade Portuguesa de Reumatologia

# Acta Reumatológica Portuguesa

Publicação Trimestral • ISSN: 0303-464X • 10 €

Vol 35 • Nº 3
Julho/Setembro 2010

publisaúde
edições médicas

# Acta Reumatológica Portuguesa




**Administração, Direcção Comercial e Serviços de Publicidade**
Publisaúde - Edições Médicas, Lda
Alameda António Sérgio 22, 4º B
Edif. Amadeo de Souza-Cardoso
1495-132 Algés
Tel: 214 135 032 • Fax: 214 135 007
*Website*: www.publisaude.pai.pt

**Redacção**
Sociedade Portuguesa de Reumatologia
Avenida de Berlim, Nº 33B
1800-033 Lisboa

**Registo**
Isenta de inscrição no I.C.S. nos termos da alínea a) do n.º 1 do artigo 12.º do Decreto Regulamentar n.º 8/99, de 9 de Junho.

**Assinaturas Anuais (4 Números)**
**Yearly Subscriptions (4 Issues)**
Individual/Personal Rate
Portugal .....45 €
Outside Portugal .....65 €
Instituições/Institutional Rate
Portugal .....55 €
Outside Portugal .....75 €

**Depósito Legal:** 86.955/95

**Tiragem:** 7.500 exemplares

**Impressão e Acabamento**
Selenova – Artes Gráficas, Lda.
Casais da Serra • 2665-305 Milharado

**Produção Gráfica**
Rita Correia

**Periodicidade**
Publicação Trimestral

**Revista referenciada no Index Medicus, Medline, Pubmed desde Janeiro 2006.**

**Journal referred in Index Medicus, Medline, Pubmed since January 2006.**

**Revista incluída nos produtos e serviços disponibilizados pela Thomson Reuters, com indexação e publicação de resumos desde Janeiro de 2007 em:**
**• Science Citation Index Expanded (also known as SciSearch®)**
**• Journal Citation Reports/Science Edition**

**Journal selected for coverage in Thomson Reuters products and custom information services. This publication is indexed and abstracted since January 2007 in the following:**
**• Science Citation Index Expanded (also known as SciSearch®)**
**• Journal Citation Reports/Science Edition**




O papel utilizado nesta publicação cumpre os requisitos da ANSI/NISO Z39.48-1992 (Permanence of Paper).
The paper used in this publication meets the requirements of ANSI/NISO Z39.48-1992 (Permanence of Paper).

Sociedade Portuguesa de Reumatologia

SEDARE DOLORES OPUS DIVINUM EST

ELEANORA REGINA

# ÓRGÃOS SOCIAIS DA SPR
# BIÉNIO 2009-2010

## DIRECÇÃO

| | |
|---|---|
| **Presidente** | Dr. Rui André Santos |
| **Vice-Presidente** | Dr.ª Viviana Tavares |
| **Vice-Presidente** | Dr. Rui Leitão da Silva |
| **Sec. Geral** | Dr.ª Patrícia Nero |
| **Sec. Geral Adjunto** | Prof.ª Dr.ª Helena Canhão |
| **Tesoureiro** | Dr.ª Maria Lúcia Costa |
| **Vogal Região Norte** | Dr. Armando Filipe Brandão |
| **Vogal Região Centro** | Dr.ª Margarida Oliveira |
| **Vogal Região Sul** | Dr.ª Graça Sequeira Munoz |
| **Vogal Ilhas** | Dr. Ricardo Ornelas Figueira |

## MESA DA ASSEMBLEIA GERAL

| | |
|---|---|
| **Presidente** | Dr. Augusto Faustino |
| **Secretário** | Dr. Walter Castelão |
| **Secretário** | Dr. José Saraiva Ribeiro |

## CONSELHO FISCAL

| | |
|---|---|
| **Presidente** | Dr. José Vaz Patto |
| **Relator** | Dr. José Miguel Bernardes |
| **Vogal** | Dr.ª Maria Manuela Parente |

## PRESIDENTE ELEITO

Dr. Luís Maurício Santos

**A Acta Reumatológica Portuguesa é o órgão oficial da Sociedade Portuguesa de Reumatologia**

Sociedade Portuguesa de Reumatologia

ACTA REUMATOLÓGICA PORTUGUESA

Vol 35 • Nº3 Julho/Setembro 2010

# SUMÁRIO / CONTENTS

## EDITORIAIS / EDITORIALS



## ARTIGOS DE REVISÃO / REVIEWS



## ARTIGOS ORIGINAIS / ORIGINAL PAPERS

Sociedade Portuguesa de Reumatologia

ACTA REUMATOLÓGICA PORTUGUESA

Vol 35 • Nº3 Julho/Setembro 2010

# SUMÁRIO / CONTENTS

## CASOS CLÍNICOS / CLINICAL CASES



## PRÁTICA CLÍNICA / CLINICAL PRACTICE



## IMAGENS EM REUMATOLOGIA / IMAGES IN RHEUMATOLOGY

Sociedade Portuguesa de Reumatologia

ACTA REUMATOLÓGICA PORTUGUESA

Vol 35 • Nº3 Julho/Setembro 2010

# SUMÁRIO / CONTENTS

# MUDAR E EVOLUIR

Helena Canhão*

*When you're finished changing,*
*you're finished*
*Benjamin Franklin*

Escrevo este editorial no último número da Acta Reumatológica Portuguesa (ARP) na condição de Editora-Chefe.

Nos últimos anos registámos enormes progressos na ARP, quer em termos de qualidade quer em termos de quantidade.

A indexação e a atribuição de factor de impacto à ARP são marcos fundamentais na sua existência, que atestam de forma independente e externa a qualidade da revista e que funcionam também como motor para a sua maior divulgação.

Em 2008 foram submetidos para publicação 105 artigos, em 2009 115 e até 15 de Setembro de 2010, 100 artigos. Podemos por isso ser cada vez mais exigentes e, em 2009, recusámos 23,5% dos artigos submetidos.

Mas podemos sempre fazer mais e melhor. O crescente rigor na selecção dos artigos publicados, redução do seu número, maior número de publicações em inglês e progressivamente tornar esta a língua oficial da revista, internacionalizar o nome da ARP, validar e promover a utilização do *site* da ARP e profissionalizar os serviços prestados são algumas medidas, já discutidas anteriormente, que podem contribuir para uma cada vez maior afirmação da ARP como revista reumatológica internacional.

Trabalhar na ARP é trabalhar com todos os reumatologistas e internos, colegas de outras áreas e especialidades, profissionais não médicos que contribuíram com a submissão de artigos, revisão, comentários e sugestões para a melhoria da ARP.

Mudar é fundamental para evoluir e a renovação do Editor-Chefe é uma medida, tão importante como as anteriores mencionadas, para a vitalidade e aumento progressivo da qualidade da revista.

Estes 2 anos foram de trabalho estimulante e gratificante, mas também muito árduo para os editores e revisores que têm múltiplas actividades para além das relacionadas com a ARP. Não quero por isso deixar de agradecer a todos os editores associados - Catarina Limbert, Elisabeth Benito Garcia, João Eurico Fonseca, João Lameiras Campagnolo, José António Pereira da Silva, José Carlos Romeu, Luís Graça, Maria José Leandro, Maria José Santos, Patrícia Nero, Raquel Lucas; a todo o corpo editorial nomeadamente Ana Rita Cravo, Eliseo Pascual, Emilia Sato, Filipa Ramos, Francisco Airton da Rocha, Ivânio Alves Pereira, Jaime Branco, John Isaacs, Juan Gomez-Reino, Loreto Carmona, Lucia Costa, Marcos Bosi Ferraz, Maria Odete Hilário, Paulo Coelho, Paulo Reis e Yrjö Konttinen e ainda a Dominique Baeten, Juan Canete, Domingos Araújo, José Alves, Elsa Sousa, Mónica Bogas, Ana Filipa Mourão, Joaquim Pereira, Ana Maria Ferreira, Cândida Silva, Anabela Barcelos, Margarida Oliveira, Margarida Cruz, Luis Inês, Mamede Carvalho, Carlos Miranda Rosa, José Melo Gomes, Luis Miranda, Sofia Ramiro, Ana Cordeiro, Marketa Fojtikova, Philipe Goupille, Pedro Machado, João Ribeiro da Silva, João Ramos, Manuela Costa, Aurora Marques, Cristina Catita, Cátia Duarte, Mónica Bogas, Ana Sofia Ribeiro, Luís Maurício Santos, Carmo Afonso,Teresa Nóvoa, Rui André Santos, Joana Caetano Lopes, Peter Taylor, Georg Schett, Barbara Goldstein, Maria João Sá, Viviana Tavares, Manuel Quartilho, Paulo Filipe, Rita Barros, Maria João Saavedra, Imaculada De la Torre, Vitor Gil, Susana Capela, Fátima Godinho, Pedro Fernandes, João Cavaleiro, António Leitão e Rita Correia pelo contributo que prestaram à ARP durante estes 2 anos; agradecer ainda a todos os autores que submeteram trabalhos para publicação; à Publisaúde, responsável pela edição da revista, a todos os patrocinadores e finalmente a todos os membros da direcção da Sociedade Portuguesa de Reumatologia pela missão comum partilhada.

Neste caso sabemos que seguramente mudar é evoluir e melhorar pelo que estamos certos que os próximos anos trarão cada vez melhor qualidade e afirmação à ARP.

Boa sorte aos próximos editores-chefes!

* Editora-Chefe, Acta Reumatológica Portuguesa

# ASPECTOS DA ATEROSCLEROSE E DA SÍNDROME METABÓLICA NO LÚPUS ERITEMATOSO SISTÊMICO

Iana Sousa Nascimento*, Caio Robledo D'Angioli Costa Quaio*, Nailú Angélica Sinicato**, Simone Appenzeller**, Jozélio Freire de Carvalho*

## Resumo

O Lúpus Eritematoso Sistêmico (LES) é uma doença inflamatória auto-imune crônica que afeta principalmente mulheres jovens, e é correlacionada à aterosclerose e a síndrome metabólica (SM).

Uma série de alterações provenientes tanto da história natural de evolução do LES como da terapêutica implica o aumento do risco cardiovascular a partir da atuação comum na origem e progressão da aterosclerose.

A SM é um grupo de fatores de risco, com origem em um metabolismo anormal, acompanhado de um risco aumentado para o desenvolvimento de doença cardiovascular aterosclerótica. Em geral, podemos dizer que a prevalência de SM varia de 5,5-55,4% na população geral e na população com LES, a prevalência da SM gira em torno dos 40% e se associa principalmente a: idade avançada, baixo índice sócio-econômico, falta de exercício, uso de doses elevadas de prednisona e atividade de doença.

O tratamento deve ser mais eficiente ao passo que esses fatores de risco sejam prontamente identificados e abordados terapeuticamente no intuito de um controle mais preciso tanto da atividade do LES como da exposição do paciente aos riscos a aterosclerose.

**Palavras-chave:** Lúpus Eritematoso Sistêmico; Síndrome Metabólica; Doença Cardiovasculoar; Dislipidemia.

*Disciplina de Reumatologia, Hospital das clínicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brasil
**Faculdade de Ciências Médicas da Universidade Estadual de Campinas, Campinas, Brasil

NA Sinicato recebeu Bolsa de Iniciação Científica da FAPESP (2009/15286-1)
S Appenzeller recebeu grants: (FAPESP 2008/02917-0, 2009/06049-6), CNPq (300447/2009-4)
JF Carvalho recebeu *grants* da Federico Foundation e CNPq (300665/2009-1)

## Abstract

Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune disease affecting mainly young women. In last decades premature atherosclerosis has been identified as an important cause of mortality due to SLE related risk factors (inflammation and treatment) and metabolic syndrome (MS). MS is a group of risk factors, originating from an abnormal metabolism, with an increased risk for developing atherosclerotic cardiovascular disease. The prevalence of MS varies from 5,5-55,4% in the general population and has been observed up to 40% in SLE, associated with advanced age, low socioeconomic status, lack of exercise, use of high doses of prednisone and disease activity. Treatment should include identification and modification of these risk factors.

**Keywords:** Systemic Lupus Erythematosus; Metabolic Dyndrome; Cardiovascular Disease; Dyslipidemia.

O Lúpus Eritematoso Sistêmico (LES) é uma doença inflamatória auto-imune recidivante crônica que afeta principalmente mulheres jovens, faixa etária, na população geral, habitualmente livre de aterosclerose e de sua conseqüente agressão cardiovascular. O arsenal terapêutico utilizado em seu tratamento foi aperfeiçoado e a sobrevida em longo prazo dos doentes aumentou nos últimos tempos, todavia está claro que os mesmos têm elevada morbi-mortalidade por doenças decorrentes da aterosclerose[1,2].

Passaram-se 30 anos desde que Murray Urowitz e cols correlacionaram, pela primeira vez, a aterosclerose e a conseqüente doença cardiovascular como complicação tardia da doença lúpica de longa duração[3]. Estudos epidemiológicos subseqüentes corroboraram os indícios de maior incidência

de infarto miocárdico precoce, com algumas descrições de até 30% de mortalidade global do lúpus relacionados com a doença arterial coronariana[2,4,5]. O risco para infarto do miocárdio é cerca de cinco vezes maior para os doentes lúpicos comparados com a população em geral; e cerca de 50 vezes maior para faixa etária de mulheres jovens com LES[2].

O objetivo desta revisão é rever os mecanismos de aterosclerose no LES, com especial atenção a síndrome metabólica.

## Mecanismo de Aterosclerose no LES

A aterosclerose constitui-se a partir de um complexo de respostas celulares e moleculares específicas que ocorrem no endotélio em grandes e médias artérias[6]. O evento inicial dessa cascata de eventos pode ser atribuído à disfunção endotelial, cujas possíveis causas incluem elevados de LDL, radicais livres (p.ex.: os causados pelo fumo), hipertensão arterial sistêmica (HAS), diabetes, alterações genéticas, entre outras[6].

Manzi sugere que a patogênese da doença arterial no lúpus é multifatorial e devido a: 1) interação de fatores de risco cardiovasculares tradicionais (como p.ex.: idade, HAS, hiperlipidemia, hiperglicemia, fumo, história familiar), 2) indução pela inflamação/desajuste imune e 3) por lesão vascular por anticorpo antifosfolípide[6]. O uso de corticosteróides e a doença renal lúpica com conseqüente HAS também têm importante papel. De fato, vários estímulos lesivos e relacionados ao LES podem interferir na função endotelial, incluindo imunocomplexos e outras toxinas, como a homocisteína. Temos como resultado aumento da permeabilidade e adesividade do endotélio, indução de propriedades pró-coagulantes e expressão de moléculas vasoativas, implicando numa proliferação celular e constituição de processo inflamatório[7].

### Processos inflamatórios

No cerne dessa cascata de eventos, processos inflamatórios estão relacionados e contribuem para a gênese e progressão da aterosclerose[1,8-10]; na verdade, a formação de estrias gordurosas, o tipo mais precoce de lesão vascular e comum em crianças, consiste puramente em uma lesão inflamatória com infiltrado de células T e macrófagos[11,12]. Níveis aumentados de elementos presentes na atividade inflamatória lúpica, como proteína C reativa, homocisteína, fixação de imunocomplexos, ativação do sistema complemento, moléculas de adesão intercelular e vascular I (ICAM-1 e VCAM-1) e ligante de CD-40, estão relacionados com aumento do risco de eventos cardiovasculares[13-15].

Trabalhos recentes demonstram, também, a associação entre processos inflamatórios crônicos e ocorrência de múltiplas alterações metabólicas, como: 1) Resistência à insluina/diabetes melito, 2) massa corpórea/obesidade, 3) dislipidemia, dentre outras alterações[16-18]. Wysocki[16] defende a hipótese de que a ativação inespecífica do sistema imune inato juntamente com a desregulação neuroendócrina decorrentes de situações de estresse, como trauma, doenças e emoções, teriam como resultado a deflagração de alterações diversas do metabolismo como mecanismos de respostas e a constituição da aterosclerose. Dessa maneira, os processos inflamatórios não seriam subjacentes ou adjuvantes às alterações metabólicas, mas se incluiriam no importante contexto imuno-metabólico da SM[1,8,9,18].

### Auto-anticorpos

Igualmente nessa circunstância, os anticorpos antifosfolípides (AAF), que são comumente relacionados com tromboses artério-venosas e perda fetal recorrente, também podem participar da aterogênese no LES por mecanismos imunológicos[19-21]. Anticorpos anticardiolipina, um tipo de AAF, podem aderir a vários componentes lipídeos, incluindo epítopos de LDL na forma oxidada[22], facilitando sua incorporação a macrófagos através de receptores Fc e, consequentemente, promovendo a formação das estrias gordurosas vasculares[6].

Nessa mesma vertente, estudos recentes evidenciaram a associação da prevalência dos recém-descobertos anticorpos contra lipoproteína lipase (anti-LPL), presentes em cerca de 40% da população com LES, com elevados níveis séricos de triglicérides e interessantemente associados à proteína C-reativa de alta sensibilidade; sendo, isso, um presumível fator aterogênico presente nesse complexo[23,24].

### Hipertensão arterial

Seguindo na análise de outra importante associação clínica, sabe-se que a prevalência de hipertensão arterial nos pacientes com LES gira ao redor de 45%[25]. Essa associação aumentada pode ser explicada por dois mecanismos: 1) terapia amplamen-

te utilizada com uso de corticosteróide[25] e 2) doença renal crônica relacionada ao LES. A ação dos altos níveis séricos de angiotensina II presentes na hipertensão está implicada com aumento do risco cardiovascular e com o processo de aterosclerose pelos mecanismos: 1) estímulo ao crescimento das células musculares lisas vasculares, 2) aumento da atividade da lipoxigenase local com conseqüente oxidação do LDL, 3) aumento de propriedades pró-inflamatórias, 4) diminuição de formação de óxido nítrico, 5) aumento de adesividade de leucocitária, dentre outros[26].

### Dislipidemia

Sob o aspecto metabólico, o LES encerra grande associação com dislipidemia, cuja prevalência gira em torno de 70% na população com LES, figurando como um dos principais fatores prognósticos de eventos cardiovasculares[27-29]. Muito dessa alteração metabólica pode ser atribuída a: 1) própria atividade inflamatória do LES, com conseqüentes diminuições das HDL e apoproteína A-I e elevações nos níveis de LDL e triglicérides[1,27,28]; e 2) o emprego terapêutico de corticosteróides, que acarreta alteração lípide de padrão distinto: aumentos séricos de colesterol total, de LDL e de triglicérides[28]. Existe evidência de correlação entre a presença e o grau de dislipidemia com: 1) dose cumulativa de coticosteróide, 2) ausência de terapia anti-malárica e 3) tempo de doença ativa[29]. Ainda nesse conceito, o nosso grupo tem demonstrado um "padrão lúpico de dislipidemia", caracterizado por aumento dos triglicérides e VLDL e uma redução dos níveis de HDL-c[30,31], isso se devendo em parte a uma menor atividade da enzima chave do metabolismo lipídico – a lipoproteína lípase[32].

## Síndrome Metabólica

A forte associação da SM com a incidência de doenças ateroscleróticas levou a uma tentativa de reconhecimento e, conseqüentemente, ao delineamento de critérios para a mesma. Com esse intuito, a Organização Mundial da Saúde (OMS)[33] definiu que o individuo com SM deve apresentar resistência à insulina e dois ou mais dos seguintes parâmetros: 1) pressão arterial maior ou igual a 140/90mmHg; 2) nível de triglicérides plasmáticos maior ou igual a 150mg/dL e o de colesterol HDL menor que 35mg/dL em homens e 39mg/dL em mulheres; 3) obesidade, definida como relação cintura-quadril maior que 0,9 para homens e 0,80 para mulheres ou índice de massa corporal (IMC) maior que 30; e excreção urinária de albumina maior do que 30µg/min[34,35].

Contudo, esse rastreamento de indivíduos com maior risco não era prático. Existem vários métodos de quantificação da resistência à insulina, mas todos complexos e dispendiosos. O mais sensível, e considerado o padrão ouro, é o *clamp* hiperinsulinêmico-euglicêmico[36], que consiste na infusão constante de insulina, mantendo uma insulinemia de 100mU/L. A glicose administrada, necessária para manter a glicemia em níveis normais, é inversamente proporcional ao grau de resistência à insulina. De um modo semelhante tem-se a prova de supressão da insulina[37], em que o teste é o mesmo, mas se suprime a insulina endógena, diminuindo-se os riscos e gastos. O modelo mínimo[38] dosa a resposta da insulina perante uma sobrecarga endovenosa de glicose, aplicando-se a mesma em modelo matemático; é mais simples do que as anteriores, mas tem limitações[39]. Em estudos epidemiológicos, porém, têm-se usado a mensuração da insulina em jejum ou após duas horas de sobrecarga oral de glicose[40] ou, mais recente, um modelo homeostático (HOMA)[41] derivado das concentrações de glicemia e insulinemia em jejum.

Assim, em 2001, o painel de especialistas do Programa Nacional de Educação-Painel de Tratamento de Adultos (NCEP-ATPIII)[42] lançou uma identificação clínica da SM, definida então como estando presente três ou mais dos seguintes fatores: 1) obesidade abdominal, caracterizada como circunferência da cintura maior que 102 cm em homens e 88 cm em mulheres; 2) nível de triglicérides maior ou igual a 150mg/dL; 3) níveis de colesterol HDL menor que 40mg/dL em homens e menor que 50mg/dL em mulheres; 4) pressão arterial maior ou igual a 130x85mmHg e 5) glicemia de jejum maior ou igual a 110mg/dL.

A medida da circunferência abdominal é feita no meio da distância entre a crista ilíaca e o rebordo costal inferior. O ponto de corte para a cintura abdominal (102 e 88cm para homens e mulheres, respectivamente) tem sido questionado por não se adequar a populações de diferentes etnias[43] e já foi sugerido a sua redução para 94 e 80cm[44].

Recentemente a Federação Internacional da diabetes (IDF), Associação Americana do Coração/Instituto do Coração, Pulmão e Sangue dos Estados Unidos (AHA/NHLBI), Federação Mundial do Coração (WHF), Sociedade Internacional da Ate-

rosclerose (IAS), Associação dos Estudos da Obesidade (IASO) formularam um consenso sobre os valores de referencia para diagnóstico de SM. A medida da circunferência abdominal deve ser enquadrada para cada grupo étnico, para a America do Sul os valores estimados são maior ou igual a 90cm para homens e maior ou igual a 80cm para mulheres; nível de triglicérides maior ou igual a 150mg/dL (medicamento para hipertrigliceridemia também é indicador alternativo), níveis de colesterol HDL menor que 40mg/dL em homens e menor que 50mg/dL em mulheres (medicamento para colesterol HDL baixo é indicador alternativo), pressão arterial maior ou igual a 130x85mmHg (uso de antihipertensivo é indicador alternativo) e glicemia de jejum maior ou igual a 100mg/dL (uso de hipoglicemiantes é indicador alternativo)[45].

### Epidemiologia

Configura-se uma tarefa árdua averiguar a prevalência da SM na população normal, pois os vários artigos a respeito utilizam critérios diferentes; os mais comuns, o da OMS e o da NCEP-ATPIII, por vezes aparecem modificados. Em geral, entretanto, podemos dizer que ela varia de 5,5-55,4% na população geral[46-48]. Em populações não-caucasianas, as prevalências verificadas por essas duas definições diferem entre si[49]. Ao se utilizar como limite de corte da glicemia nos critérios diagnósticos da SM o valor de 100mg/dL – como foi recomendado pela *International Diabetes Federation* – a prevalência de glicemia de jejum alterada aumenta de 5,5% para 20,4%[47]. Se o teste de tolerância oral à glicose fosse incluído nos critérios da NCEP, a prevalência da SM aumentaria[50]. Quando ajustado à idade, a SM é vista mais freqüentemente nos homens[51].

Dentre os componentes da SM, obesidade central e baixa HDL são mais freqüentes nas mulheres; sendo que a hiperglicemia, hipertensão e hipertrigliceridemia, nos homens[52].

### Lúpus Eritematoso Sistêmico e Síndrome Metabólica

A prevalência da SM no LES varia em diversos estudos. Numa coorte de 102 de pacientes com LES pareados por idade e sexo com 101 controles saudáveis, a prevalência de SM foi significantemente maior que os controles pelos critérios da Organização Mundial de Saúde (OMS) (32,4% vs. 10,9%); entretanto, não atingiram significância pelos critérios da NCEP/ATPIII (29,4% vs. 19,8%). De forma interessante, os autores encontraram correlação positiva entre a presença de síndrome metabólica e altos valores de PCR, porém sem associação com os escores de atividade e cronicidade do lúpus[53].

Em um estudo brasileiro utilizando-se os critérios NCEP/ATPIII, os pacientes lúpicos apresentaram maior prevalência de síndrome metabólica e seus componentes individuais comparados com os controles (20 vs. 5,4%, p=0,03) e não esteve associada à duração da doença[54].

Avaliando-se 160 pacientes lúpicos de origem espanhola e 245 controles saudáveis, outro estudo encontrou uma freqüência similar de SM nessa população (20 vs. 13%, p=0,083), entretanto avaliando-se uma a população com 40 anos de idade ou menos, os autores encontraram essa associação (15,8 vs. 4,2%, p<0,001). Adicionalmente, o número de critérios de síndrome metabólica bem como a freqüência de doença cardiovascular foi significativamente maior nos pacientes do que nos controles. Os pacientes com SM apresentavam maiores valores de marcadores inflamatórios do que aqueles sem essa síndrome. Na análise multivariada, o nível educacional, triglicérides, HDL, níveis de C3 e uso de hidroxicloroquina foram independentemente associados com a síndrome metabólica[55].

O estudo de Bultink *et al.,* analisando 121 mulheres holandesas com lúpus, segundo os critérios NCEP/ATPIII, encontraram uma prevalência de 16% de SM. Esta freqüência foi, embora, comparável à população normal daquele país. Aquelas pacientes lúpicas com síndrome metabólica apresentaram uma maior freqüência de história de eventos cardiovasculares que aquelas sem essa síndrome[1].

A SM tem especial associação com idade avançada, maior tempo de duração de doença, vigência de atividade inflamatória, uso de prednisona e presença de insuficiência renal[1,8,9,54,56].

## Efeitos do tratamento sobre a SM no LES

Existem outros subsídios que alimentam a crença de interconexão da etiogênese de processos metabólicos que levam à aterosclerose e processos inflamatórios na prática clínica: 1) imunossupressores, como a ciclosporina, inibem a proliferação da musculatura lisa vascular[29], 2) a hidroxicloroquina, imunomodulador amplamente utilizado no tratamento do LES, pode reduzir o colesterol plasmático[57], 3) as estatinas, drogas utilizadas para contro-

le de lipemia, têm importante efeito anti-inflamatório[58,59], 4) a presença de critérios para SM associa-se fortemente à atividade do LES[8,9].

Uma nova visão acerca das alterações metabólicas e conseqüente doença vascular no LES devem ser adotadas vistos os novos conceitos imuno-metabólicos dos fatores de risco cardiovascular e da interface de congruência dos processos inflamatórios em ambos os processos: LES e SM. A importância e seriedade da abordagem do assunto são retratadas em diversos trabalhos recentes espalhados pelo mundo[1,8,9,54]. À medida que as complicações mais graves do LES são controladas com um arsenal terapêutico cada vez mais eficiente e poderoso, alterações antes vistas como secundárias, como as alterações metabólicas, entram na vanguarda da semiotécnica diagnóstica e passam a ocupar local de destaque na busca de um padrão mais mensurável e controlável.

Em vista disso, Manzi[6] sugere que parâmetros inflamatórios e imunológicos sejam inclusos na etiologia da doença cardiovascular juntamente com os parâmetros de risco tradicionais. Dessa forma, o controle agressivo da atividade do LES e a supressão de respostas inflamatórias da doença devem ser inclusos nos métodos de prevenção de eventos cardiovasculares juntamente com medidas que modifiquem a exposição a fatores de risco tradicionais.

No conjunto de pacientes com LES, a ocorrência concomitante de SM associa-se principalmente a: idade avançada, baixo índice sócio-econômico, falta de exercício, uso de doses elevadas de prednisona e atividade de doença (trombocitopenia, aumento de VHS, dor, *status* funcional)[8,9]. Dados brasileiros sugerem uma prevalência menor da SM na população com LES, comparando-se as populações americanas com LES[54], sugerindo uma provável influência de hábitos e estilo de vida e também das diferenças étnicas que alicerçam as díspares populações.

Em conclusão, fatores de risco tradicionais e não tradicionais para aterosclerose devem ser prontamente identificados e abordados terapeuticamente no intuito de um controle mais preciso tanto da atividade do LES como da exposição aos riscos a aterosclerose.

Esses novos conhecimentos sobre a participação ativa do LES nas alterações metabólicas correlatas podem agregar novos conceitos sobre patogênese e oferecer novas perspectivas para diagnóstico, tratamento e bem-estar dos doentes.

**Correspondência para**
Jozélio Freire de Carvalho
Disciplina de Reumatologia
Faculdade de Medicina da Universidade de São Paulo
Av. Dr. Arnaldo, 455, 3º andar,
Sala 3190, Cerqueira César
São Paulo-SP, CEP: 01246-903;
Fone/fax: 11-3061-7490
E-mail: jotafc@gmail.com

**Referências**

1. Bultink IE, Turkstra F, Diamant M, Dijkmans BA, Voskuyl AE. Prevalence of and risk factors for the metabolic syndrome in women with systemic lupus erythematosus. Clin Exp Rheumatol 2008;26:32-38.
2. Manzi S, Meilahn EN, Rairie JE, et al. Age-specific incidence rates of myocardial infarction and angina in women with systemic lupus erythematosus: comparison with the Framingham Study. Am J Epidemiol 1997;145:408-415.
3. Urowitz MB, Bookman AA, Koehler BE, Gordon DA, Smythe HA, Ogryzlo MA. The bimodal mortality pattern of systemic lupus erythematosus. Am J Med 1976;60:221-225.
4. Aranow C, Ginzler EM. Epidemiology of cardiovascular disease in systemic lupus erythematosus. Lupus 2000;9:166-169.
5. Petri M, Perez-Gutthann S, Spence D, Hochberg MC. Risk factors for coronary artery disease in patients with systemic lupus erythematosus. Am J Med 1992;93:513-519.
6. Manzi S. Systemic lupus erythematosus: a model for atherogenesis? Rheumatology (Oxford) 2000;39:353--359.
7. Ross R. The pathogenesis of atherosclerosis: a perspective for the 1990s. Nature 1993;362:801-809.
8. Negrón A, Molina M, Mayor A, Rodríguez V, Vilá L. Factors associated with metabolic syndrome in patients with systemic lupus erythematosus from Puerto Rico. Lupus 2008;17:348-354.
9. Zonana-Nacach A, Santana-Sahagún E, Jiménez-Balderas FJ, Camargo-Coronel A. Prevalence and factors associated with metabolic syndrome in patients with rheumatoid arthritis and systemic lupus erythematosus. J Clin Rheumatol 2008;14:74-77.
10. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. N Engl J Med 1997;336:973-979. [Erratum, N Engl J Med 1997;337:356].
11. Stary HC, Chandler AB, Glagov S, et al. A definition of initial, fatty streak, and intermediate lesions of atherosclerosis: a report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association. Circulation 1994;89: 2462-2478.
12. Napoli C, D'Armiento FP, Mancini FP, et al. Fatty streak formation occurs in human fetal aortas and is greatly enhanced by maternal hypercholesterolemia:

intimal accumulation of low density lipoprotein and its oxidation precede monocyte recruitment into early atherosclerotic lesions. J Clin Invest 1997;100:2680--2690.
13. Ridker PM, Buring JE, Shih J, Matias M, Hennekens CH. Prospective study of C-reactive protein and the risk of future cardiovascular events among apparently healthy women. Circulation 1998;98:731-733.
14. Ridker PM, Hennekens CH, Roitman-Johnson B, Stampfer MJ, Allen J. Plasma concentration of soluble intercellular adhesion molecule 1 and risks of future myocardial infarction in apparently healthy men. Lancet 1998;351:88-92.
15. Schönbeck U, Varo N, Libby P, Buring J, Ridker PM. Soluble CD40L and cardiovascular risk in women. Circulation 2001; 104: 2266-2268.
16. Wysocki J, Skoczynski S, Strozik A, Hochul B, Zygula M. Metabolic or immunometabolic syndrome? Wiad Lek 2005;58:124-127.
17. Wisse BE. The inflammatory syndrome: the role of adipose tissue cytokines in metabolic disorders linked to obesity. J Am Soc Nephrol 2004;15:792-800.
18. Duncan BB, Schmidt MI. Chronic activation of the innate immune system may underlie the metabolic syndrome. Sao Paulo Med J 2001;119:122-127.
19. Galtier-Dereure F, Biron C, Vies M, Bourgeois V, Schved JF, Bringer J. Vascular complications of diabetes mellitus: what role for phospholipid-binding antibodies? Lupus1998;7:469-474.
20. Wu R, Nityanand S, Berglund L, Lithell H, Holm G, Lefvert AK. Antibodies against cardiolipin and oxidatively modified LDL in 50-year-old men predict myocardial infarction. Arterioscler Thromb Vasc Biol 1997;17:3159-3163.
21. Vaarala O, Mänttäri M, Manninen V, et al. Anti-cardiolipin antibodies and risk of myocardial infarction in a prospective cohort of middle-aged men. Circulation 1995;91:23-27.
22. Witztum JL. The oxidation hypothesis of atherosclerosis. Lancet 1994;344:793-795.
23. Reichlin M, Fesmire J, Quintero-Del-Rio AI, Wolfson-Reichlin M. Autoantibodies to lipoprotein lipase and dyslipidemia in systemic lupus erythematosus. Arthritis Rheum 2002;46:2957-2963.
24. de Carvalho JF, Borba EF, Viana VS, Bueno C, Leon EP, Bonfa E. Anti-lipoprotein lipase antibodies: a new player in the complex atherosclerotic process in systemic lupus erythematosus? Arthritis Rheum 2004;50:3610-3615.
25. Doria A, Shoenfeld Y, Wu R, et al. Risk factors for subclinical atherosclerosis in a prospective cohort of patients with systemic lupus erythematosus. Ann Rheum Dis 2003;62:1071-1077.
26. Ross R. Atherosclerosis--an inflammatory disease. Engl J Med 1999;340:115-126.
27. Borba EF, Bonfa E. Dyslipoproteinemias in systemic lupus erythematosus: influence of disease, activity, and anticardiolipin antibodies. Lupus 1997;6:533--539.
28. Ilowite NT, Samuel P, Ginzler E, Jacobson MS. Dyslipoproteinemia in pediatric systemic lupus erythematosus. Arthritis Rheum 1988;31:859-863.
29. Bruce IN, Urowitz MB, Gladman DD, Hallett DC. Natural history of hypercholesterolemia in systemic lupus erythematosus. J Rheumatol 1999;26:2137--2143.
30. de Carvalho JF, Bonfá E, Borba EF. Systemic lupus erythematosus and "lúpus dyslipoproteinemia". Autoimmun Rev 2008;7:246-250.
31. Borba EF, Carvalho JF, Bonfá E. Mechanisms of dyslipoproteinemias in systemic lupus erythematosus. Clin Dev Immunol 2006;13:203-208.
32. de Carvalho JF, Borba EF, Viana VS, Bueno C, Leon EP, Bonfá E. Anti-lipoprotein lipase antibodies: a new player in the complex atherosclerotic process in systemic lupus erythematosus? Arthritis Rheum 2004;50:3610-3615.
33. WHO consultations: Definition, diagnosis and classification of diabetes mellitus and its complications. WHO/NCD/NCS/992:31-33.
34. Lopes HF. Síndrome Metabólica: aspectos históricos, prevalência, e morbidade e mortalidade. Rev Soc Cardiol 2004; 4:539-543.
35. Alberti RG. Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med 1998; 15:539-553.
36. DeFronzo RA, Tobin JD, Andres R. Glucose clamp technique: a method for quantifying insulin secretion and resistance. Am J Physiol 1979;237:E214-223.
37. Harano Y, Ohgaku S, Hidaka H, et al. Glucose, insulin and somatostatin infusion for the determination of insulin sensitivity. J Clin Endocrinol Metab 1977;45: 1124-1127.
38. Bergman RN, Ider YZ, Bowden CR, Cobelli C. Quantitative estimation of insulin sensitivity. Am J Physiol 1979;236:E667-677.
39. Caumo A, Vicini P, Cobelli C. Is the minimal model too minimal? Diabetologia 1996;39:997-1000.
40. Laakso M. How good a marker is insulin level for insulin resistance? Am J Epidemiol 1993;137:959-965.
41. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412-419.
42. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). Jama 2001;285:2486-2497.
43. World Health Organisation, Western Pacific Region, The Asia-Pacific Perspective. Redefining Obesity and its Treatment, WHO/IASO/IOTF (2000).
44. Lean ME, Han TS, Morrison CE. Waist circumference as a measure for indicating need for weight management. Bmj 1995;311:158-161.

45. Alberti KGMM, Eckel RH, Scott M, et al. Harmonizing the Metabolic Syndrome: A Joint Interim Statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 2009;120; 1640-1645.
46. Wannamethee SG, Lowe GD, Shaper AG, Rumley A, Lennon L, Whincup PH. The metabolic syndrome and insulin resistance: relationship to haemostatic and inflammatory markers in older non-diabetic men. Atherosclerosis 2005;181:101-108.
47. Ford ES, Abbasi F, Reaven GM. Prevalence of insulin resistance and the metabolic syndrome with alternative definitions of impaired fasting glucose. Atherosclerosis 2005;181:143-148.
48. Rosenbaum P, Gimeno SG, Sanudo A, Franco LJ, Ferreira SR. Analysis of criteria for metabolic syndrome in a population-based study of Japanese-Brazilians. Diabetes Obes Metab 2005;7:352-359.
49. Aguilar-Salinas CA, Rojas R, Gomez-Perez FJ, et al. The metabolic syndrome: a concept hard to define. Arch Med Res 2005;36:223-231.
50. Rodriguez A, Muller DC, Engelhardt M, Andres R. Contribution of impaired glucose tolerance in subjects with the metabolic syndrome: Baltimore Longitudinal Study of Aging. Metabolism 2005;54:542-547.
51. Ishizaka N, Ishizaka Y, Toda E, Hashimoto H, Nagai R, Yamakado M. Hypertension is the most common component of metabolic syndrome and the greatest contributor to carotid arteriosclerosis in apparently healthy Japanese individuals. Hypertens Res 2005;28:27-34.
52. Bo S, Gentile L, Ciccone G, et al. The metabolic syndrome and high C-reactive protein: prevalence and differences by sex in a southern-European population-based cohort. Diabetes Metab Res Rev 2005;21:515-524.
53. Chung CP, Avalos I, Oeser A, et al High prevalence of the metabolic syndrome in patients with systemic lupus erythematosus: association with disease characteristics and cardiovascular risk factors. Ann Rheum Dis 2006; 66: 208-214.
54. Azevedo GD, Gadelha RG, Vilar MJ. Metabolic syndrome in systemic lupus erythematosus: lower prevalence in Brazil than in the USA. Ann Rheum Dis 2007;66:1542.
55. Sabio J, Zamora-Pasadas M, Jiménez-JáimezMEZ J, et al. Metabolic syndrome in patients with systemic lupus erythematosus from Southern Spain. Lupus 2008; 17: 849-859.
56. Pereira RM, de Carvalho JF, Bonfá E. Metabolic syndrome in rheumatological diseases. Autoimmun Rev 2009; 8:415-419.
57. Petri M, Lakatta C, Magder L, Goldman D. Effect of prednisone and hydroxychloroquine on coronary artery disease risk factors in systemic lupus erythematosus: a longitudinal data analysis. Am J Med 1994;96:254-259.
58. Takemoto M, Liao JK. Pleiotropic effects of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors. Arterioscler Thromb Vasc Biol 2001;21:1712--1719.
59. Crisby M, Nordin-Fredriksson G, Shah PK, Yano J, Zhu J, Nilsson J. Pravastatin treatment increases collagen content and decreases lipid content, inflammation, metalloproteinases, and cell death in human carotid plaques: implications for plaque stabilization. Circulation 2001;103:926-933.

# TOCILIZUMAB – A NEW STEP IN RHEUMATOID ARTHRITIS TREATMENT

Brandão F*, Coelho P**, Pinto P***, Combe B****

## Abstract

Rheumatoid Arthritis is a chronic systemic inflammatory disease characterized by joint pain, stiffness and swelling, with progressive destruction of small joints of the hands and feet.

Methotrexate remains the most commonly used therapy and has been the recommended standard against which new drugs should be evaluated and, to date, there is limited evidence that monotherapy with other treatments is superior to MTX.

The introduction of biologic agents, such as TNFα–antagonists, represented an advance in the treatment of RA. However, there are still patients with no or inadequate response, patients in whom responsiveness to treatment is lost over time, and patients in whom safety issues may develop.

Thus, patients may benefit from treatment with newer biologic agents with a different mechanism of action.

Tocilizumab is an IL-6 receptor inhibitor which shows significant (and rapid) clinical efficacy in the treatment of Rheumatoid Arthritis patients, as assessed by ACR responses and DAS remission rates, with an acceptable safety profile.

**Keywords:** Tocilizumab; Rheumatoid Arthritis; Remission; IL-6.

## Introduction

Rheumatoid Arthritis (RA) is a chronic systemic autoimmune inflammatory disease affecting approximately 0.5-1% of the population[1]. It is characterized by joint pain, stiffness and swelling due to synovial inflammation, with progressive destruction of the small joints of the hands and feet, accompanied by limitations (or loss) of physical function, fatigue, anemia, increased risk for osteoporosis and coronary heart disease, progressive disability and increased morbidity and mortality[2,3]. Although the exact cause of the disease is still unknown, insights into its pathogenesis have confirmed the role of pro-inflammatory cytokines – e.g. tumor necrosis factor α (TNF-α), interleukin-1 and interleukin-6 – in disease pathways[4,5].

Rheumatoid Arthritis is often treated with disease-modifying anti-rheumatoid drugs (DMARDs) that relieve inflammatory processes and can slow disease progression[6]. Although methotrexate (MTX) is the most commonly used DMARD, other drugs such as leflunomide, sulfasalazine, and antimalarials, alone or in combination with MTX, are used[4]. For patients with an inadequate response to conventional DMARDs, biologic agents that inhibit the action of cytokines (e.g. tumor necrosis factor α and interleukin-1) or limit B-cell function or T-cell co-stimulation, especially in combination with MTX, are indicated[4,7-10]. Moreover, in some situations, they are even indicated prior to DMARDs.

Despite the efficacy of these agents, none of them leads to response in all patients, and even among the patients that respond the improvement is sometimes limited[4,11,12], as a substantial proportion of patients continue to have active synovitis and/or systemic symptoms or fail to maintain clinical benefit from these therapies[6,10,13-15].

Furthermore, with TNF inhibitors (alone or in combination with DMARDs) 20-40% of RA patients show inadequate response[16].

## Interleukin-6 and Rheumatoid Arthritis

An alternative target for RA treatment is inter-

*Rheumatology Department, S. João Hospital, Oporto-Portugal
**Rheumatology Department, Portuguese Rheumatology Institut, Lisbon-Portugal
***Rheumatology Unit, V. N. Gaia/Espinho Hospital, V. N. Gaia-Portugal
****Rheumatology Department, Lapeyronie Hospital, Montpellier I – University Montpellier, France

leukin-6, a pleiotropic pro-inflammatory cytokine (IL-6) produced by a variety of cell types including lymphocytes, monocytes, and fibroblasts. It affects the function of neutrophils, T-cells, B-cells, monocytes and osteoclasts - cells that are highly activated in RA – and is involved in diverse immunologic physiological and pathological processes, such as T-cell activation, B-cell proliferation, and stimulation of hematopoietic precursor cell growth, differentiation, and trafficking[17,18].

In the joint, IL-6 perpetuates chronic inflammation and autoimmunity via activation of neutrophils, B-cells and T-cells. Synoviocytes are potent sources of this cytokine and produce vascular endothelial growth factor (VEGF) that may contribute to development of pannus[19]. This granulation tissue is associated with deterioration of joint surface and releases tissue degrading enzymes, like metalloproteinases that cause joint destruction.

It is also the major inducer of the hepatic acute-phase response, which is also a key feature of RA that is correlated with disease activity and joint destruction[20-22]. IL-6 stimulates hepatocytes to produce C-reactive protein (CRP), fibrinogen, haptoglobin and serum amyloid (SAA)[23]. Concurrently, it induces the secretion of the liver hormone pepcidin, which regulates iron metabolism, inhibiting intestinal absorption and impairing its release from macrophages, thus decreasing the iron available for erythropoiesis[24].

Interleukin-6 cell signaling is mediated by binding to the IL-6 receptor (CD126, IL-6R α), which is expressed on cell surfaces and as a circulating soluble form. In order to transduce a signal, the IL-6/IL-6R complex must also bind with a ubiquitous trans-membrane protein – glycoprotein 130 (gp130) to activate transcription[25,26].

Of particular relevance to RA, IL-6 induces osteoclast differentiation, contributing to joint destruction, bone resorption and osteoporosis[18].

Chronic joint inflammation in RA leads to the production of IL-6 and its receptor (IL-6R), which is expressed on effector cells that cause and prolong inflammation. Interleukin-6 is over-expressed in synovial tissue in patients with Rheumatoid Arthritis, with raised concentrations in serum and synovial fluid[27,28].

IL-6 knockout mice have been shown to be protected from developing joint symptoms in an arthritis model in vivo[29,30] and we also know that elevated serum and synovial fluid IL-6 levels correlate with disease activity in patients with RA[31,32].

Thus, overall, targeting interleukin-6 seems an attractive therapeutic option in this disease, since it has a pivotal role in mediating inflammation, auto-antibody production, joint destruction and also systemic manifestations of RA[33], and some studies suggest that it is the most abundant cytokine in joints and serum of RA patients and its levels are correlated with disease activity[34].

## Tocilizumab – Clinical Trials in RA

Tocilizumab has been evaluated in several randomized controlled clinical trials, but here we describe only five of the most important, in which it was studied for its efficacy (and safety) in RA patients: OPTION, TOWARD, AMBITION, RADIATE and LITHE.

### Methods

#### Patients

Adult (≥ 18 years) patients with moderate-to-severe RA of more than six (≥ 3 in the AMBITION study) months' duration, diagnosed according to the American College of Rheumatology (ACR) 1987 revised criteria for the classification of RA.

At baseline, active disease was defined by a swollen joint count of six (of 66) or more plus a tender joint count of eight (of 68) or more and C-reactive protein over 1 mg/dl or Erythrocyte Sedimentation Rate (ESR) of 28 mm/h or more.

Oral corticosteroids (≤10 mg/day prednisone or equivalent) and non-steroidal anti-inflammatory drugs (NSAIDs/cyclooxygenase-2 inhibitors were permitted if the doses were stable for ≥ 6 weeks before inclusion).

To minimize MTX-related toxicity, all patients received a stable dose of folic acid (≥ 5 mg/week).

Main exclusion criteria were other autoimmune diseases or significant systemic involvement secondary to RA (eg, vasculitis, pulmonary fibrosis, or Felty's syndrome), functional class IV Rheumatoid Arthritis, previous or current inflammatory joint disease other than RA, currently active or previous recurrent bacterial, viral, fungal, or other infections including, but not limited to, tuberculosis and atypical mycobacterial disease, clinically significant abnormalities on chest x-rays, hepatitis B and C, and recurrent herpes zoster. Patients were also excluded if they had active liver disease (indicated by screening and baseline concentrations of aminotransferases of 1-5 times the upper limit of

normal or more), history of malignancies, cytopenias, immunodeficiency (primary or secondary) and treatment with cell depleting agents. Tuberculosis screening was managed according to local practice.

#### Efficacy Endpoints

The primary efficacy endpoint was the proportion of patients who had achieved a response according to the ACR criteria for 20% improvement (ACR20) at week 24[43]. Secondary efficacy endpoints included the proportion of patients with an ACR50 and ACR70 responses, and the time to onset of ACR20/50/70 responses. Changes from baseline at week 24 in disease activity score (DAS28) were also evaluated. The proportion of patients in clinical remission (DAS28 < 2.6), with low disease activity (DAS28 ≤ 3.2), and with EULAR good/moderate responses were assessed[44,45]. Hemoglobin concentrations were also assessed. Improvement in physical function was assessed by change from baseline at week 24 in Health Assessment Questionnaire-Disability Index (HAQ-DI). Medical Outcomes Study 36 – Item Short-Form General Health Survey (SF36)[46], and Functional Assessment of Chronic Illness Therapy (FACIT) – Fatigue assessment[47,48], done at baseline and week 24, were used to assess health-related quality-of-life.

#### Safety Assessments

Patients were monitored for adverse events (AEs), serious AEs, infections, infusion reactions, withdrawals due to AEs, deaths, and clinically significant changes in vital signs and laboratory tests.

#### Study drug and dose selection

Study drug was Tocilizumab at a dose of 4 mg/kg and/or 8 mg/kg versus placebo administered in a blinded manner, intravenously as a 60-minute infusion every 4 weeks. Dose selection was based on results of the phase II CHARISMA study[49].

#### Statistical analysis

The primary efficacy analysis was done on the intention-to-treat population (ITT) – i.e., all patients randomized who received at least one infusion of study drug – except in AMBITION study were it was done *per protocol* (PP). Safety analysis included all randomized patients who received at least one infusion of study medication and who had at least one assessment of safety after randomization. Patients that withdrew before week 24, who received rescue therapy and whose data were insufficient to determine endpoints, were classified as non-responders for the ACR20, 50, 70 and EULAR endpoints.

### OPTION (tOcilizumab Pivotal Trial in methotrexate Inadequate respONders) study[50]

This study was designed to assess efficacy (and safety) of TCZ (either 4 or 8 mg/kg) plus MTX, compared with MTX monotherapy, in RA patients with inadequately response to a stable dose of MTX.

A 24-week, phase III, three arm, randomized, double-blind, placebo-controlled, parallel group study involving patients with RA and inadequate response to MTX for 12 weeks or longer and a stable dose for at least 8 weeks (10 to 25 mg/week).

Patients were randomized to receive placebo, TCZ 4 mg/kg or TCZ 8 mg/kg intravenously every 4 weeks, in combination with weekly stable dose of MTX. All other DMARDs were discontinued before the start of the study, in each case respecting the half-life period for effective washout.

Patients who had not achieved at least 20% improvement in both swollen joint count (SJC) and tender joint count (TJC) by week 16 were eligible for rescue therapy with TCZ 8 mg/kg and, if necessary, intra-articular steroids or an increase in oral corticosteroid dose (maximum 10 mg/day).

The study included 622 patients, in the ITT population, and their baseline characteristics and disease activity were similar in all three groups.

#### Results

More patients in the TCZ 4 mg/kg group than in the 8 mg/kg group or the placebo group withdrew prematurely from the study, and, overall, the major reasons for withdrawal were AEs, insufficient response and refusal of treatment.

By week 24, ACR20, ACR50 and ACR70 responses (59%, 44% and 22% in the TCZ 8 mg/kg group, respectively; 48%, 31% and 12% in the TCZ 4 mg/Kg group, respectively) were significantly more frequent in patients receiving TCZ than in those receiving placebo (26%, 11% and 2%, respectively; $p<0.0001$), for both individual TCZ groups. A clear difference between the placebo and the TCZ 8 mg/kg group was observed at week 2 for ACR20, at week 4 for ACR50 and at week 8 for ACR70. Significantly superior responses in all variables, including DAS28, were seen with both doses of TCZ versus placebo. DAS28 decreased rapidly with TCZ therapy (two weeks) and DAS28 remission was sig-

nificantly more frequent in the TCZ groups than the placebo group at week 24 (27%, 13% vs. 0.8%, in the TCZ 8 mg/kg and 4 mg/kg vs. placebo groups, respectively). Moreover, 79% of the TCZ 8 mg/kg group had good or moderate EULAR responses.

Mean CRP concentrations normalized by week 2 and remained stable until week 24 of treatment with TCZ 8 mg/kg, but not in the 4 mg/kg group, where the decrease was less evident and not so stable over the 24 weeks. ESR normalized with TCZ 8 mg/kg but not in the 4 mg/kg group.

Mean hemoglobin concentrations increased from baseline by 4 weeks in both TCZ groups and continued to increase until week 24. By contrast, those concentrations did not change in the placebo group during the study.

There were significant greater improvements from baseline in physical function and fatigue with both doses of TCZ, as judged by HAQ-DI, FACIT-Fatigue and SF36 scores.

### TOWARD (Tocilizumab in cOmbination With traditional DMARD) study[51]

This study was aimed to evaluate efficacy (and safety) of TCZ in combination with a range of DMARDs in RA patients who had inadequate response to at least one conventional DMARD at a stable dose.

It's a 24-week, phase III, randomized, double-blind, placebo-controlled study involving RA patients which had received stable doses of DMARDs (methotrexate, chloroquine, hydroxychloroquine, parenteral gold, sulfasalazine, azathioprine or leflunomide) for ≥ 8 weeks prior to study entry.

1220 patients were randomized in a 2:1 ratio to receive either 8 mg/kg of TCZ or placebo, intravenously every 4 weeks, combined with their stable dose of DMARD therapy.

Patients who were unsuccessfully treated with an anti-TNF agent or were previously treated with any cell-depleting therapy were excluded.

Patients who failed to achieve ≥ 20% improvement in both the SJC and the TJC by week 16 could receive rescue therapy consisting of adjustment of the background DMARD dosage and/or a different DMARD, and/or intra-articular/oral corticosteroid. Such patients were non-responders for the analysis of ACR20, 50, 70 and EULAR responses endpoints but remained under study.

The study included 1220 patients, in the ITT population, and the two groups were well balanced with respect to baseline demographics, disease characteristics, and concomitant DMARD, corticosteroid and NSAID use.

#### RESULTS

During the study, 96 patients withdrew from initial treatment, 40 of these due to safety reasons. Overall, 76% of patients were treated with 1 DMARD, 23% were treated with ≥ 2 DMARDs and the most commonly used was methotrexate (mean dosage 15 mg/week). The proportion of patients that completed the study, including those who switched to rescue therapy, was higher in the TCZ group.

By week 24, the proportion of ACR20, ACR50 and ACR70 responders was significantly higher in the TCZ group (61%, 38% and 21%, respectively) than in the placebo group (25%, 9% and 3%, respectively; $p<0.0001$). A clear difference in both the ACR20 and ACR50 responses between the TCZ and placebo groups was apparent at week 2, and by week 4 for the ACR70 response. The mean DAS28 improved incrementally over time and, by week 24, mean changes from baseline were greater in the TCZ group than the placebo group. Rates of DAS28 remission responses were also higher in the TCZ group than the placebo group (30% vs. 3%; $p< 0.0001$).

Moreover, 45% of patients in the TCZ group experienced low disease activity (DAS28 ≤ 3.2) and 80% had a good or moderate EULAR response.

The levels of inflammation markers (CRP and ESR) decreased significantly in the TCZ group by week 24, with normalization of mean CRP levels as early as week 2.

Mean hemoglobin levels also increased at week 2, with incremental improvement over time in patients with TCZ until week 24. In contrast, the placebo group showed no change in these levels.

There were greater improvements from baseline in physical function and fatigue with the TCZ group than the placebo group, as assessed by HAQ-DI, FACIT-Fatigue and SF36 scores.

### AMBITION (Actemra versus Methotrexate double-Blind Investigative Trial In mONotherapy) study[52]

This non-inferiority study was designed to assess the efficacy (and safety) of TCZ 8 mg/kg monotherapy compared to methotrexate monotherapy in active RA patients who had not previously failed MTX or biologics treatment.

This 24-week, double-blind, parallel-group

study, randomized patients to either TCZ 8 mg/kg intravenously every 4 weeks, or to MTX oral capsules, weekly (escalating dose regimen: initial 7.5 mg, increasing to 15 mg at week 4 and to 20 mg at week 8). Methotrexate dose reduction to 10 mg weekly was permitted for safety reasons.

Patients were excluded if they had been unsuccessfully treated with an anti-TNF agent, had received MTX in the 6 months preceding randomization or discontinued previous MTX treatment because of clinically important adverse effects or lack of efficacy.

Patients who had temporarily discontinued MTX treatment due to side effects or desired to become pregnant and those who discontinued anti-TNF treatment for reasons other than efficacy (e.g. cost, side effects) could be included in the study.

A total of 673 patients were randomized into the study and most completed 24 weeks' treatment. General demographic and baseline characteristics were well balanced. The majority of patients were MTX-naïve (67% per arm) with mean disease duration of 5 years. The mean weekly MTX dose over 24 weeks was 15.5 mg, with 74% of patients attaining 20 mg weekly at week 8.

**RESULTS**

After establishing non-inferiority in the PP population (ACR20 at week 24, 71% TCZ vs. 52% MTX), TCZ was confirmed as superior to MTX using the ITT population ($p<0.0001$). Furthermore, TCZ was superior to placebo at week 8. The proportion of ACR50 (44% TCZ vs. 33% MTX) and ACR70 (28% TCZ vs. 15% MTX) responders at week 24 was also statistically superior for TCZ ($p=0.0023$ and $p=0.0002$, respectively).

The proportion of patients in remission at week 24 (DAS28 remission 34% TCZ vs. 12% MTX) was greater in the TCZ group, and TCZ patients were over 5-times more likely to achieve DAS28 remission (odds ratio [95% CI]: 5.8 [3.3, 10.4]).

A clear difference in ACR20 response rate between TCZ and MTX was seen as early as week 2, with the difference between the groups increasing over time. Compared with MTX, ACR50 and ACR70 responses were consistently observed in more TCZ-treated patients from week 4 and week 8 onwards.

A greater improvement in physical function and health-related quality of life was also reflected by the higher mean changes from baseline in HAQ-DI, FACIT-Fatigue and SF36, with TCZ.

Notably, mean CRP levels were within normal range as early as week 2 with TCZ, as well as the improvement in hemoglobin concentrations.

### RADIATE (Research on Actemra Determinig efficacy after Anti-TNF failurEs) study[53]

This study examined the efficacy (and safety) of TCZ (with MTX) in patients with active RA who had failed (or had intolerance to) at least one TNF-antagonist.

This 24-week, phase III, double-blind, placebo-controlled, parallel group study, randomized 499 patients to TCZ 8 mg/kg or 4 mg/kg, or placebo intravenously every 4 weeks (controls). All patients received a stable dose of MTX for 24 weeks and no other DMARDs were allowed.

Patients discontinued etanercept (≥2 weeks), infliximab or adalimumab (≥8 weeks), leflunomide (≥12 weeks) and all DMARDs other than MTX before receiving study medication, and had to be treated with MTX for ≥ 12 weeks prior to baseline (stable dose ≥ 8 weeks).

Rescue therapy of 8 mg/kg TCZ + MTX was offered at week 16 in all cases of treatment failure (<20% improvement in both SJC and TJC).

The three groups were reasonably well-balanced for demographics and RA characteristics at baseline.

**RESULTS**

TCZ treatments showed superior benefits to diminish RA signs and symptoms after a 24-week therapy. At week 24, patients treated with 8 mg/kg of TCZ + MTX achieved significant improvement assessed by ACR20 responses (50% vs. 30.4% and 10.1%, in the 4 mg/kg and placebo groups, respectively), compared to the placebo group ($p<0.0001$). DAS28 remission rates at 24 weeks were 30.1%, 7.6%, and 1.6% in the 8 mg/kg, 4 mg/kg, and control groups, respectively ($p=0.0001$ – 8 mg/kg; $p=0.053$ – 4 mg/ /kg both vs. control). Patients responded similarly regardless of most-recently failed anti-TNF or the number of failed treatments.

Responses to 8 mg/kg TCZ + MTX were noticeable after 2-4 weeks of treatment and progressively improved until the end of the study.

Health-related quality of life was also better in a higher proportion of patients treated with TCZ + MTX.

By week 24, there were concomitant reductions of CRP and ESR, and elevations of hemoglobin levels, with both TCZ doses starting as early as week 2.

### LITHE (TociLIzumab Safety and THE Prevention of Structural Joint Damage) study[54]

This study was aimed at assessing the efficacy (and safety) of TCZ in the inhibition of structural joint damage in RA patients with inadequate response to a stable dose of MTX.

This 2-year, phase III, double-blind, placebo-controlled, randomized 1196 patients into three arms to receive TCZ (either 4 or 8 mg/kg) or placebo, intravenously every 4 weeks, plus MTX weekly (10-25 mg).

From the second year, patients were receiving an open-label treatment with 8 mg/kg TCZ plus MTX, except for those patients achieving a ≥ 70% improvement from baseline in SJC and TJC at two consecutive visits, who had the option to continue their blinded randomized therapy until the end of year 2.

A switch to blinded rescue treatment (TCZ 8 mg/ /kg) was available at weeks 16 and 28 for patients who had not achieved at least 20% improvement in both swollen joint count and tender joint count.

Patients received MTX as a single DMARD for at least 12 weeks (last 8 weeks prior to baseline at a stable dose – 10 to 25 mg/week) and all other DMARDs were withdrawn prior to randomization. Patients could have been treated with TNF-antagonists (terminated due to cost or discomfort with the subcutaneous injections), but not have failed due to lack or loss of efficacy.

Another inclusion parameter was radiographic evidence of at least 1 joint with an erosion typical of RA.

Beyond ACR20 response at 24 weeks, the primary endpoints also included changes from baseline in Genant-modified Sharp score (linear extrapolation for missing data) and the area under the curve (AUC) in HAQ-DI (standardization for missing data), at week 52.

Additionally, these structural and functional changes were assessed again at the end of year 2.

The analysis population (ITT) included 1196 randomized patients, and the baseline demographics and disease activity were similar in the three groups.

#### Results

After 24 weeks of treatment, TCZ (8 mg/kg) plus MTX significantly reduced signs and symptoms, compared with MTX monotherapy, assessed by ACR responses (ACR20 57% vs. 27%; ACR50 32% vs. 10%; ACR70 13% vs. 2%, respectively; p<0.0001).

At year 1, mean changes from baseline in total Genant-modified Sharp score was significantly lower in patients treated with both doses of TCZ plus MTX (inhibition of radiographic progression compared to control was 74% in the 8 mg/kg group) indicating a significant delay in the progression of structural joints damage.

By 52 weeks, DAS28 remission rates were significantly higher in the TCZ 8 mg/kg group (47.2% vs. 30.2% and 7.9% in the 4 mg/kg and placebo groups, respectively) compared with control (p<0.0001), and low disease activity rates were significantly higher with both TCZ groups.

By week 52, the mean AUC of the change from baseline in HAQ-DI significantly decreased in TCZ-treated patients compared with control (p<0.0001).

More patients treated with MTX monotherapy (50%) required rescue therapy, compared with the 8 and 4 mg/kg TCZ + MTX groups (15 and 24%, respectively), and withdrawals were also higher in this group.

### SAFETY

The overall incidence of AEs was similar in all (TCZ and placebo) groups in the AMBITION and in the RADIATE studies, and most were mild to moderate. In the other three trials, the incidence of AEs was higher in the TCZ groups.

The incidence of serious AEs was similar in the OPTION and in the AMBITION studies.

In the particular case of the RADIATE study, there was no obvious influence of prior type or number of TNF-antagonist treatments, and there were more serious AEs in the control group than in the TCZ treatments groups, primarily related to RA complications.

The most common AEs were infections, with upper respiratory tract, skin and subcutaneous tissue infections being the most frequently reported. There were no cases of tuberculosis detected.

Infusions were generally well tolerated, with minor incidences of nausea, rash or hypertension occurring during or within 24 hours of infusion. In spite of that, some patients had to discontinue the treatment because of hypersensitivity reactions.

The most frequent detected laboratory abnormalities in the TCZ groups were all transient.

A higher proportion of patients in the TCZ groups had a reversible decrease in the neutrophil count, but there was no association with the occurrence of infection-related AEs.

More patients in the TCZ groups had an increa-

se in the aminotransferase levels, however no concurrent increase in total bilirubin or alkaline phosphatase, and no clinical signs of hepatitis or hepatic dysfunction were detected.

Total cholesterol and LDL elevations were observed in more patients in the TCZ groups, but there was no evidence of an increased risk of cardiovascular events, and on average LDL lowered or stabilized with statins.

At 1 year, in the LITHE study, the safety profile was consistent with the other studies and did not change from 6 to 12 months.

## Discussion

The data on these five trials provide evidence that inhibition of interleukin-6 pro-inflammatory effects significantly and rapidly improves the signs and symptoms of RA.

Thus, Tocilizumab is an effective agent for the treatment of patients with moderate to severe Rheumatoid Arthritis.

Methotrexate remains the most commonly used therapy and has been the recommended standard against which new drugs should be evaluated and, until recently, there was limited evidence that monotherapy with other treatments is superior to MTX.

The AMBITION study demonstrated superior efficacy of TCZ monotherapy over MTX monotherapy regardless of previous MTX exposure.

It is very difficult to compare results across clinical trials due to different patient populations with varying prior treatment and disease history, however, considering results of other trials comparing anti-TNF agents with MTX, it appears that TCZ is the first biologic treatment to show statistically significant clinical efficacy using standard endpoints, compared with a standard MTX dose regimen in a 6-month study (AMBITION).

Moreover, about 30% (27 to 34%, depending on the trial) of patients treated with TCZ 8 mg/kg achieved DAS28 remission by 24 weeks, so TCZ demonstrates consistent results in achieving the goal of remission in RA patients.

In the LITHE study, at 1 year, 8 mg/kg of TCZ demonstrated 47% of DAS28 remission rates, which suggests an improved response for TCZ treatment compared to placebo (8%; $p<0.0001$).

We should expect that the long-term extension of these studies - currently ongoing - will clarify on that.

Furthermore, impairment of physical function and health-related quality of life, as well as fatigue (a major debilitating factor in RA), were all improved more with TCZ than with placebo, reflecting substantial functional benefits for the patients.

Rapid and sustained improvements in the acute-phase response markers (the CRP and ESR levels), as well as in hemoglobin concentrations (low levels indicative of severe chronic inflammation), were seen especially with TCZ 8 mg/kg, suggesting a reduction in the severity of systemic inflammation, besides the improvement of synovitis. Particularly in the AMBITION study, TCZ was associated with anemia correction, an effect not seen with MTX in this study.

Clinically relevant improvements with TCZ (DAS28 remission rates and ACR responses) were apparent as early as week 2 to 4, after treatment initiation, and were maintained or further improved over the treatment period (24 weeks), with the dose of 8 mg/kg providing the more rapid, frequent and robust therapeutic effect.

Finally, in the interim analysis of the LITHE study, at 1 year, TCZ therapy significantly inhibited the progression of structural joint damage.

The overall incidence of AEs was very similar (or somewhat higher in the TCZ groups) between treatment groups and controls, and most were mild to moderate in intensity.

The overall incidence of serious infections was increased but in the same range as we can find with the other biologic treatments in RA patients.

In the case of the TOWARD study, TCZ was well tolerated in combination with conventional DMARDs, and the safety profile was not affected by the type or number of DMARDs used.

A greater reduction in the mean number of neutrophils was seen in the TCZ groups compared with the control groups, but the transient decreases were not temporally associated with infection. Some possible mechanisms by which TCZ may result in lower neutrophil counts include blocking IL-6-induced neutrophil survival, down-regulation of other inflammatory cytokines, and margination of neutrophils from the circulation into tissues[55-58]. The transient nature of neutropenia and the lack of association with infection suggest that this effect is not a significant issue; however, evaluation of the impact of lower neutrophil counts during long-term treatment will require long-term follow up with periodic monitoring.

TCZ therapy was associated with increases in

mean hepatic aminotransferase concentrations, typically single events without concomitant increase in bilirubin, and no patient experienced clinical symptoms of hepatic disease.

In the case of the TOWARD study, there was no evidence that elevations in the hepatic aminotransferase levels were associated with any particular type of DMARD or DMARD combination used.

In the case of the AMBITION study, elevations in the aminotransferases occurred in both treatment groups, and were more common with MTX, leading to more patients discontinuing MTX than TCZ.

Nonetheless, long-term follow up is required to determine the implications of these observations.

In association with the inflammatory process, patients with active rheumatoid arthritis often have lower lipid concentrations than the general population[59] and increases have been seen with improvement in chronic inflammation[60]. Mean fasting plasma lipid concentrations were raised in the TCZ groups, which coincided with decreases in CRP levels and were stable over the treatment periods. Therefore, the increase in lipid levels may, in part, be a consequence of effective reduction of inflammation. Increases in atherogenic indices were seen in a minority of patients and in the short term there was no indication of an increase in major adverse cardiac events. Nevertheless, monitoring lipid profile, as well as full blood count and aminotransferases, is recommended in all RA patients under TCZ treatment.

Interestingly, increases from lower than normal baseline lipid concentrations, have been observed with other efficacious therapies, including TNF inhibitors[61-64]. Studies in which the inflammatory response in RA was reduced, as with TNF inhibitors, have shown decreased rates of cardiovascular events, despite the increase in lipid concentrations[65-69].

Furthermore, considering the recognized higher incidence of cardiovascular (CV) mortality in RA patients[59-61,70,71], traditional risk factors for CV disease, including dyslipidaemia, are not necessarily predictive of events for patients with RA.

Nevertheless, there remains a need for longer term follow-up during chronic treatment to determine any implications of this effect and further studies are needed to fully assess the effects of TCZ on cardiovascular risk.

There are several limitations to these studies.

First, although the 6-month trial time is sufficient to judge efficacy, persistence of clinical and functional improvement will need long-term follow-up, as in the case of the LITHE study.

Second, the clinical consequences of the increase in lipid levels observed, together with the significant decreases in CRP and inflammation, are unclear. Long-term studies in this population may determine if the effects of TCZ on lipid levels are clinically meaningful, although it is apparent that this effect may require treatment with statins, according to standards developed to lower CV risk.

Third, these trials did not assess long-term safety and these results will only be available from long-term extension studies. Nevertheless, no new types of adverse events were observed when compared with early phase trials[49,72,73].

## Conclusions

Tocilizumab, an IL-6 receptor inhibitor, was evaluated for efficacy in several types of RA treatment scenarios, in patients with moderate to severe active disease.

Regardless of the safety profile, with lipid elevations and reversible neutropenia associated with IL-6R inhibition, TCZ's superior efficacy seems to provide evidence of a benefit-risk that supports its use in patients with active moderate to severe RA.

DAS28 remission was evaluated, and overall we could see a proportion of approximately 30% remission rates, at 24 weeks. DAS28 remission scores continued to improve throughout the 24 week period (the LITHE study), which suggests that remission rates with TCZ may continue to improve with longer treatment periods.

The efficacy of TCZ monotherapy in patients with relatively early active RA, who have not previously failed MTX, was superior to that of MTX monotherapy.

The association of TCZ plus MTX provided more efficacy than MTX alone in RA patients with inadequate response to MTX and/or with inadequate response to TNF antagonists, regardless of number of prior failed agents.

TCZ combined with any of the DMARDs was also effective in patients with moderate to severe RA in whom the response to these agents was inadequate.

Finally, TCZ therapy demonstrated significantly inhibition of the progression of structural joint damage at 52 weeks.

**Correspondence to**
Filipe M. Brandão
Rua Eng. Custódio Guimarães,
nº 46 2º Hab. 3
4100-006 Porto
Tlm: 916 920 284
E-mail:fbrandao.mribeiro@gmail.com

**References**

1. Gabriel SE. The epidemiology of rheumatoid arthritis. Rheum Dis Clin North Am 2001;27:269-281.
2. Choy EH and Panayi GS. Cytokine pathways and joint inflammation in rheumatoid arthritis. N Engl J Med 2001;344:907-916.
3. Kirwan JR, Hewlett S. Patient perspective: reasons and methods for measuring fatigue in rheumatoid arthritis. J Rheumatol 2007;34:1171-1173.
4. Smolen JS, Aletaha D, Koeller M, Weisman MH, Emery P. New therapies for treatment of rheumatoid arthritis. Lancet 2007;370:1861-1874.
5. Firestein GS. Evolving concepts of rheumatoid arthritis. Nature 2003;423:356-361.
6. Gaffo A, Saag KG, Curtis JR. Treatment of rheumatoid arthritis (review). Am J Health Syst Pharm 2006;63:2451-2465.
7. Emery P, Fleischmann R, Filipowicz-Sosnowska A et al. The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment: results of a phase IIB randomized, double-blind, placebo-controlled, dose-ranging trial. Arthritis Rheum 2006;54:1390-1400 .
8. Jiang Y, Genant HK, Watt I et al. A multicenter, double-blind, dose-ranging, randomized, placebo-controlled study of recombinant human interleukin-1 receptor antagonist in patients with rheumatoid arthritis: radiologic progression and correlation of Genant and Larsen scores. Arthritis Rheum 2000;43:1001-1009.
9. Kremer JM, Genant HK, Moreland LW et al. Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis: a randomized trial. Ann Intern Med 2006;144:865-876.
10. Lipsky PE, van der Heijde DM, St Clair EW et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. N Eng J Med 2000;343:1594-1602.
11. Emery P, Salmon M. Early rheumatoid arthritis: time to aim for remission? Ann Rheum Dis 1995;54:944--947.
12. Mierau M, Schoels M, Gonda G, Fuchs J, Aletaha D, Smolen JS. Assessing remission in clinical practice. Rheumatology (Oxford) 2007;46:975-979.
13. Olsen NJ, Stein CM. New drugs for rheumatoid arthritis (review). N Engl J Med 2004;350:2167-2179.
14 - Weinblatt ME, Kremer JM, Bankhurst AD et al. A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. N Eng J Med 1999;340:253-259.
15. Weinblatt ME, Keystone EC, Furst DE, et al. Adalimumab, a fully human anti-tumor necrosis factor α monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. Arthritis Rheum 2003;48:35-45.
16. Vander Cruyssen B, Van LS, Wyns B et al. Four-year follow-up of infliximab therapy in rheumatoid arthritis patients with long-standing refractory disease: attrition and long-term evolution of disease activity. Arthritis Res Ther 2006;8:R112.
17. Kishimoto T. Interleukin-6: discovery of a pleiotropic cytokine. Arthritis Res Ther 2006;8 Suppl 2:S2.
18. Tamura T, Udagawa N, Takahashi N et al. Soluble interleukin-6 receptor triggers osteoclast formation by interleukin-6. Proc Natl Acad Sci USA 1993;90:11924--11928.
19. Kudo O, Sakobar A, Pocock A et al. Interleukin-6 and interleukin-11 support human osteoclast formation by a RANKL-independent mechanism. Bone 2003;32:1-7.
20. Naka T, Nishimoto N, Kishimoto T. The paradigm of IL-6: from basic science to medicine. Arthritis Res 2002;4:S233-242.
21. Aletaha D, Nell VP, Stamm T et al. Acute phase reactants add little to composite disease activity indices for rheumatoid arthritis: validation of a clinical activity score. Arthritis Res Ther 2005;7:R796-806.
22. van Leeuwen MA, van der Heijde DM, van Rijswijk MH et al. Interrelationship of outcome measures and process variables in early rheumatoid arthritis. A comparison of radiologic damage, physical disactivity, joint counts, and acute phase reactants. J Rheumatol 1994;21:425-429.
23. Castell JV, Gomez-Lechon MJ, David M, Hirano T, Kishimoto T, Heinrich PC. Recombinant human interleukin-6 (IL-6/BSF-2/HSF) regulates the synthesis of acute phase proteins in human hepatocytes. FEBS Lett 1988;232:347-350.
24. Nemeth E, Rivera S, Gabayan V et al. IL-6 mediates hypoferremia of inflammation by inducing the synthesis of the iron regulatory hormone hepcidin. J Cli Invest 2004;113:1271-1276.
25. Heinrich PC, Behrmann I, Haan S et al. Principles of interleukin (IL)-6-type cytokine signaling and its regulation. Biochem J 2003;374:1-20.
26. Rose-John S, Waetzig GH, Scheller J et al. The IL-6/IL-6R complex as a novel target for therapeutic approaches. Expert Opin Ther Targets 2007;11:613-624.
27. Firestein GS, Alvaro-Gracia JM, Maki R. Quantitative analysis of cytokine gene expression un rheumatoid arthritis. J Immunol 1990;144:3347-3353.
28. Steiner G, Tohidast-Akrad M, Witzmann G et al. Cytokine production by synovial T-cells in rheumatoid arthritis. Rheumatology (Oxford) 1999;38:202--213.
29. Alonzi T, Fattori E, Lazzaro D al. Interleukin-6 is required for the development of collagen-induced arthritis. J Exp Med 1998;187:461-468.

30. Hata H, Sakagushi N, Yoshitomi H et al. Distinct contribution of IL-6, TNF-α, IL-1 and IL-10 to T-cell-mediated spontaneous autoimmune arthritis in mice. J Clin Invest 2004;114:582-588.
31. Sack U, Kinne RW, Marx T, Heppt P, Bender S, Emmrich F. Interleukin-6 in synovial fluid is closely associated with chronic synovitis in rheumatoid arthritis. Rheumatol Int 1993;13:45-51.
32. Madhock R, Crilly A, Watson J, Capell HA. Serum interleukin-6 levels in rheumatoid arthritis: correlations with clinical and laboratory indices of disease activity. Ann Rheum Dis 1993;52:232-234.
33. Nishimoto N, Kishimoto T. Interleukin-6: from bench to bedside. Nature Clinical Practice Rheumatology 2006;11:19-26.
34. Yoshizaki K, Nishimoto N, Mihara M et al. Therapy of rheumatoid arthritis by blocking IL-6 signal transduction with humanized anti-IL-6 receptor antibody. Springer Seminar Immunopathol 1998;20:247-259.
35. Hirano T. Interleukin-6 and its receptor: ten years later. Int Rev Immunol 1998;16:249-284.
36. Guerne PA, Zuraw BL, Vaughan JH, Carson DA, Lotz M. Synovium as a source of interleukin-6 in vitro: contribution to local and systemic manifestations of arthritis. J Clin Invest 1989;83:585-592.
37. Houssiau FA, Devogelaer JP, Van Damme J, de Deuxcaisnes CN, Van Snick J. Interleukin-6 in synovial fluid and serum of patients with rheumatoid arthritis and other inflammatory arthritides. Arthritis Rheum 1988;31:784-788.
38. Wendling D, Racadot E, Wijdenes J. Treatment of severe rheumatoid arthritis by anti-interleukin-6 monoclonal antibody. J Rheumatol 1993;20:259-262.
39. Sato K, Ohtomo T, Hirata Y et al. Humanization of an anti-human IL-6 mouse monoclonal antibody glycosylated inn its heavy chain variable region. Hum Antibodies Hybridomas 1996;7:175-183.
40. FDA Center for Drug Evaluation and Research. Actemra/Tocilizumab (BLA 125276). Briefing Document for the Arthritis Advisory Committee Meeting (July 29) – Summary of FDA review of clinical efficacy and safety. Silver Spring, MD: Division of Anesthesia, Analgesia and Rheumatology Products (FDA Department of Health and Human Services); 2008.
41. Hashizume M, Mihara M. IL-6 plus soluble IL-6R induces osteoclast formation via upregulation of RANKL expression on fibroblast-like synovial cell (Abstract 9th Annual European Congress of Rheumatology). Ann Rheum Dis 2008;67:84.
42. Emery P. Biography of Tocilizumab for Rheumatoid Arthritis. 2009.
43. Felson DT, Anderson JJ, Boers M et al. American College of Rheumatology preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum 1995;38:727-735.
44. Fransen J and van Riel PL. The Disease Activity Score and the EULAR response criteria. Clin Exp Rheumatol 2005;23:S93-99.
45. Prevoo ML, van't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995;38:44-48.
46. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473-483.
47. Cella D, Lai JS, Chang CH, Peterman A, Slavin M. Fatigue in cancer patients compared with fatigue in the general United States population. Cancer 2002; 94:528-538 .
48. Cella D, Yount S, Sorensen M, Chartash E, Sengupta N, Grober J. Validation of the Functional Assessment of Chronic Illness Therapy Fatigue Scale relative to other instrumentation in patients with rheumatoid arthritis. J Rheumatol 2005;32:811-819.
49. Maini RN, Taylor PC, Szechinski J et al, for the CHARISMA Study Group. Double-blind randomized controlled clinical trial of the interleukin-6 receptor antagonist tocilizumab, in European patients with rheumatoid arthritis who had an incomplete response to methotrexate. Arthritis Rheum 2006;54:2817--2829.
50. Smolen JS, Beaulieu A, Rubbert-Roth A et al. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomized trial. Lancet 2008;371;987-997.
51. Genovese MC, McKay JD, Nasonov EL et al. Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying anti-rheumatic drugs: the TOWARD study. Arthritis Rheum 2008;58; 2968-2980.
52. Jones G, Sebba A, Gu J et al. Comparison of tocilizumab monotherapy versus methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: the AMBITION study. Ann Rheum Dis 2009;0:1-9. doi:10.1136/ard.2008.105197.
53. Emery P, Keystone E et al. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-TNF biologics: results from a 24-week multicenter, randomized, placebo-controlled trial: the RADIATE study. Ann Rheum Dis 2008;67:1516-1523.
54. Kremer JM, Fleischmann RM et al. Tocilizumab inhibits structural joint damage in rheumatoid arthritis patients with an inadequate response to methotrexate: the LITHE study.
55. Asensi V, Valle E, Meana A et al. In vivo interleukin-6 protects neutrophils factor apoptosis in osteomyelitis. Infect Immun 2004;72:3823-3828.
56. Noursadeghi M, Pepys MB et al. Relationship of granulocyte colony stimulating factor with other acute phase reactants in man. Clin Exp Immunol 2005;140:97-100.
57. Sabroe I, Prince LR et al. Selective roles for Toll-like receptor (TLR) 2 and TLR4 in the regulation of neu-

trophil activation and life span. J Immunol 2003;170:5268-5275.
58. Suwa T, Hogg JC et al. The effect of interleukin-6 on L-selectin levels on polymorphonuclear leukocytes. Am J, Physiol Heart Circ Physiol 2002;283:879-884.
59 - Sattar N, McCarey DW et al. Explaining how "high grade" systemic inflammation accelerates vascular risk in rheumatoid arthritis. Circulation 2003;108: 2957-2963.
60. Dursunoglu D, Evrengul H et al. Lp(a) lipoprotein and lipids in patients with rheumatoid arthritis: serum levels and relationship to inflammation. Rheumatol Int 2005;25:241-245.
61. Sattar N, Crompton P et al. Effects of TNF blockade on cardiovascular risk factors in psoriatic arthritis: a double-blind, placebo-controlled study. Arthritis Rheum 2007;56:831-839.
62. Vis M, Nurmohamed MT et al. Short term effects of infliximab on the lipid profile in patients with rheumatoid arthritis. J Rheumatol 2005;32:252-255.
63. Dahlqvist SR, Engstrand S et al. Conversion towards an atherogenic lipid profile in rheumatoid arthritis patients during long-term infliximab therapy. Scand J Rheumatol 2006;354:107-111.
64. Allanore Y, Kahan A et al. Effects of repeated infliximab therapy on serum lipid profile in patients with refractory rheumatoid arthritis. Clin Chim Acta 2006;365:143-148.
65. Choi HK, Hernan MA et al. Methotrexate and mortality in patients with rheumatoid arthritis: a prospective study. Lancet 2002;359:1173-1177.
66. Jacobsson LT, Turesson C et al. Joint swelling as predictor of death from cardiovascular disease in a population study of Pima Indians. Arthritis Rheum 2001;44;1170-1176.
67. Turesson C, Matteson EL. Cardiovascular risk factors, fitness and physical activity in rheumatoid diseases. Curr Opin Rheumatol 2007;19:190-196.
68. Wolfe F, Freundlich B, Straus WL. Increase in cardiovascular and cerebrovascular disease prevalence in rheumatoid arthritis. J Rheumatol 2003;30:36-40.
69. Wolfe F, Michaud K. Heart failure in rheumatoid arthritis: rates, predictors, and the effect of anti-TNF therapy. Am J Med 2004;116:305-311.
70. Situnayake RD and Kitas G. Dyslipidemia and rheumatoid arthritis. Ann Rheum Dis 1997;56:341-342.
71. Gonzalez A, Maradit-Kremers H et al. The widening mortality gap between rheumatoid arthritis patients and the general population. Arthritis Rheum 2007;56:3583-3587.
72. Nishimoto N, Yoshizaki K et al. Treatment of rheumatoid arthritis with humanized anti-interleukin-6 receptor antibody: a multicenter, double-blind, placebo-controlled trial. Arthritis Rheum 2004;50: 1761-1769.
73. Nishimoto N, Hashimoto J et al. Study of active controlled monotherapy used for rheumatoid arthritis, an IL-6 inhibitor (SAMURAI): evidence of clinical and radiographic benefit from an x-ray reader-blinded randomized controlled trial of tocilizumab. Ann Rheum Dis 2007;66:1162-1167.

# 1st Porto's Autoimmune Meeting

## Porto, Portugal,
## 8 a 9 de Outubro 2010

# NEAR study: Needs and Expectations in Rheumatoid ARthritis – do we know our patients needs?

Luís Cunha-Miranda*, Lúcia Costa**, José Saraiva Ribeiro***

## Abstract

**Introduction:** Rheumatoid arthritis is a chronic systemic inflammatory rheumatic disease whose characteristics have a clear impact on the life of the patient and his/ her family. Doctor-patient relationship is increasingly based on communication and information transfer. In the case of chronic diseases and especially in RA, that information is fundamental for a better compliance, but also for the prevention of problems and the patient's better management of the disease on a daily basis.

**Objectives:** To determine in a population of RA patients which are the principal sources of information about the disease, what unmet needs exist and the level of patient involvement in therapeutic decision.

**Methods:** We applied a questionnaire in person and by telephone to a population of patients with rheumatoid arthritis fulfilling the criteria of the ACR, which were followed at several departments of rheumatology in mainland Portugal, about their expectations, the degree and type of information they expected, and their unmet needs.

**Results:** A total of 223 RA patients filled in the questionnaire, 82.5% of which were female, mean age 55.13 +/- 14.49 years and whose mean duration of disease was above 5 years in 69.5% of the individuals. Of these, 17.5% found that RA had an impact on quality of life, 15.7% felt that RA affected their ability to enjoy life and 14.3% had difficulties in performing activities of daily living.

Some activities were found to be more difficult for a patient with RA (on a scale of 0 to 10), such as gardening (6.36) and practicing sports (5.79). Other basic tasks were also considered difficult, as are the case of household chores (5.76) sleeping (5.08) walking (4.99) and working (4.86). Regarding the clinical impact of RA, as expected pain is almost a universal factor (87.9%), although the majority of patients also refer arthritis (78%), pain when moving (65.5%), fatigue (60.1%) and joint deformities (58.3%) as very common symptoms.

Diminishing pain (81.2%), a general improvement of symptoms (73.1%) in a lasting way (57.4%) and reducing arthritis (59.2%) appeared as the main concerns of patients with RA. Regarding quality of information, 68.2% of patients consider they are well informed about the disease, but these numbers decrease if we consider information about treatment options (46.2%), the concept of remission (20.6%) or the recognition of the DAS 28 scale (17%). As preferred sources of information about the disease, 67.7% of individuals indicate their rheumatologist, 31.4% their general practitioner, 17% the Internet and 9% the attending nurse. The same order is obtained when asked about treatment information. As to the need for additional information, the patients refer «more information about therapies/treatments» (26.9%), «new scientific developments and social support» (17.5% each), «how to improve symptoms and live better in everyday life» (16.6%). «What is the disease» (6.7%) is referred last, being that only 8.1% of patients consider they are well informed. In what concerns discussion and participation in the process of clinical decision about medication, 56.1% of patients say that they share it with their doctors during their consultation.

**Conclusion:** These results, which somewhat differ from the existing literature, demonstrate that there are important issues that should be considered in clinical practice, both relating to clinical issues and the unmet needs of our patients.

We are unaware of the results coming from a treatment strategy designed to increase the RA patient's perception of their general state of health or of their perception of function. We should, however, keep in mind that pain, wellbeing and disease activity (as well as remission) should be important

*Instituto Português de Reumatologia
**Centro Hospitalar do Alto Minho
***Departamento Médico Roche

goals in therapeutic strategies that are to be increasingly shared with our patients.

**Keywords:** Patient Perception; Needs; Expectation; Rheumatoid Arthritis.

## Introduction

Rheumatoid arthritis is a chronic systemic inflammatory rheumatic disease which, due to its characteristics, has a clear impact in the life of the patient and his/ her family.

Doctor-patient relationship is increasingly based on communication and information transfer. In the case of chronic diseases and especially in RA, that information is fundamental for a better compliance, but also for the prevention of problems and a better and adequate management by the patient on a daily basis.

Nowadays, the making of clinical decisions by doctor and patient together is reflected in many health policies of various countries[1].

Patients are eager to know more about their disease and, according to some studies, only half actually acquire that knowledge in a clinical environment (Kay 1988).

Current clinical practice is increasingly less about a decision taken within the scope of a more or less informed consent by the patient. It is a dynamic process and the patient is involved in making the clinical and therapeutic decision. The different value given by the patient and by the doctor to different aspects of health often lead to difficulties in the relationship and in achieving the goals that should in principle be common ones[2].

In the patient's point of view, the medical appointment is a partnership in which his/ her perspective is considered and which influences the final treatment decision.

Other functions the consultation has are sharing symptom and care information, being a place of *feedback* about progress, having access to a specialist, being a source of supporting information, a way of reassuring the patient about his/ her doubts and incorporating the dimension of feeling in the relationship between doctor and patient – empathy[3].

But which is the main source of information about the disease and treatment options?

In an American study, doctors and nurses were considered the biggest source of information, and occupational therapists and physiotherapists were given less prominence. The internet was referred by only 14% of patients, which is inferior to what another study states (25%)[4]. We also know that women and younger patients have a higher need for information than older patients[5].

Other sources of information, such as leaflets, may also have a continuing impact of a few months in terms of information quality, even more if they are given out at the consultation by the specialist[6].

Thus, several studies demonstrate that patients with RA want to understand their disease and its available treatments better, but also want to know how to manage the variable symptoms of the disease and pain deriving from it.

There is evidence that patient education improves understanding of disease progression, treatment types and prognosis. Such understanding appears to be even more relevant in early arthritis.

For all these reasons, the rheumatology consultation and the relationship with patients with RA have a significant impact, for they contribute decisively towards a perception of disease control on part of patients. There seem to be three points to consider: 1 – the involvement in consultation 2- the way of expressing the type of medical care to patients 3 – specialized knowledge.

Diminishing physical symptoms as pain or stiffness must be attained for the patient to consider that the disease is under control.

When talking about expectations in the case of a potentially debilitating and incapacitating disease, there's the need to define two types of expectations – those of the doctor and those of the patient.

The expectations the patients hold have to do with their projects and personal concerns, as well as with trying to lead as normal a life as possible.

The doctor's expectations will take into account the way how he thinks clinical control of disease activity will allow him to help his patient regain the physical and mental capacities that will let him live life as fully as possible. How can the doctor assess and structure a strategy to obtain this goal? Will the doctor talk about remission or low disease activity as objectives or should he follow the opposite road and, as a form of avoiding failures and of protecting the patient from disappointments, speak only of improvement or diminishing disease activity?

As such, the doctor will have to correctly assess the disease and its evolution. It is common

knowledge that the way a patient responds to treatment can be assessed through the response criteria of the American College of Rheumatology (ACR)[7] or the criteria of the European League Against Rheumatism (EULAR)[8].

However, in opposition to what happens in diseases like diabetes or hypertension, there is no gold standard evaluation for rheumatic diseases for assessment and follow-up of patients.

Resorting to composite indexes is one of the possibilities and some have been developed to evaluate patients with rheumatoid arthritis. Some are used more than others, as is the case of DAS 28 (disease activity score)[9,10], SDAI (simplified disease activity index)[11] or CDAI (clinical disease activity index)[12].

Most of these complex indexes include joint count of painful and/or swollen joints, which are the most specific and valued factor for rheumatologists in their assessment of patients[13,14].

The time needed to perform joint count limits the interaction between doctor and patient, since while the patient has the expectation of discussing other matters of relevance to himself/ herself, the doctor has to interrupt this interaction in order to register the resulting data.

As some authors advise, the main role of a rheumatologist should be making clinical decisions, not simply recording data[13].

Among rheumatologists there are different perspectives about the core set and its value in disease activity. When asked about which values confer low disease activity or remission in RA, there is a variation between the answers given by specialists. The ESR value and the global assessment by the patient (the patient's VAS) are more consistent, whereas swollen and painful joints and PCR are harder to consider in a homogeneous way. Doctors accept a patient's VAS higher than their own, but tend to give more value to the latter[15].

We are aware that increasing care quality for rheumatic patients is obtainable through the application of quantitative assessments, but not all rheumatologists perform joint counts, nor do they apply questionnaires. In a study done with 550 rheumatologists (16 of which were Portuguese) only 44% of rheumatologists performed joint counts on 50% of consultations or more, and 45% of surveyed rheumatologists on less than one in every four consultations[16].

Clinical practice in rheumatology everywhere is broadly based on qualitative impressions ("gestalt"). Instead of being based upon evidence, it is based upon prominence, eloquence and elegance[14,16-18].

The use of other complementary forms of assessment, such as the application of questionnaires to be easily filled in by the patient, may provide the quantitative data about the disease that are so necessary to the highest standards of care[13,14,19,20].

This connection between better patient information for a better assessment and follow-up alone will conscientiously lead to sharing the management of disease with the patient. Both patient and specialist must boost the dynamics in the consultation so that more clinical data are obtained (in order for the doctor to be more capable to make choices) or information about the disease to be given (in order that the patient gets to know his/ her disease better).

As a specialist, the rheumatologist should keep in mind these two fundamental items when interacting with the patient. Information provides the power of decision-making. If such information is not correctly obtained by both parties, a winning strategy will not be achieved.

## Methods

This was a cross-sectional study based upon the application of a questionnaire which was presented to patients being followed at a rheumatology consultation. Patients with a diagnosis of rheumatoid arthritis which fulfilled the criteria of the American College of Rheumatology[21] were given the questionnaire in person and by telephone.

233 questionnaires were completed, of which 140 were applied randomly at the outpatient clinic of several Rheumatology units or departments - Hospital Conde Bertiandos (Ponte de Lima), Hospital de São João, Hospital Militar Regional nº 1 (Porto), Hospital de São Marcos, Hospitais da Universidade de Coimbra, Hospital de Santa Maria, Hospital Garcia da Orta and Hospital de Faro. The other 83 questionnaires were done by telephone, via contacts provided by consultants after informed consent was obtained in writing and provided by their patients.

## Results

233 patients participated in the study, most of

**Table I. Distribution by age group**

| Age | no | (%) |
|---|---|---|
| 40 years or less | 41 | 18.4 |
| 41-55 years | 74 | 33.2 |
| 56-70 years | 69 | 30.9 |
| 71 years or more | 39 | 17.5 |
| Total | 223 | 100.0 |

**Table II. Distribution by time of diagnosis**

| Time of diagnosis | no | (%) |
|---|---|---|
| Less than 2 years | 26 | 11.7 |
| Between 2 and 5 years | 39 | 17.5 |
| Over 5 years | 155 | 69.5 |
| DNK/DNA | 3 | 1.3 |

**Table III. Impact of Rheumatoid Arthritis in various aspects of everyday life (percentage)**

| | % of enquired that fully agrees with the statement (1) | % of enquired that tends to agree with the statement (2) |
|---|---|---|
| Above all, RA has an impact on my quality of life | 17.5 | 32.3 |
| RA has affected my ability to enjoy life | 15.7 | 26.4 |
| I experience difficulties in performing some daily tasks due to RA | 14.3 | 31.8 |
| My family does not understand how RA affects my life | 11.4 | 18.2 |
| RA forces me to depend too much on other people | 9.0 | 21.1 |
| RA symptoms control my life | 8.5 | 25.1 |
| I feel constantly tired due to RA | 8.1 | 25.1 |
| I sometimes feel tired due to RA | 7.8 | 20.3 |
| RA affects my work capacity | 6.8 | 24.7 |
| I feel alone in my fight against the disease | 6.7 | 22.4 |
| RA affects my sexual life. | 6.5 | 17.2 |
| I cannot take responsibility for myself or other people due to my RA symptoms. | 4.5 | 13.9 |
| RA affects my relationship with my family. | 4.0 | 19.6 |
| RA affects my relationship with my friends. | 3.2 | 11.4 |

(1) % of individuals who answered 10, in a 1 to 10 agreement scale, in which 10 means full agreement
(2) % of individuals who answered 8, 9 or 10, in a 1 to 10 agreement scale, in which 10 means full agreement

which were female (184, 82.5%; 39 of males, 17.5%), mean age 55.13 +/- 14.49 years. Most of the patients had a disease evolution of more than 5 years.

For a relative majority of the 223 patients that were surveyed (32.3%), rheumatoid arthritis was a disease that has an impact in quality of life. 31.8% of patients expressed high difficulty in performing activities of daily living, 25.1% said they felt constantly tired, 26.4% recognized that rheumatoid arthritis made them less able to enjoy life and 24.7% said it affected their ability to work (Table III).

About a quarter of the individuals (25.1%) stated that the symptoms of arthritis controlled their daily lives. 22.4% of patients confessed they felt alone in fighting the disease or that they did not receive much support from outside to do it.

Among the activities of daily living that patients find harder to perform due to the disease are tasks like gardening, practicing sports, performing household chores and simply being able to sleep, having all a mean score above 5 in a scale of difficulty with 10 as maximum score, which means extreme difficulty in perform the task (Figure 1).

The consequences of rheumatoid arthritis are also visible at work, through the patient's absenteeism over the previous three months. In fact, of the 102 patients with professional activity at the time, 21.6% admitted having been absent from work due to illness. These absences had a mean duration of 16-17 days.

The value given to some symptoms was one of the focuses of the questionnaire. 87.9% of patients said that they had pain caused by arthritis more or less frequently, and a significant percentage of in-

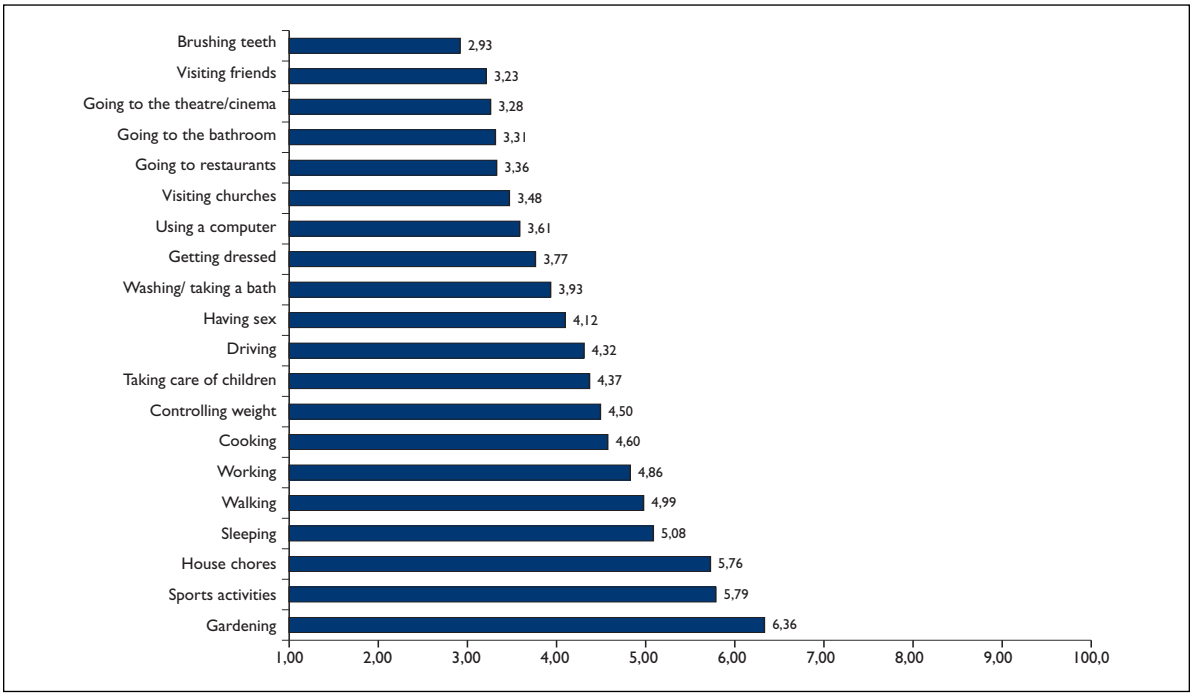



**Figure 1.** Level of difficulty associated to each activity of daily living (average values) (1)
1-10 scale, where 10 means extreme difficulty in performing the task

**Table IV. Most frequent symptoms related to Rheumatoid Arthritis (percentage)**

| | Most frequent symptoms related to rheumatoid arthritis (1) |
|---|---|
| Pain | 87.9 |
| Joint swelling | 78.0 |
| Pain when moving | 65.5 |
| Morning stiffness | 64.1 |
| Fatigue/tiredness | 60.1 |
| Joint deformities | 58.3 |
| Lack of joint flexibility | 52.9 |
| Body pain (not only in the joints) | 47.1 |
| Problems affecting other organs (eyes/lungs) | 29.6 |
| Flu symptoms | 10.8 |
| Other symptoms | 1.3 |

(1) Multiple answer. n = 223

dividuals (78.0%) referred to joint swelling as a common symptom.

Among other symptoms mentioned by the individuals are pain when moving (65.5%), morning stiffness in the limbs (64.1%) and fatigue/tiredness (60.1%). We could still add that approximately 50% of interviewees referred to joint deformities (58.3%), lack of flexibility in the joints (52.9%) and to general body pain (47.1%) (Table IV).

In practice, this sample of patients live almost daily with the consequences of the disease, among which pain occupies a central position, contributing to a physical discomfort with implications in social and professional activities. Furthermore, this situation is clearly visible in the way patients express their wants as to the management and treatment of rheumatoid arthritis: 81.2% of individuals said that they would like to have less joint pain, 73.1% would like to feel a general improvement of arthritis, 59.2% wanted to have less joint swelling and 57.4% would aim to achieve lasting relief of rheumatoid arthritis symptoms (Table V).

Regarding involvement in the course of treatment, 68.2% of patients considered they were well informed about rheumatoid arthritis, although the knowledge they declared having on the disease is less significant when they are questioned about specific issues related to treating and monitoring the disease: 46.2% said they knew of available treat-

**Table V. Aspirations of Rheumatoid Arthritis Patients (percentage)**

| | Aspirations of Rheumatoid Arthritis patients (1) |
|---|---|
| Less joint pain | 81.2 |
| General improvement of arthritis | 73.1 |
| Less joint swelling | 59.2 |
| Lasting relief of RA symptoms | 57.4 |
| More joint flexibility | 52.5 |
| Improvement in morning stiffness in the limbs | 43.9 |
| Less tiredness/Less fatigue | 41.7 |

n=223
(1) Multiple answer.

**Table VI. Declared knowledge of areas connected to Rheumatoid Arthritis treatment (percentage)**

| | |
|---|---|
| State to have knowledge on treatment options | 46.2 |
| Recognize the concept of remission | 20.6 |
| Recognize the DAS scale | 170 |

n=223

ment options; 20.6% recognized the concept of remission; 17.0% identified the DAS scale (Table VI).

Faced with this reality, 77.6% of individuals considered that their consultant had paid him/her due attention and care, and 56.1% also admitted talking to their doctor about treatment options in a context where 32.3% of patients said they have some weight in decision-making about treatment.

Access to medication was referred as difficult by 18.4% of enquired patients, insofar as these barriers are more intense among patients who are followed outside a hospital environment: 26.5% of patients that are not treated in a hospital referred difficulties, whereas the same applies to 13.6% of patients treated in a hospital.

Among those who felt difficulties in this area, 46.3% pointed out financial issues as the main barrier, followed by treatment availability in pharmacies (22.0%).

There are sources of information that patients find they prefer. Doctors are the biggest source of information patients have on the disease and respective treatments. In fact, 67.7% of patients said they obtained information about the disease from their rheumatologist and 31.4% stated the same about their general practitioner. Concerning information on treatments, the same order is maintained, although the relative distance between rheumatology and general practitioners is larger: 85.2% referred their rheumatologist and 25.1% indicated their general practitioner (Table VI).

9.9% of patients resort to nurses to obtain information on the disease and 6.3% also approach the nurse to acquire information about their treatment. The Internet is nowadays also somewhat important and is consulted by 17.0% and 10.3% of patients, respectively for obtaining information about the disease or about treatments (Table VII).

Although it was clear that most patients consider they are well informed about the disease, 78.0% expressed additional needs in information. Among these are to be highlighted their want in knowing more about therapies and treatments (26.9%), available social support (17.5%), news scientific developments (17.5%) and their will to learn new ways to improve their symptoms and live better in everyday life (16.6%) (Table VIII).

## Discussion

The patient's clinical perception is a factor that should be increasingly more valued in the case of chronic diseases and especially in RA. Some results of this study should cause us to reflect about the strategies used in the follow-up of these patients.

If pain is a universal symptom in clinical terms and is greatly valued by the patients, other symptoms such as joint swelling, fatigue and stiffness are considered more relevant by the patients, while joint deformities are given less importance. In this group of patients, pain, a general improvement of symptoms and reducing signs and symptoms of arthritis come up as the three first concerns of patients with RA. Other studies are coincident in having pain as a major determinant of incapacity in RA[22,23].

Is the control of pain an urgent need that is not being valued? In the case of our patients, as equally happens in other studies, pain is an important symptom and it is not possible to value it [9, 24].

Pain influences the perception of disease con-

**Table VII. Information sources considered for the disease and treatments (percentage)**

| | Information sources about the disease (1) | Information sources about the treatments (1) |
|---|---|---|
| Rheumatologist | 67.7 | 85.2 |
| General practitioner | 31.4 | 25.1 |
| Internet | 17.0 | 10.3 |
| Nurse | 9.9 | 6.3 |
| Other RA patients | 7.2 | 1.3 |
| I do not search for information about the disease/ treatments | 2.7 | 6.7 |
| Other information sources | 2.7 | 4.0 |
| Conferences or talks | 2.7 | 2.7 |
| Media | 2.7 | 6.3 |
| Documents from Patients Associations | 1.3 | 0.0 |
| Portuguese Rheumatology Institute | 2.7 | 1.3 |
| Pharmacist | 1.3 | 1.3 |
| Books | 1.3 | 0.0 |

n=223
(1) Multiple answer

**Table VIII. Additional information required on Rheumatoid Arthritis (percentage)**

| | Additional information required (1) |
|---|---|
| Therapies / treatments | 26.9 |
| Social support | 17.5 |
| New scientific developments | 17.5 |
| Learn how to improve symptoms and live better in everyday life | 16.6 |
| What is the disease | 6.7 |
| Causes / Origin of the disease | 6.3 |
| Disease progress | 4.5 |
| Would like to know more in general | 4.0 |
| Studies made | 2.7 |
| What I can and cannot do – conditionings | 2.7 |
| Concomitant diseases | 2.7 |
| Treatment consequences | 1.3 |
| Nothing; I consider myself well informed | 8.1 |
| DNK/DNA | 22.0 |

n=223
(1) Multiple answer.

trol inversely. An increase in pain is felt as a reduction in disease control. Pain unbalances the person's life concerning his/ her relationship with others, self-esteem, the capacity to fulfill tasks and his/ her daily life[3].

There are activities recognizably harder for a patient with RA (gardening, practicing sports), but some basic tasks are equally considered hard by our patients, such as household chores, sleeping and walking.

The most referred sources or information are mainly medical (the rheumatologist and the general practitioner), but the Internet is clearly already the third most important source of information, coming before nurses and being much more relevant than the media. Such data reinforces the role of these new platforms, but also stresses the weak appeal of rheumatic diseases to the media in general.

In several previous studies, the rheumatologist was also considered the main source of information in several studies, followed by the nurse, which did not prove the same among this group of patients[1,25,26].

In the 2009 RAISE study, McInnes *et al*[24], in an assessment of 586 patients with RA coming from 9 different countries came to somewhat different conclusions than those of our study, insofar as the internet and the written media were the main sources, which may indicate a future pathway concerning sources of information, or merely be the mir-

ror of the different socio-cultural characteristics existing in those countries when comparing with Portugal and Spain.

Even so, about two thirds of patients (68,2%) say they were well informed about the disease, a figure which is reduced to less than half when they are asked about treatment options (46,2%), being that only 20,6% knew the concept of remission and a mere 17% knew what is a DAS 28 score.

In a study by Van Campen, the assessment patients made of their doctors demonstrated that the practitioner's efficiency and the sharing of information were the most valued factors, although sharing the decision as to follow-up, treatments and other solutions, as well as the fact of being taken seriously with their complaints, were equally highly valued by the patients[27].

Disease impact is important and 32.3% of individuals referred that RA had an impact on their quality of life, limiting their activities of daily living (31.8%). It should be highlighted that more than a quarter of patients said that RA stopped them from enjoying life (26.4%), that the disease controlled their life (25.1%) and that they were constantly fatigued (25.1%), which became visible in their ability to work (24.7%).

We know that when patients consult with rheumatologists their prognosis improves in the case of patients with RA[28-31].

Some of the data resulting from this work reflects the need for more time and a greater involvement of the rheumatologist in the follow-up of patients with RA. In order to share data and information, the specialist needs more time in each consultation so that care quality is achieved. Naturally, as in the rest of the world, in Portugal DAS 28 is calculated in a percentage that is supposed not to reach 50% of patients, however that percentage is much inferior to the 17% of patients who recognize the scale. This means that although it is calculated, such information is not shared nor is it valued[14,16-18].

## Conclusion

A study which is based upon the expectations and assessments of patients holds an important set of limitations. It has two types of data collection - in person and by telephone. The inexistence of data about education, income, disease activity, incapacity, exact duration of RA, the existence of a rheumatoid factor or not and joint erosions, among other factors, limits some of the conclusions, since they can be cause for confusion.

However, the high number of patients, the fact that all were consulted in rheumatology units and the descriptive and personal character of the questions give this work some range and quality.

There is a clear difference between the aspirations of patients and those of doctors. Patients want a stronger control over their own lives and that the doctors ask them about their lives and not only about their disease. Doctors want to reduce inflammation, prevent structural damage and incapacity and aim at remission[24, 32, 33, 34].

We are unaware of the results coming from a treatment strategy aimed at increasing RA patients' perception of their general state of health or their perception of function. Nevertheless, we should keep in mind that pain, wellbeing and disease activity should be important objectives within the treatment strategy[35].

Being able to listen and to influence through providing correct information is something that is closely linked to medical practice, but over the latest years is coming against the set objectives of consultation numbers, quotas and exceedingly controlled activity.

If we continue to ignore the needs and expectations of patients, we may be irrevocably stepping away from an ideal solution for each patient as a person. A patient-centered vision should increasingly be our goal, regarding the patient's expectations about the disease, treatments, but also about his/ her consultant[34].

Thus arises the need for deciding what to do concerning our role as specialists. Should we maintain this attitude of being information collectors or should we opt for another strategy, resorting to automatic questionnaire systems and new technologies in a way that we concentrate on being an informed decision-maker while including the patient in the decision made? Will we be for much longer still the main source of information for our patients? Do we want to be that source? Do we acknowledge that the Internet and other platforms will overcome this function and use them as a way of improving the quality of information?

This study allows us to think about the distance which still exists between what we intend to achieve and what the patient wants. The concept of remission and low disease activity should represent what we can achieve nowadays, if not in all cases,

at least in a significant amount of patients, and we should decide on a common strategy to obtain such objectives together with our patients.

**Correspondence to**
Luís Cunha-Miranda
Instituto português de Reumatologia
Rua da Benificência nº7
1050-034 Lisboa
E-mail: luis.miranda@ipr.pt

**References**

1. Goodacre L, Goodacre J. Factors influencing the beliefs of patients with rheumatoid arthritis regarding disease-modifying medication. Rheumatology 2004; 43: 583-586.
2. Ortendahl M. Shared decision-making based on different risk factors in the context of diabetes mellitus and rheumatoid arthritis. Therap Clin Risk Manag 2007;3:1175-1180.
3. Ryan S, Hassell A, Dawes P, Kendall S. Control perception in patients with rheumatoid arthritis: the impact of the medical consultation. Rheumatology 2003;42:135-140.
4. Gordon M, Capell H, Madhok R. The use of internet as a resource for health information among patients attending a rheumatology clinic. Rheumatology 2002;41:1402-1405.
5. Neame R, Hammond A, Deighton C. Need for information and for involvement in decision making among patients with rheumatoid arthritis: a questionnaire survey. Art Rheum 2005; 53:249-255.
6. Barlow J, Wright C. Knowledge in patients with rheumatoid arthritis: a longer term follow up of a randomized controlled patient education leaflets. Br J Rheumatol 1998;37:373-376.
7. Felson DT, Anderson JJ, Boers M et al. American College of Rheumatology preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum 1995;38:44-48.
8. Van Gestel AM, Prevoo ML, Van´tHof MA, Van Rijswijk MH, Van de Putte LB, Van Riel PL. Development and validation of the European League Against Rheumatism response criteria in Rheumatoid Arthritis: comparison with the preliminary American College of Rheumatology and the world health organization/International League Against Rheumatism criteria Arthritis Rheum 1996;39:34-40.
9. van der Heijde DMFM, van't Hof MA, van Riel PLCM et al. Judging disease activity in clinical practice in rheumatoid arthritis: first step in the development of a disease activity score. Annals Rheum Dis 1990; 49: 916-920.
10. van der Heijde DMFM, van't Hof M, van Riel PLCM, van de Putte LBA. Development of a disease activity score based on judgment in clinical practice by rheumatologists. J Rheumatol 1993; 20: 579-581.
11. Smolen JS, Breedveld FC, Schiff MH et al. A simplified disease activity index for rheumatoid arthritis for use in clinical practice. Rheumatology 2003; 42: 244--257.
12. Aletaha D & Smolen J. The simplified disease activity index (SDAI) and the clinical disease activity index (CDAI): a review of their usefulness and validity in rheumatoid arthritis. Clin Exp Rheumatol 2005; 23: 100-108.
13. Pincus T, Yazici Y, Bergman M, Maclean R, Harrington T. A proposed continuous quality improvement approach to assessment and management of patients with rheumatoid arthritis without formal joint counts, based on a quantitative routine assessment of patient data (RAPID) scores in a multidimensional health assessment questionnaire (MDHAQ). Best Pract Res Clin Rheumatol 2007; 21:789-804.
14. Wolfe F, Pincus T, Thompson AK, Doyle J. The assessment of rheumatoid arthritis and the acceptability of self-report questionnaires in clinical practice. Arthritis Care and Research 2003; 49: 59-63.
15. Aletaha D, Machold KP, Nell VPK, Smolen JS. The perception of rheumatoid arthritis cores set measures by rheumatologists. Results of a survey. Rheumatol 2006;45:1133-1139.
16. Pincus T, Segurado OG. Most visits of most patients with rheumatoid arthritis to most rheumatologists do not include a formal quantitative joint count. Annals Rheum Dis 2006; 65: 820-822.
17. Pincus T, Tugwell P. Shouldn't Standard Rheumatology Clinical Care Be Evidence-Based Rather Than Eminence-Based, Eloquence-Based, or Elegance-Based? J Rheumatol 2007;34:1-4.
18. Yazici Y, Bergman M, Pincus T. Time to score quantitative rheumatoid arthritis measures: 28 joint count, disease activity score, Health assessment questionnaire (HAQ), Multidimensional HAQ (MHAQ), and routine assessment of patient index data (RAPID) scores. J Rheumatol 2008; 35:603-608.
19. Kirwan JR, Hewlett SE, Heiberg T et al. Incorporating the patient perspective into outcome assessment in Rheumatoid Arthritis - progress at OMERACT 7. J Rheumatol 2005;32:2250-2256.
20. Yazdany J, MacLean C. Quality of care in the rheumatic diseases: current status and future directions. Curr Opin Rheumatol 2008; 20:159-166.
21. Arnett FC, Edworthy SM, Bloch DA, McShane DJ et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988; 31:315-324.
22. Berry D, Bradlow A, Bersellini E. Perceptions of risk and benefits of medicines in patients with rheumatoid arthritis and other painful musculoskeletal conditions. Rheumatology 2004; 43: 901-905.
23. Minnock P, Fritzgerald O, Bresnihan B. Women with established rheumatoid arthritis perceive pain as the predominant impairment of health status. Rheumatology 2003; 42:995-1000.
24. McInnes I, Combe B, Burmester G. Rheumatoid Arthritis: insights strategies and expectations - global results of the RAISE Patient needs survey. Ann

Rheum Dis 2009; 68:240.
25. Cortés M, Fernández S, Peiró G, Corominas H, Llobet J, Diaz C. Nivel de conocimiento de los pacientes con arthritis reumatoide sobre su enfermedad y tratamiento. Rev Esp Reumatol 2003; 30: 124.
26. Werner A, Kalliski S, Salazar K, Bustos L, Rojas M, Baumert C, Leal H. Nivel do conocimiento de los pacientes con arthritis reumatoide acerca de su enfermedad y tratamento. Rev Med Chile 2006;134: 1500--1506.
27. Van Campen C, Sixma H, Kerssens J, Peters L, Rasker J. Assessing patients' priorities and perceptions of quality of health care: the development of quote-rheumatic-patients instrument. Br J Rheumatol 1998; 37:362-368.
28. Goekoop-Ruiterman Y, Vries- Bouwstra J, Allart et al. Comparison of treatment strategies in early rheumatoid arthritis: a randomized controlled trial. Ann Intern Med 2007; 146: 406-415.
29. Grior C, Capell H, Stirling et al. Effect of a treatment strategy to tight control for rheumatoid arthritis (the TICORA study): a single-blind Randomized control trial. Lancet 2004; 364-369.
30. Pincus T. The DAS is the most specific measure, but a patient questionnaire is the most informative measure to assess rheumatoid arthritis. J Rheumatol 2006; 33: 834-837.
31. Fransen J, Stuckl G, Twisk J et al. Effectiveness of measurement feedback system on outcome in rheumatoid arthritis: a controlled clinical trial. Ann Rheum Dis 2003; 62:624-629.
32. Berkanovic E, Hurwicz M, Lachenbruch P. Concordant and discrepant views of patients' physical functioning. Arthritis Care Res 1995; 8:94-101.
33. Hewlett S, Smith A, Kirwan J. Values for function in rheumatoid arthritis: patients, professionals, and public. Ann Rheum Dis 2001; 60:928-933.
34. Kvien T, Heiberg T. Patient perception in outcome assessments - perceptions or something more? J Rheumatol 2003; 30: 873-876.
35. Kievit W, Welsing M , Adang E, Eijsbouts A, Krabbe P, Riel P. Comment on the use of self-reporting instruments to assess patients with rheumatoid arthritis: The longitudinal association between the DAS 28 and the VAS general health. Arthritis Rheum 2006, 55:745-750.

# XII Fórum de Apoio ao Doente Reumático

## Portugal
## 8 a 9 de Outubro 2010

# CARDIOVASCULAR RISK PROFILE IN SYSTEMIC LUPUS ERYTHEMATOSUS AND RHEUMATOID ARTHRITIS: A COMPARATIVE STUDY OF FEMALE PATIENTS

Maria José Santos[*,**], Filipe Vinagre[**], José Canas da Silva[**], Victor Gil[***], João Eurico Fonseca[*,****]

## Abstract

**Objective**: Premature atherosclerosis is well-documented both in Systemic Lupus Erythematosus (SLE) and in Rheumatoid Arthritis (RA) patients, but cardiovascular (CV) risk is particularly high in lupus women. Although conventional CV risk factors do not fully explain the excessive risk in inflammatory diseases, they remain major contributors to atherosclerosis. The aim of the present study was to investigate whether CV risk factors are differentially associated with SLE and RA.

**Methods**: One hundred women with SLE, 98 with RA and 102 controls matched on age and without overt CV or renal disease were assessed for the presence of Framingham (hypertension, hypercholesterolemia, low HDL, diabetes, smoking) and other CV risks (atherogenic index of plasma (AIP), insulin resistance, obesity, central obesity, metabolic syndrome, uric acid, sedentarism, hypothyroidism and family history of premature CV disease).

**Results**: Modifiable CV risk factors are highly prevalent and occur more frequently in SLE and RA than in age-matched controls. Some differences in Framingham risk factors were found between SLE and RA, with hypertension being more common in young lupus women, hypercholesterolemia more frequent in RA and low HDL-C more frequent in SLE. However, the estimated 10-year Framingham CHD risk or the Reynolds Risk Score was comparable in both diseases. Although hypercholesterolemia was more frequent in RA, lupus women display a more atherogenic lipid profile, with significantly lower HDL-C levels (56.5±16 mg/dl versus 63.7±18; p=0.005), and more cases above the high risk cut-points for cholesterol/HDL-C (14% versus 4.1%; p=0.01) and for AIP (15% versus 6.1%; p=0.03). Also, uric acid levels are higher in SLE women (4.8±1.5 mg/dl) than in RA (4.1±1.1 mg/dl), p=0.001. On the other hand, insulin resistance is significantly higher in women with RA as compared with SLE (median HOMA-IR 3.5 [6.4]) versus 0.72 [2.5]; p<0.0001) and the difference remained significant after adjustment for BMI and corticosteroids.

**Conclusions**: Cardiovascular risk profile is distinct in SLE and RA women and the contribution of traditional CV risk factors to atherogenesis may be different in these two diseases. Prospective studies are necessary to understand how the control of modifiable risks can improve CV outcome in different inflammatory settings.

## Introduction

The importance of premature atherosclerosis in Systemic Lupus Erythematosus (SLE) and Rheumatoid Arthritis (RA) is well established in population and cohort-based studies. Atherosclerotic complications account for the majority of late deaths in SLE[1] and represent the primary cause of death in half of the RA patients[2,3]. The incidence rates of myocardial infarction (MI) and angina in premenopausal lupus women is 50 times higher than in matched controls[4] and among RA women the observed incidence of MI is also greater than expected[5]. Furthermore, studies dealing with subclinical atherosclerosis showed the magnitude of this problem to be superior in SLE and RA as compared to the general population[6,7].

However, some differences in CV risk appear to exist between the two diseases. While the reported risk of ischemic heart disease is 5-8 folds higher in SLE patients[8,9], this increased risk is only 2-3 folds higher in RA patients[10,11]. In both diseases the rela-

*Rheumatology Research Unit, Instituto de Medicina Molecular da Faculdade de Medicina da Universidade de Lisboa, Lisbon, Portugal
**Rheumatology Department, Hospital Garcia de Orta, Almada, Portugal
***Cardiology Department, Hospital Fernando Fonseca, Amadora, Portugal
****Rheumatology and Metabolic Bone Diseases Department, Centro Hospitalar Lisboa Norte, Hospital de Santa Maria, Lisbon, Portugal

tive risk is more pronounced in youngest females[4,6,7].

Accelerated atherosclerosis in SLE and RA cannot be fully explained by traditional CV risk factors[8,11]. Nevertheless, conventional risk factors explain a substantial part of premature atherosclerosis[12,13] and, as many of them are modifiable, recommendations for their screening and control in inflammatory rheumatic disease have been developed[14,15].

The prevalence of hypertension, dyslipoproteinemia and sedentary lifestyle seems to be increased both in SLE and RA, though different studies provide a wide range of results [4,8,16,17,18]. However, there is limited information about the relative prevalence of CV risk factors in SLE and RA and to what extent this could account for the observed difference in CV events.

We examined the presence of classic Framingham and other conventional CV risk factors in SLE and RA women of similar age and without overt cardiovascular disease or renal function impairment to specifically address whether major differences exist between these two chronic inflammatory diseases of different pathogenesis. The Framingham 10-year risk of major heart events was estimated and, given the inflammatory setting of the study population, Reynolds Risk Score was also calculated. In addition, we assessed the distribution of CV risk factors in a control group to distinguish which factors are overrepresented in SLE and RA.

## Material and methods

### Patients

Adult women, fulfilling the American College of Rheumatology criteria for SLE or RA and attending the rheumatology clinic at Hospital Garcia de Orta in Almada, Portugal, on a regular basis, were recruited between January and December 2009. The control group consisted of women without chronic inflammatory disorders (patients with tendinitis or with low back pain) attending the same clinic. Exclusion criteria were: pregnancy, breastfeeding, prevalent myocardial infarction, angina pectoris, coronary revascularization, ischemic stroke and impaired renal function. In order to guarantee representativeness of different age groups, participants were enrolled in a consecutive way and allocated according to age frequency to obtain a final sample of 30% aged 18-39 years, 45% aged 40-59 years, and 25% aged ≥60 years. The study was approved by the local Ethics Committee and participants provided written informed consent.

### Assessments

Participants underwent a structured interview, physical examination and laboratory evaluation. Age, ethnicity, menopausal status, number of years of education, smoking, physical activity, disease duration from the physician's diagnosis, current medication, co-morbidities and family history of CV events was assessed. Information on cumulative corticosteroid dose was obtained from review of patients' medical records. Current disease activity was evaluated using the SLE Disease Activity Index 2000 (SLEDAI2K)[19] and in RA patients 28 joints were examined for tenderness and swelling, and the disease activity score (DAS28) was calculated using erythrocyte sedimentation rate[20]. Damage was scored according to the Systemic Lupus International Collaborating Clinics/ACR Damage Index (SDI)[21] and RA functional status was evaluated using the Stanford Health Assessment Questionnaire Disability Index (HAQ)[22].

Standing height, weight, waist circumference and blood pressure were measured and body mass index (BMI) ($Kg/m^2$) calculated. A fasting blood sample was obtained for measurement of plasma glucose, insulin, total cholesterol, high density lipoprotein (HDL-C), low density lipoprotein (LDL-C), triglycerides, uric acid and thyroid stimulating hormone (TSH). Insulin resistance was estimated by homeostasis model assessment (HOMA-IR) using the formula HOMA-IR= [fasting insulin (μU/ml) × fasting glucose (mmol/l)]/22.5. The ratio total cholesterol/HDL-C and the atherogenic index of plasma (AIP), defined as the logarithm of the ratio plasma triglycerides (mmol/l)/HDL (mmol/l)[23], were calculated. Cardiovascular risk factors were defined as follows: hypertension as a recorded blood pressure ≥140/90 mm/Hg or use of antihypertensive medication; dyslipidemia as a total cholesterol ≥200 mg/dl or LDL cholesterol ≥130 mg/dl or HDL cholesterol < 50 mg/dl or triglycerides ≥150 mg/dl or use of lipid-lowering agents; diabetes as a fasting glucose level ≥126 mg/dl, a self-reported physician diagnosis or pharmacologic treatment; insulin resistance was defined by an HOMA-IR in the top quartile of a non-diabetic population (>2.114)[24], impaired fasting glucose (≥110mg/dl) or diabetes; obesity was considered if

BMI ≥30 Kg/m2; central obesity if the waist circumference was above the IDF population recommended cut-points[25]; current smoker if the participant smoked ≥1 cigarettes per day during the last month; sedentary lifestyle if the amount of self-reported weekly exercise during the last 12 months was <3 times or <30 min per session; family history of premature CV events was defined as myocardial infarction or ischemic stroke occurred in a first-degree relative before the age of 55 years in males or before the age of 65 years in females. Metabolic syndrome was diagnosed according to the joint definition of the International Diabetes Federation, National Heart Lung and Blood Institute, American Heart Association, World Heart Federation, International Atherosclerosis Society and International Association for the Study of Obesity and using waist circumference ≥80 cm as the threshold for abdominal obesity[26].

For estimation of absolute 10-year risk for major coronary heart disease (CHD) events we utilized the predictive model based on the Framingham risk score algorithm developed by Wilson *et al*[27]. This algorithm assesses the probability of having a MI or cardiac death during the next 10 years on the basis of the risk factor profiles and was developed for people 30 to 74 years old. The model includes gender, age, diabetes, smoking status, blood pressure, total cholesterol and HDL cholesterol as risk predictors. The Reynolds Risk Score predicts global cardiovascular risk (MI, coronary revascularization, ischemic stroke and cardiovascular mortality) and incorporates C-reactive protein levels (CRP) and family history of premature CV disease[28]. The 10-year risks were categorized into low (predicted risk <10%), intermediate (predicted risk 10-20%) and high (predicted risk >20%)[29].

### Statistical analysis

Calculations were performed using SPSS 17.0 software for Windows and a 2-tailed p value <0.05 was selected as significant. Continuous variables are presented as means ± standard deviations or medians and inter-quartile ranges depending on whether the data were normally distributed or not. Categorical variables are reported as proportions. Comparisons between SLE and RA groups were made using chi-square or Fisher's exact test and Student t-tests for independent samples. The Mann Whitney U tests were used to compare variables that were highly skewed. Intergroup differences in CV risk factors were also calculated between each age stratum: 18-39 years, 40-59 years and ≥ 60 years. We also compared the disease group (SLE plus RA) with the control group using the same tests.

To evaluate the independence of the association between the diagnosis and CV risk factors we used binary logistic regression analysis. HOMA-IR, AIP and cholesterol/HDL-C ratio were dichotomized below and above high risk cutoffs. Multiple linear regression analysis was used to assess the independent relationship between diagnosis and lipid levels.

## Results

### Demographic and disease characteristics

We studied 300 women, 100 with SLE, 98 with RA and 102 controls, with a similar mean age, but a higher proportion of non-Caucasians among patients (14% of SLE and 11.2% of RA versus 2.9% of controls). The educational level and the proportion of postmenopausal women were comparable in the three groups (Table I). The median duration since SLE diagnosis was 6.6 (range 0.5 - 34) years. Arthritis had occurred in 78%, renal disease in 28%, serositis in 26%, hemolytic anemia in 15% and lupus psychosis in 5% of SLE cases. All SLE patients were ANA positive, 80% were anti-dsDNA positive and 37% tested positive either for anti-cardiolipin, lupus anticoagulant or both. At the time of the evaluation 83% had low disease activity (SLEDAI2K <6) and 42% presented some irreversible damage (SDI≥1). Sixty patients were taking steroids in a median daily dose of 7.5 mg (range 1.25 to 60 mg) of prednisolone equivalent. The majority (73%) was currently on antimalarials and 24% on immunossupressants.

The median duration of RA was 7.6 (range 0.5 to 30) years, 59.2% had erosive disease and 88.8% tested positive either for rheumatoid factor (RF), anti-CCP antibodies or both. The mean disease activity score (DAS28) was 4.24 and the mean HAQ 1.15. Fifty two (53.1%) patients were taking corticosteroids in a median dose of 5 mg/day (range 2.5 to 15 mg), 89 (91%) were currently receiving synthetic DMARDs, the most commonly used was methotrexate in 81 cases, and 39 (40%) were on biologics.

### Framingham CHD risk factors and predicted 10-year risk

The presence of Framingham CHD risk factors, i.e. hypertension, hypercholesterolemia, low-HDL,

**Table I. Demographic and clinical characteristics of study subjects**

| Characteristic | SLE (n = 100) | RA (n = 98) | Controls (n = 102) |
|---|---|---|---|
| Age, years | 46.6 ± 13.4 | 49.2 ± 13.7 | 47.7±13.4 |
| Caucasian, (%) | 86 (86) | 87 (88.8) | 99 (97.1 ) |
| Education, years | 8.5 [8] | 9 [8] | 9 [8] |
| Postmenopausal, (%) | 50 (50) | 54 (55.7) | 55 (53.9) |
| Disease duration, years | 6.6 [6.8] | 7.6 [9.1] | – |
| SLEDAI2K | 2 [4] | – | – |
| DAS 28 | 4.24 ± 1.28 | – | – |
| SDI | 0 [1] | – | – |
| HAQ | 1.15 ± 0.7 | – | – |
| NSAIDs, (%) | 28 (28) | 62 (63.3) | 23 (22.5) |
| Steroids, (%) | 60 (60) | 52 (53.1) | – |
| Current steroid dose, mg | 7.5 [12] | 5 [0] | – |
| Cumulative steroid dose, g | 7.7 [18] | 6.4 [15] | – |
| Methotrexate therapy, (%) | 9 (9) | 81 (82.7) | – |
| Antimalarial therapy, (%) | 73 (73) | 19 (19.4) | – |
| TNF blocker therapy, (%) | – | 39 (40) | – |
| Immunosuppressive therapy, (%) | 24 (24) | – | – |

Continuous variables are presented as means ± SD or median [IQR] according to the distribution and categorical variables as absolute values and proportions (%)

diabetes and smoking, occurred very often in the studied population: 83% of SLE, 79.6% of RA and 81% of control women presented at least on risk factor. The mean number of Framingham CHD risk factors was similar in SLE, RA and controls (1.56±0.9; 1.57±0.9 and 1.51±1.1, respectively). Patients were significantly more likely to have hypertension (OR=1.97, 95%CI 1.19-3.24, p=0.008); otherwise the distribution of CHD risk factors was similar in the 3 groups. The mean Framingham 10-year risk of major CHD events was 4.4% for SLE, 4.9% for RA and 4.5% for controls. Similarly, Reynolds Risk Score did not show significant differences among the groups: SLE 2.5%; RA 2.8%; controls 2.2%.

Hypertension was significantly more prevalent in SLE women aged 18-39 years (34.3%) than in RA women within the same age range (11%; p=0.04). The mean values of systolic and diastolic blood pressure in SLE and RA were 128±21/76±11 mmHg and 127±21/75±12 mmHg, respectively, but more women in the SLE group received anti-hypertensive treatment (45% vs 32.6%; p=0.05). Differences between SLE and RA groups could be detected in the prevalence of hypercholesterolemia and low-HDL, but again lupus patients were found to receive lipid-lowering treatment more frequently than RA (39% vs 20.4%; p=0.004).

### Lipid levels and atherogenic index of plasma

Fasting lipid levels were measured in all participants and mean values are shown in Table III. To determine the independent association of SLE and RA diagnosis with lipid levels we used multiple regression analysis adjusted for the identified potential confounders (lipid lowering therapy and current corticosteroid dose). SLE diagnosis was significantly associated with lower levels of total cholesterol as well as HDL-C and LDL-C. However, when we calculated the balance between risk and protective lipid fractions, lupus women were more likely to have cholesterol/HDL ratio (OR=3.92, 95%CI 1.24 to 12.48, p=0.02) and AIP values (OR=2.77, 95%CI 1.03-7.49, p=0.04) above the high risk cut-points.

### Distribution of other CV risk factors

Several CV risk factors have been described beyond the classic Framingham ones. We evaluated the presence of insulin resistance, obesity, abdominal obesity, metabolic syndrome, hypothyroidism, uric acid levels and family history of premature CV disease. Table IV shows the presence of these risk factors in SLE, RA and control women.

HOMA index and uric acid levels are significantly higher in patients than in controls, as well as the proportion of insulin resistance, central obesity,

**Table II. Distribution of traditional Framingham CHD risk factors in women with SLE, RA and non-inflammatory controls**

| | SLE (n =100) | RA (n = 98) | p-value | Controls (n=102) |
|---|---|---|---|---|
| Hypertension, (%) | 53 (53) | 43 (43.9) | ns | 33 (32.4)* |
| 18-39y | 12 (34.3) | 3 (11.1) | 0.04 | 2 (6.5)† |
| 40-59y | 25 (58.1) | 16 (36.4) | ns | 16 (33.3) |
| ≥60y | 16 (72.7) | 24 (88.9) | ns | 15 (65.2) |
| Hypercholesterolemia, (%) | 37 (37) | 53 (54) | 0.01 | 57 (55.9) |
| 18-39y | 12 (34.3) | 9 (33.3) | ns | 13 (41.9) |
| 40-59y | 11 (25.6) | 26 (60.5) | 0.001 | 27 (56.3) |
| ≥60y | 7 (37.2) | 18 (66.7) | ns | 17 (73.9) |
| Low HDL-C, (%) | 39 (39) | 20 (20.4) | 0.005 | 24 (23.8) |
| 18-39y | 15 (45.5) | 5 (18.5) | 0.02 | 7 (22.3) |
| 40-59y | 15 (37.5) | 9 (20.9) | ns | 11 (23.4) |
| ≥60y | 9 (37.4) | 6 (22.2) | ns | 6 (26.1) |
| Diabetes, (%) | 8 (8) | 7 (7.1) | ns | 7 (6.9) |
| Current smoker, (%) | 15 (15) | 17 (17.3) | ns | 19 (18.6) |
| 18-39y | 7 (20) | 6 (22) | ns | 9 (29) |
| 40-59y | 8 (18.6) | 11 (25) | ns | 10 (20.8) |
| ≥60y | 0 | 0 | ns | 0 |
| Framingham CHD risk ≥ 10%, (%) | 11/88 (12.5) | 16/91(17.6) | ns | 15/91 (16.5) |

*significant difference between patients and controls p=0.008; †p=0.04

**Table III. Lipid levels and atherogenic index of plasma**

| | SLE (n=100) | RA (n=98) | Adjusted p* | Controls (n=102) |
|---|---|---|---|---|
| Total cholesterol, mg/dl | 191.6 ± 43.5 | 203.3 ± 33.8 | 0.001 | 206.9 ± 33.8 |
| LDL-C, mg/dl | 114.7 ± 37 | 122.8 ± 28 | 0.01 | 127.9 ± 29 |
| HDL-C, mg/dl | 56.5 ± 16 | 63.7 ± 18 | 0.006 | 62.2 ± 15 |
| Triglycerides, mg/dl | 125.3 ± 78 | 103.9 ± 44 | ns | 98 ± 41 |
| Cholesterol/HDL-C >5, (%) | 14 (14) | 4 (4.1) | 0.01 | 9 (8.8) |
| AIP >0.21, (%) | 15 (15) | 6 (6.1) | 0.03 | 6 (5.9) |

The proportion of patients receiving lipid lowering medication was: SLE-39%; RA-20.4%; controls- 24.5% (p=0.009)
AIP– atherogenic index of plasma
*adjusted for use of lipid lowering therapies, and current corticosteroid dose

metabolic syndrome and hypothyroidism. More RA than SLE women are insulin resistant (OR=3.33, 95%CI 1.75-6.36, p=<0.0001) and the association between insulin resistance and RA diagnosis remained significant after adjustment for BMI and current corticosteroid dose (p=0.02).

We found uric acid concentration to be higher in lupus women, even in the absence of renal impairment or history of gout. The relationship between uric acid and SLE diagnosis remained significant irrespective of the use of anti-hypertensive medication (p=0.004). Additionally, more RA patients had a positive family history of premature cardiovascular events.

## Discussion

In the present study we found CV risk factors to be very common in SLE and RA women and that some

**Table IV. Distribution of other conventional cardiovascular risk factors**

| | SLE (n =100) | RA (n = 98) | p-value | Controls (n=102) |
|---|---|---|---|---|
| HOMA-IR | 0.72 [2.5] | 3.5 [6.4] | 0.0001 | 0.46 [0.9]* |
| Insulin resistant, n (%) | 35 (35) | 61 (62.2) | 0.0001 | 20 (19.6)* |
| Obesity, n (%) | 28 (28) | 31 (32) | ns | 28 (27.5) |
| 18-39y | 8 (22.9) | 5 (19.2) | ns | 3 (9.3) |
| 40-59y | 15 (27.3) | 12 (34.9) | ns | 14 (29.2) |
| ≥ ≥60y | 5 (22.7) | 14 (51.4) | ns | 11 (47.8) |
| Central obesity, n (%) | 72 (72) | 78 (79.6) | ns | 64 (62.3)** |
| 18-39y | 20 (57.1) | 20 (66.3) | ns | 11 (35.5)** |
| 40-59y | 35 (81.4) | 33 (75.6) | ns | 34 (70.8) |
| ≥60y | 17 (77.3) | 25 (95.8) | ns | 19 (82.6) |
| Sedentary lifestyle, n (%) | 84 (84) | 87 (88.7) | ns | 83 (82.2) |
| 18-39y | 28 (80) | 20 (74.1) | ns | 24 (80) |
| 40-59y | 35 (81.4) | 42 (95.5) | ns | 42 (87.5) |
| ≥60y | 21 (95.5) | 25 (92.6) | ns | 17 (73.9) |
| Metabolic Syndrome | 27 (27) | 25 (25.5) | ns | 16 (15.7)† |
| 18-39y | 5 (14.3) | 2 (7.7) | ns | 0 (0)† |
| 40-59y | 12 (27.9) | 12 (27.3) | ns | 7 (14.6) |
| ≥60y | 10 (45.5) | 10 (37) | ns | 9 (39.1) |
| Hypothyroidism (%) | 7 (7) | 11 (11.2) | ns | 3 (2.9)† |
| Uric acid, mg/dl | 4.8 ± 1.5 | 4.1 ± 1.1 | 0.001 | 3.8 ± 1.0* |
| Family history of premature CV disease, n (%) | 2 (2) | 14 (14.3) | 0.002 | 14 (13.7) |

*significant difference between patients and controls p=0.0001; ** p=0.02; †p=0.04

differences could be detected between these two inflammatory diseases and the control population. Metabolic syndrome, as well as some features of this syndrome, such as hypertension, insulin resistance, and central obesity, are overrepresented among SLE and RA patients. Decreased thyroid function was also found more frequently in both patient groups.

We could also depict differences in the prevalence of CV risk factors between SLE and RA women. With regard to Framingham risk factors, hypertension is more common in young lupus women and the alterations in lipid profile are distinct in SLE and RA patients. Despite lower total cholesterol, lupus women present a more atherogenic lipid profile characterized by lower HDL-C and a more harmful balance between risk and protective lipid fractions. Furthermore, the association of atherogenic lipid profile with SLE diagnosis persists, irrespective of the use of lipid-lowering agents or corticosteroids. Indeed, systemic inflammation may induce alterations in lipoprotein profile and in SLE patients it was shown that both disease activity and medication (corticosteroids and lipid-lowering agents) contribute to the changes in lipids that occur over time[30]. Active RA is also associated with a more atherogenic lipid profile and these changes have been documented even years before RA was diagnosed[31]. Furthermore, not only the levels of atheroprotective lipids are decreased, but also their function may be impaired in inflammatory rheumatic diseases[32]. Thus, identification of a more atherogenic lipid profile in lupus women, despite low disease activity and greater use of lipid-lowering agents is of interest because this suggests that the mechanisms underlying dyslipoproteinemia may differ in different inflammatory conditions.

In the general population, increased uric acid levels are an independent marker of cardiovascular disease[33] and arterial stiffness may represent the link between hyperuricemia and atherosclerosis[34]. We found higher uric acid levels in lupus women, despite normal creatinine levels and the absence

of gout. This increase was independent of the use of anti-hypertensive medication. We cannot rule out a subclinical renal impairment underlying the increased uric acid. Nevertheless, elevated uric acid may represent an additional risk for CV disease in lupus patients.

Insulin resistance, which is fundamental to the metabolic syndrome, was associated with symptomatic cardiovascular disease in the general population[35]. We found HOMA-IR to be significantly increased in RA as compared with SLE and this increase to be independent of BMI or corticosteroids. A previous study also demonstrated higher HOMA index in RA than in SLE and the association of insulin resistance with inflammation and coronary atherosclerosis[36]. This may be an important target to reduce CV risk in this patient population.

Hypothyroidism is associated with a wide range of metabolic changes, including increased BMI and adverse lipoprotein profile. There is also a relationship between hypothyroidism, vascular dysfunction and accelerated atherosclerosis[37]. Although hypothyroidism was more frequent in patients than in controls, its prevalence was similar in SLE and RA women.

A comprehensive identification of cardiovascular risk profile of SLE and RA is an opportunity to improve health management of these patients. As most of the identified risk factors are susceptible of intervention and modification, future research is crucial in order to establish to what extent the control of modifiable risk factors can improve cardiovascular outcome of these patients.

**Correspondence to**
Maria José Santos, MD
Rheumatology Research Unit
Instituto de Medicina Molecular da Faculdade de Medicina da Universidade de Lisboa
Edifício Egas Moniz
Av Prof Egas Moniz,
1649-028 Lisbon, Portugal.
E-mail: mjps@netvisao.pt

**References**

1. Urowitz M, Bookman A, Koehler B, Gordon D, Smythe H, Ogryzlo M. The bimodal mortality pattern of systemic lupus erythematosus. Am J Med 1976; 60: 221-225.
2. Maradit-Kremers H, Nicola PJ, Crowson CS, Ballman KV, Gabriel SE. Cardiovascular death in rheumatoid arthritis: a population-based study. Arthritis Rheum 2005;52:722-732.
3. Koivuniemi R, Paimela L, Leirisalo-Repo M. Causes of death in patients with rheumatoid arthritis from 1971 to 1991 with special reference to autopsy. Clin Rheumatol 2009;28:1443-1447.
4. Manzi S, Meilahn EN, Rairie JE, et al. Age-specific incidence rates of myocardial infarction and angina in women with systemic lupus erythematosus: comparison with the Framingham Study. Am J Epidemiol 1997;145:408-415.
5. Turesson C, Jarenros A, Jacobsson L. Increased incidence of cardiovascular disease in patients with rheumatoid arthritis: results from a community based study. Ann Rheum Dis 2004;63:952-955.
6. Roman MJ, Shanker BA, Davis A, et al. Prevalence and correlates of accelerated atherosclerosis in systemic lupus erythematosus. N Engl J Med 2003; 349:2399-2406.
7. Roman MJ, Moeller E, Davis A, et al. Preclinical carotid atherosclerosis in patients with rheumatoid arthritis. Ann Intern Med 2006;144:249-256.
8. Ward MM. Premature morbidity from cardiovascular and cerebrovascular diseases in women with systemic lupus erythematosus. Arthritis Rheum 1999;42: 338-346.
9. Esdaile JM, Abrahamowicz M, Grodzicky T, et al. Traditional Framingham risk factors fail to fully account for accelerated atherosclerosis in systemic lupus erythematosus. Arthritis Rheum 2001;44:2331-2337.
10. Solomon DH, Karlson EW, Rimm EB, et al. Cardiovascular morbidity and mortality in women diagnosed with rheumatoid arthritis. Circulation 2003;107:1303-1307.
11. del Rincón ID, Williams K, Stern MP, Freeman GL, Escalante A. High incidence of cardiovascular events in a rheumatoid arthritis cohort not explained by traditional cardiac risk factors. Arthritis Rheum 2001;44:2737-2745.
12. del Rincón I, Freeman GL, Haas RW, O'Leary DH, Escalante A. Relative contribution of cardiovascular risk factors and rheumatoid arthritis clinical manifestations to atherosclerosis. Arthritis Rheum 2005;52: 3413-3423.
13. Selzer F, Sutton-Tyrrell K, Fitzgerald SG, et al. Comparison of risk factors for vascular disease in the carotid artery and aorta in women with systemic lupus erythematosus. Arthritis Rheum 2004;50:151-159.
14. Mosca M, Tani C, Aringer M, et al. European League Against Rheumatism recommendations for monitoring patients with systemic lupus erythematosus in clinical practice and in observational studies. Ann Rheum Dis 2010;69:1269-1274.
15. Peters MJ, Symmons DP, McCarey D, et al. EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. Ann Rheum Dis 2010;69:325-331.
16. Bruce IN, Urowitz MB, Gladman DD, Ibañez D, Steiner G. Risk factors for coronary heart disease in women with systemic lupus erythematosus: the Toronto Risk Factor Study. Arthritis Rheum 2003;48:3159--3167.
17. Solomon DH, Curhan GC, Rimm EB, Cannuscio CC, Karlson EW. Cardiovascular risk factors in women

with and without rheumatoid arthritis. Arthritis Rheum 2004;50:3444-3449.
18. Gonzalez A, Maradit Kremers H, et al. Do cardiovascular risk factors confer the same risk for cardiovascular outcomes in rheumatoid arthritis patients as in non-rheumatoid arthritis patients? Ann Rheum Dis 2008;67:64-69.
19. Gladman DD, Ibañez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. J Rheumatol 2002;29:288-291.
20. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995;38:44-48.
21. Gladman D, Ginzler E, Goldsmith C, et al. The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index for systemic lupus erythematosus. Arthritis Rheum 1996; 39:363--369.
22. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum 1980;23:137-145.
23. Dobiasova M, Frohlich J. The plasma parameter log (TG/HDL-C) as an atherogenic index: correlation with lipoprotein particle size and esterification rate in apoB-lipoprotein-depleted plasma (FERHDL). Clin Biochem 2001;34:583-588.
24. Reilly MP, Wolfe ML, Rhodes T, Girman C, Mehta N, Rader DJ. Measures of insulin resistance add incremental value to the clinical diagnosis of metabolic syndrome in association with coronary atherosclerosis. Circulation 2004;110:803-809.
25. http://www.idf.org/webdata/docs/MetS_def_update2006.pdf
26. Alberti KG, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: a joint interim statement of the international diabetes federation task force on epidemiology and prevention; national heart, lung, and blood institute; American heart association; world heart federation; international atherosclerosis society; and international association for the study of obesity. Circulation 2009;120:1640-1645.
27. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation 1998; 97: 1837-1847.
28. Ridker P, Buring J, Rifai N, Cook N. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women. JAMA 2007;297:611-619.
29. Nair D, Carrigan TP, Curtin RJ, et al. Association of coronary atherosclerosis detected by multislice computed tomography and traditional risk-factor assessment. Am J Cardiol 2008 ;102:316-320.
30. Nikpour M, Gladman DD, Ibanez D, Harvey PJ, Urowitz MB. Variability over time and correlates of cholesterol and blood pressure in systemic lupus erythematosus: a longitudinal cohort study. Arthritis Res Ther 2010;12:125.
31. van Halm VP, Nielen MM, Nurmohamed MT, et al. Lipids and inflammation: serial measurements of the lipid profile of blood donors who later developed rheumatoid arthritis. Ann Rheum Dis 2007;66:184--188.
32. Hahn BH, Grossman J, Ansell BJ, Skaggs BJ, McMahon M. Altered lipoprotein metabolism in chronic inflammatory states: proinflammatory high-density lipoprotein and accelerated atherosclerosis in systemic lupus erythematosus and rheumatoid arthritis. Arthritis Res Ther 2008;10:213.
33. Gagliardi A, Miname M, Santos R. Uric acid: A marker of increased cardiovascular risk. Atherosclerosis 2009;202:11-17.
34. Kuo CF, Yu KH, Luo SF, et al. Role of uric acid in the link between arterial stiffness and cardiac hypertrophy: a cross-sectional study. Rheumatology (Oxford). 2010;49:1189-1196.
35. Bonora E, Kiechl S, Willeit J, et al. Insulin resistance as estimated by homeostasis model assessment predicts incident symptomatic cardiovascular disease in caucasian subjects from the general population: the Bruneck study. Diabetes Care 2007;30:318-324.
36. Chung CP, Oeser A, Solus JF, et al. Inflammation-associated insulin resistance: differential effects in rheumatoid arthritis and systemic lupus erythematosus define potential mechanisms. Arthritis Rheum 2008;58:2105-2112.
37. Napoli R, Guardasole V, Zarra E, et al. Impaired endothelial- and nonendothelial-mediated vasodilation in patients with acute or chronic hypothyroidism. Clin Endocrinol (Oxf) 2010;72:107-111.

# TRANSLATION INTO BRAZILIAN PORTUGUESE, CULTURAL ADAPTATION AND VALIDATATION OF THE SYSTEMIC LUPUS ERYTHEMATOSUS QUALITY OF LIFE QUESTIONNAIRE (SLEQOL)

Freire EAM[*,**,***], Bruscato A[***,****], Leite DRC[*], Sousa TTS[*], Ciconelli RM[**,***]

## Abstract

**Objectives:** Translate into Brazilian Portuguese, cross cultural adaptation and assess the reliability and validity of the Systemic Lupus Erythematosus Quality of Life Questionnaire (SLEQOL).
**Material and Methods:** *Study population:* 107 SLE patients, answered the SLEQOL questionnaire. *Translation*: into Portuguese and cross-cultural adaptation was performed in accordance with studies on questionnaire translation methodology into other languages. *Reliability:* Was analyzed using three interviews with different interviewers, two on the same day (interobserver) and the third within 14 days of the first assessment (intraobserver). *Validity:* Validity was assessed by correlating clinical and quality of life parameters with the SLEQOL. *Statistical analysis:* A descriptive analysis of the study sample. Reproducibility was assessed using an intraclass correlation coefficient (ICC). Internal consistency was assessed using Cronbach's alpha coefficient. To assess validity we used Pearson's correlation coefficient. Five percent was the level of significance adopted for all statistical tests.
**Results:** The SLEQOL was translated and culturally adapted. The main findings were: a 0.807 internal consistency correlation coefficient for all questions and domains. The inter and intraobserver correlation coefficients were 0.990 and 0.969 respectively. Validation showed good correlation with the SF-36 and poor correlation with lupus activity or damage indices.
**Conclusions:** The quality of life parameter has been increasingly taken into account for chronic diseases. To date there are no tools to assess Quality of Life in Systemic Lupus Erythematosus (SLE) written in the Portuguese language. The questionnaire is valid and reliable for SLE patients in Brazil.

**Keywords:** Systemic Lupus Erythematosus; Quality of Life; Translations; Reproducibility of Results.

## Introduction

Prevalence of Systemic Lupus Erythematosus (SLE) is increasing and SLE mortality is decreasing. The most important component of SLE medical care is to reduce the consequences and disabilities associated with SLE, bearing in mind both health related quality of life issues as well as longevity. The main objective of medical treatment is to reduce disabilities and defficiencies[1]. The quality of life assessment is based on applying tools or questionnaires that, for the most part, were originally written in English and focus on the English speaking population. Therefore these tools must be translated before they can be applied in another language, and the assessment properties demonstrated within a specific cultural context[2-6]. Scales that assess quality of life measure the changes in physical, psychological and social function as a result of disease, and reflect the patient's perception of his or her health. Generic quality of life instruments are valid for measuring the quality of life of SLE patients and enable comparison across a range of rheumatic diseases. However, critics argue that such tools are not adequately understood by the patients[1,7]. Specific quality of life scales include domains that are important for a specific disease. With respect to SLE, these domains must assess disease progress, the extent or patient organ involvement and their response to treatment[8].
In 2005 LEONG et al. published a paper describing

*Department of Internal Medicine, Federal University of Paraíba UFPB
**Department of Internal Medicine, Federal University of São Paulo UNIFESP
***Member of the Pronuclear Project, Brazilian Rheumatology Society
****Insper Institute of Education and Research, São Paulo

the development and preliminary validation of a specific Systemic Lupus Erythematosus Quality of Life questionnaire in English (SLEQOL). This questionnaire is made up of 40 items split into six domains: physical function, occupational activity, symptoms, treatment, mood and self-image. Each domain score varies from 1 to 7, with higher scores indicating poorer quality of life. Total scores vary between a low of 40 and a high of 280. The questionnaire was applied to 275 SLE patients and demonstrated good internal consistency, a Cronbach's alpha of 0.95 and intraobserver reproducibility of 0.83. Responsiveness was tested using a global assessment scale that varies between +7 and -7, submitted to statistical calculations that assess responsiveness, demonstrating that the SLEQOL questionnaire is more sensitive to changes over time[9] than the Short Form-36 (SF-36. a generic instrument). This questionnaire has not yet been translated into, or validated in Brazilian Portuguese. This then became the objective of our study, especially in light of the fact that there are no Portuguese language quality of life questionnaires specific for SLE.

The objective of this effort is to translate the SLEQOL into Brazilian Portuguese, culturally adapt it and check its measurement properties so that it may be applied as a quality of life assessment tool to Brazilian SLE patients.

## Material and Methods

One hundred and seven SLE patients over the age of 16, who fulfill the American College of Rheumatology[10] diagnostic criteria, do not present any cognitive impairment and signed the Term of Consent is accepted for this study. In order to be eligible for this study patients had to be clinically stable so as not to be submitted to any change in medication or other procedure for a period of 15 days or less, thus enabling an assessment of the questionnaire reproducibility. All of these patients were outpatient clinics randomly selected from the Rheumatology Clinic at Hospital São Paulo, UNIFESP or in the Rheumatology Clinic at Hospital Universitário, UFPB. Patients with other inflammatory diseases, fibromyalgia and hypothyroidism were excluded from the study. These diseases are excluded through clinical examination and laboratorial data. In addition to an overall assessment of the patient's health by the patient and her physician, a protocol listing clinical and demographic characteristics was applied and disease activity measured using SLEDAI- 2K[11] and BILAG[12];chronic damage was assessed using SLICC/ACR DI[13] and Quality of Life using SF-36[2].

**Translation and Cultural Adaptation:** The methodology for translation and cultural adaptation of these questionnaire was based on previous work discussing methodology used to translate the questionnaire into other languages[4-6].

**Initial translation:** the questions in the English language version of the SLEQOL questionnaire were translated into Brazilian Portuguese by two independent English language teachers, both Brazilian and both aware of the objectives of the survey. We stressed that the translation should be conceptual, rather than strictly literary. Both translations were compared by the translators themselves and by the study coordinator and, where there were differences, adjustments were made until a consensus was reached for the initial version (Version 1 in Portuguese).

**Assessment of the initial translation:** Version 1 in Portuguese was back translated by two different English language teachers, also Brazilian, who had not participated in the previous steps of this study. The back translation was compared to the original questionnaire in English and a committee analyzed the differences. Where necessary the statements or questions in Portuguese were rewritten until a consensus was reached, thus generating Version 2 in Portuguese.

**Assessment of the Cultural Equivalence (pretesting):** The questionnaire was applied to a group of ten SLE patients randomly selected from the Rheumatology Outpatient Clinic at Hospital São Paulo. To each of the study questions we added the option "does not apply" to find questions that were not understood or that were not truly relevant to our population and therefore culturally inappropriate. Questions considered to be "not applicable" 25% or more of the time were selected and analyzed by a group of researchers trying to obtain a consensus and replace these questions with others similar in concept so as not to significantly change the structure and assessment properties of the question. These changes generated a new version (Version 3 in Portuguese) This version was replicated until no more than 15% of the patients considered any single item to be "not applicable".

**Assessment of questionnaire measurement properties:** Reliability was analyzed based on three

interviews as follows: Two interviews were conducted by two separate interviewers (1 and 2) on the same day (interobserver), and a third interview was conducted by interviewer 1 within no more than 14 days following the first assessment (intraobserver) with the same patients; item consistency within the questionnaire was also assessed. All of the interviews were conducted at the same time of day.

**Validation:** Questionnaire validation was assessed by checking the relationship between its six domains scores , with higher scores indicating poorer quality of life and total scores vary between a low of 40 and a high of 280, and the scores obtained using existing quality of life questionnaires such as SF-36 where in each of eight domains scores varies from 0 to 100, with higher scores indicating best quality of life , and other clinical parameters such as disease activity by SLEDAI 2K and BILAG scores, Overall Physician and patient Assessment and severity by SLICC/ACR damage index during the assessment.

**Statistical analysis:** A descriptive analysis to characterize sample demographics and clinical status. Patient responses were evaluated using averages and standard deviations. To assess intraobserver reproducibility we calculated the intraclass correlation coefficient (ICC). Internal consistency of questionnaire items was assessed using Cronbach's alpha (Cronbach 1951). Validation was assessed using Pearson's correlation coefficient between quality of life questionnaires SLEQOL and SF-36, and other disease activity and severity parameters such as SLEDAI 2K ,BILAG, Overall Physician and patient Assessment and SLICC/ACR DI . Five percent was the level of significance adopted for all statistical tests.

## Results

107 SLE patients were assessed. Their socioeconomic and demographic characteristics are described in Table I. In all cases we used an interviewer to apply the questionnaire, given the socio-cultural level of the study population. During the cultural equivalence phase (pre testing) we found it hard to explain the scores (1 through 7) for each question, which required a bit more time when applying the questionnaire. Given that question 6 elicited more than 15% of "do not understand" responses, for physical function we replaced "walk for 3 km" with "walk for 1 hour". In question 7 and 8 under the occupational activity domain we switched "performance" and "interference" with "domestic chores or work outside the home" and "hampered career or education". In question 28 under mood we replaced "self consciousness" with "feels different from other people" and in question 34, under self image, we replaced "low self esteem" with "felt inferior to others". Once changed, the questions were considered to be appropriate or culturally equivalent by more than 95% of the patients and by the panel of experts that supported this project. The average time to apply the questionnaire was 10 minutes. Table II has the average value for each of the SLEQOL questionnaire components. The worst scores were in the "self image" and "occupational activity" domains and the best were in "treatment" and "mood" domains. In terms of the correlation coefficients, the internal consistency coefficient was 0.807 on average for all questions and domains; interobserver correlation was 0.990 and interobserver correlation 0.969 (Table III).

A total of 107 patients filled out the clinical protocol to assess validation. We correlated the questionnaire with the clinical and Quality of Life measurements already validated and in common use. By convention correlations may be positive or negative. According with Leong and colleagues we considered very strong correlations those with r >

**Table I. Clinical and socio-demographic characteristics of 107 SLE patients**

| | |
|---|---|
| Gender | |
| Female n (%) | 99 (99.5) |
| Male n (%) | 8 (7.5) |
| Age (years) | |
| Average, SD | 36.8; 12 |
| Minimum-Maximum | 17-68 |
| Disease duration (years) | |
| Average, SD | 5.9; 5.6 |
| Minimum-Maximum | 0.8-45 |
| Race (%) | |
| White | 46 (43) |
| Non white | 61 (57) |
| Education (years of schooling) | |
| Average, SD | 6.7; 3 |
| Minimum - Maximum | 3-16 |
| Income (US Dollars) | |
| Average, SD | 120; 80 |
| Minimum-Maximum | 60-220 |

**Table II. Values obtained for the SLEQOL questionnaire and domains applied to 107 SLE patients**

| | Minimum | Maximum | Average | SD |
|---|---|---|---|---|
| **SLEQOL** | | | | |
| Domains | | | | |
| Total Score | 42 | 260 | 116 | 52 |
| Physical Function | 6 | 40 | 14.5 | 9.9 |
| Occupational Activity | 9 | 57 | 19.7 | 10.6 |
| Symptoms | 8 | 40 | 17.8 | 8.4 |
| Treatment | 4 | 25 | 10.4 | 5.1 |
| Mood | 4 | 28 | 11 | 5.7 |
| Self Image | 9 | 60 | 22,1 | 12 |

**Table III. SLEQOL internal consistency and reproducibility in 50 patients assessed using an intraclass correlation coefficient and Cronbach's alpha**

| Correlation coefficients | SLEQOL |
|---|---|
| Intraobserver | 0.969 |
| Interobserver | 0.990 |
| Internal Consistency | 0.807 Total |
| | 0.807 by domain |

p< 0.001

7, as strong those with r =0.4 to 0.69, as moderate those with r = 0.3 to 0.39 and as poor those with r = 0.20 to 0.29, and established the level of correlation found.

Table IV shows the correlation between SLEQOL and activity, damage and quality of life indicators. There was a strong correlation between the total score of SLEQOL and SF-36 for physical and emotional issues. In terms of mood and self image domains, there was a strong correlation between SLEQOL and SF-36 for emotional issues. All other SLEQOL domains correlated poorly with the SF-36 domains.

Regarding the activity criteria, the symptoms, treatment and self image domains of SLEQOL showed moderate correlation with disease activity measured using SLEDAI 2K, which was not the case with BILAG.

The overall health assessment by a physician showed strong correlation with the overall SLEQOL score, but within the domains correlation was poor. The patient's global health assessment showed strong correlation with the total SLEQOL score as well as with the activities and self image domains.

Chronic damage showed strong correlation with total SLEQOL score, but moderate and poor with the domains.

## Discussion

Patient perception of their health and quality of life, as well as the impact of the disease and treatment on their life is being broadly recognized as a topic of research in clinical and epidemiological studies. However, most of the tools used to assess quality of life in these patients can only be found in English.

Experts agree that translating these tools to another language must not only be accurate, but that it is also important to test the psychometric measurements in a specific cultural context. Each society has its own sets of beliefs, attitudes, habits, behaviors and social values. These give people a sense of identity, how they should behave and consequently what they should and should not do. These rules or concepts reflect and distinguish the culture of a given country. When we proposed to translate a questionnaire, it should be presented in simple language that is easy to understand and remain equivalent in terms of the cultural concepts[2]. The differences in terms of culture and lifestyle make it difficult to find exact equivalents for a number of terms, which is why the translation must be carefully done and thoroughly tested in the new environment[14].

The SLEOQL was developed by Leong et al.[9] in English. I reported the problems our patients had in understanding the questionnaire in a personal communication with the author, primarily due to

**Table IV. Assessment of the correlation between SLEQOL, including its domains and SF-36. SLEDAI, overall Physician Assessment, overall Patient Assessment, BILAG and SLICC/ACR DI in 107 SLE patients**

| | SLEQOL | | | | | | |
|---|---|---|---|---|---|---|---|
| SF-36 | Total Score | Physical Function | Activities | Symptoms | Treatment | Mood | Self Image |
| Physical Functioning | 0.008 | 0.166 | 0.188 | - 0.264** | - 0.202* | 0.12 | 0.16 |
| Role Physical | - 0.573*** | -0.222* | 0.077 | 0.125 | 0.035 | 0.05 | 0.04 |
| Bodily Pain | 0.145 | 0.026 | 0.123 | - 0.232** | - 0.275** | 0.14 | 0.08 |
| General Health | 0.141 | 0.022 | 0.109 | 0.153 | 0.153 | 0.08 | 0.11 |
| Vitality | 0.120 | 0.128 | 0.104 | - 0.221* | 0.158 | 0.058 | 0.071 |
| Social functioning | - 0.240** | 0.012 | 0.076 | 0.171 | 0.164 | 0.094 | 0.090 |
| Role Emotional | - 0.450*** | - 0.270* | 0.005 | 0.152 | - 0.210* | - 0.531*** | - 0.780*** |
| Mental Health | 0.125 | 0.018 | 0.160 | - 0.225* | - 0.250* | - 0.271** | 0.130 |
| SLEDAI 2K | 0.001 | 0.110 | 0.190 | 0.361* | 0.385* | 0.231* | 0.380* |
| Overall Physician Assessment | - 0.480*** | - 0.240** | - 0.281* | - 0.230* | 0.150 | 0.181 | - 0.270* |
| Overall Patient Assessment | - 0.482*** | - 0.290* | - 0.430*** | - 0.291* | - 0261* | - 0.382* | - 0.401* |
| BILAG | 0.250* | 0.120 | 0.181 | 0.241* | 0.010 | 0.183 | 0.170 |
| SLICC/ACR DI | 0.412* | 0.340* | 0.310* | 0.030 | 0.221* | 0.190 | 0.210* |

* P < 0.05; **P < 0.01; ***P < 0.001

the socio-intellectual level of our patients compared to those in Singapore. We had the author's support in all phases of the translation and cultural adaptation of the questionnaire.

Leong et al. (2005) achieved similar results to ours in terms of the highest scores in the "occupational activity" and "self image" domains. This is likely due to the fact that active SLE is an incapacitating disease that also changes the patient's appearance, in addition to the side-effects of treatment with steroids and immune suppressants. The better results in the Treatment and Mood domains may reflect a component of patient adaptation to the disease.

Every assessment instrument should be reproducible over time – in other words, it should produce equal or very close results in two or more instances with the same patients, evidently assuming no change in clinical status. Test-retest reproducibility has been demonstrated. The internal consistency of the Portuguese language of the SLEQOL, assessed by the correlation between the various questions proved to be adequate, with a coefficient of 0.8. This is an important observation as some of the questions were altered. In the translation and cultural adaptation to Chinese, the SLEQOL items in English could be precisely translated into Chinese, so the translation proceeded smoothly. Once translated, the SLEQOL-C was applied to 638 patients with no problem in terms of understanding the questions[15].

The fact that during the validation process the questionnaire correlated only moderately with disease activity and damage is consistent with other publications[16]. This suggests the possibility that activity and damage do not directly interfere in quality of life, as in the patient's overall health assessment the correlations were better than with these indicators were already established, or it could be that they truly do not capture this facet of the disease. A possible explanation might be adaptation to chronic disease or the type of personality influencing the subjective perception of overall quality of life[17].

Gladman (2006) reported that, during the past two decades a number of tools have been developed to assess SLE activity and damage, however quality of life has been assessed using a generic tool. Recently SF-36 has been shown not to be very sensitive to changes[18], which is why its use in clinical trials has been questioned. The author goes on to state that specific tools to assess quality of life in SLE patients are necessary, such as the SLEQOL that has been well tested in terms of its measure-

ment properties, and encourages that it be applied and validated with other populations[19].

In conclusion, we have translated, culturally adapted, checked the reliability and validated the SLEQOL using international methodology and demonstrated that the questionnaire is valid and reproducible. Studies are already underway to demonstrate this instrument's sensitivity to change.

**Correspondence to**
Eutilia Freire
AV. Cabo Branco 3524/501-B
Cabo Branco – João Pessoa
58045-010 - Paraíba – Brazil
E-mail: eutilia@terra.com.br

**References**

1. Testa MA, Simonson DC. Assesment of quality-of-life outcomes. N Engl J Med 1996;334: 835-840.
2. Ciconelli R, Ferraz M, et al. Tradução para lingua portuguesa e validação do questionário genérico de avaliação de qualidade de vida SF-36 (Brasil SF-36). Rev Bras Reumatol 1999;39:143-150.
3. Mathias SD, Fifer SK, et al. Rapid translation of quality of life measures for international clinical trials: avoiding errors in the minimalist approach. Qual Life Res 1994;3: 403-412.
4. Guillemin F. Cross-cultural adaptation and validation of health status measures. Scand J Rheumatol 1995;24: 61-63.
5. Guillemin F, Bombardier C, et al. Cross-cultural adaptation of health-related quality of life measures: literature review and proposed guidelines. J Clin Epidemiol 1993;46:1417-1432.
6. Beaton DE, Bombardier C, et al. Guidelines for the process of cross-cultural adaptation of self-report measures. Spine 2000;25: 3186-3191.
7. Dobkin PL, Da Costa D, et al. Quality of life in systemic lupus erythematosus patients during more and less active disease states: differential contributors to mental and physical health. Arthritis Care Res 1999;12:401-410.
8. Murawski MM, Miederhoff PA. On the generalizability of statistical expressions of health related quality of life instrument responsiveness: a data synthesis. Qual Life Res 1998;7:11-22.
9. Leong KP, Kong KO, et al. Development and preliminary validation of a systemic lupus erythematosus-specific quality-of-life instrument (SLEQOL). Rheumatology (Oxford) 2005;44: 1267-1276.
10. Tan EM, Cohen AS, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982; 25:1271-1277.
11. Gladman DD, Ibanez D, et al. Systemic lupus erythematosus disease activity index 2000. J Rheumatol 2002;29: 288-291.
12. Isenberg DA, Rahman A, et al. BILAG 2004. Development and initial validation of an updated version of the British Isles Lupus Assessment Group's disease activity index for patients with systemic lupus erythematosus. Rheumatology (Oxford) 2005.
13. Gladman DD, Urowitz MB, et al. The reliability of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index in patients with systemic lupus erythematosus. Arthritis Rheum 1997; 40: 809-813.
14. Ferraz MB, Oliveira LM, et al. Crosscultural reliability of the physical ability dimension of the health assessment questionnaire. J Rheumatol 1990;17: 813--817.
15. Kong KO, Ho HJ, et al. Cross-cutural adaptation of Systemic Lupus Erythematosus Quality of Life Questionnaire into Chinese. Arthritis Rheum 2007;57:980--985.
16. Freire EA, Maia IO, et al. Damage index assessment and quality of life in systemic lupus erythematosus patients (with long-term disease) in Northeastern Brazil. Clin Rheumatol 2007;26: 423-428.
17. Snoek FJ, Pouwer F, et al. Diabetes related emotional distress in Dutch and US diabetic patients: cross cultural validity of the problem areas in diabetes scale. Diabetes Care 2000; 23:305-309.
18. Panopalis P, Petri M, et al. The systemic lupus erythematosus tri-nation study: longitudinal changes in physical and mental well-being. Rheumatology (Oxford) 2005;44: 751-755.
19. Gladman DD. A novel, disease-specific quality-of-life instrument for patients with SLE. Nat Clin Pract Rheumatol 2006;2:132-133.

# ASSOCIATION BETWEEN SADDLE NOSE DEFORMITY AND RETRO-ORBITAL MASS IN WEGENER'S GRANULOMATOSIS

Guilherme Laranja Gomes*, Ari Stiel Radu Halpern*,
Fernando Henrique Carlos de Souza*, Samuel Katsuyuki Shinjo*

## Abstract

**Objectives:** The relationship between saddle nose deformity (SND) in Wegener's granulomatosis (WG) and other clinical features, including retro-orbital mass formation (ROM), has been poor described. Therefore, this relationship was analyzed retrospectively from 2000 to 2010.

**Patients and Methods:** Eighteen consecutive WG patients with SND diagnosed by computed tomography were matched to 36 WG patients without SND (control group) for gender, age at WG diagnosis and disease duration.

**Results:** No difference was found between the two groups in relation to WG type (limited and systemic forms), ethnicity, laboratory features, constitutional symptoms or clinical manifestations, including upper respiratory tract, and treatment, except for ROM (33.3 *vs.* 2.8% in SND(+) and SND(-) groups, respectively; $p$=0.004) and subglottic stenosis (22.2 *vs.* 2.8%; $p$=0.038). However, on multivariate analysis, only ROM (OR 17.15; 95% CI 1.11-265.52) was statistically associated to SND. In addition, in more than half of the cases, SND manifested prior to ROM.

**Conclusions:** Results of this prospective analysis showed that SND was strongly associated to ROM in WG. Since early diagnosis and aggressive treatment of orbital involvement could lead to better prognosis, the presence of SND warrants additional vigilance.

**Keywords:** Subglottic Stenosis; Wegener's Granulomatosis; Retro-orbital Mass; Saddle Nose; Systemic Vasculitis.

*Division of Rheumatology, Faculdade de Medicina da Universidade de São Paulo, Brazil

## Introduction

Wegener's granulomatosis (WG) is a systemic disease characterized by necrotizing granulomatous vasculitis, affecting mainly the upper airways, lungs and kidneys[1-3].

The incidence of WG ranges from 3 to 9.7 cases per million / year[4]. The disease is more prevalent in the Caucasian population and the average age of involvement is about 40 years[2,5,6].

Eye/nose/throat (ENT) involvement in WG occur in more than 75% of cases, reaching 90-100% during disease evolution[2,5,7-24]. It is responsible for considerable morbidity and chronic damage in WG[2,5,7-24].

Ophthalmologic involvement is also prominent consisting of episcleritis, scleritis, lacrimal gland obstruction, ptosis, ocular pain, diplopia, amaurosis, periorbital cellulitis and retro-orbital mass (ROM) formation[14-20]. The latter occurs in 15-50% of WG cases and can represent an isolated manifestation of WG or as a consequence of adjacent paranasal sinuses inflamation[11,18-23]. However, this association has not yet been well established in the literature. In addition, the early ROM diagnosis could be important, when there is predominance of granulomatous inflammation and focal vasculitis, instead of irreversible fibrosis[24], allowing appropriate treatment meant to keep a good prognosis.

Sinonasal manifestations described include epistaxis, nasal crusting, smell disturbances, nasal congestion, purulent rhinorrhea, and nasopharyngeal ulceration[2,10,11]. During the evolution of the disease the submucosa and mucosa areas become more involved causing ulcerations, chronic sinusitis, nasal septal perforations, paranasal sinus mucocele formation from chronic outflow tract obstruction, and nasal bone destruction with classic presentation of saddle nose deformity (SND) which occurs in 10-25% of cases[9-13]. Despite the importance of sinonasal findings in WG, there are relative few studies on sinonasal profile in WG, mainly SND.

Therefore, in the present study we analyzed the relationship between SND and other systemic features in WG, including possible ROM formation.

## Patients and Methods

The present study was based on a single center retrospective cohort that spanned from January 2000 to January 2010 and where the patients were prospectively studied. Eighteen consecutive WG patients with SND were followed at Division of Rheumatology, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Brazil.

For each patient, two other WG patients without SND (control group) were randomly selected and matched for age, gender, age at WG diagnosis, and disease duration.

All patients fulfilled at least two of the five modified American College of Rheumatology (ACR) criteria for the classification of WG (in the modified ACR criteria, a positive serum enzyme immunoassay for antibodies against proteinase 3 (ELISA) was added to the original four criteria[24]. For the limited form of WG, diagnosis was based on the modified ACR criteria for the classification of WG, in the absence of disease features that posed immediate threats to either a critical individual organ or to the patient's life[2,25,26].

ROM was diagnosed by computed tomography made as a routine evaluation of WG patients in our service. All patients were also analyzed for nasal sinus involvement, mainly, nasal septum destruction and saddle nose deformity.

All information regarding demographic, clinical and laboratory features were extensively reviewed and obtained from the patients' medical files. The following variables over the first three years of follow up were recorded: age, sex, ear/nose/ /throat (ENT) involvement (defined as rhinorrhea, epistaxis, oral or nasopharyngeal ulceration, chronic sinusitis, saddle nose deformity, mastoiditis), pulmonary involvement (subglottic stenosis, hemoptysis, or abnormal thoracic imaging in the absence of concomitant infectious pneumopathy such as pulmonary infiltrate and/or nodules or cavitations, respiratory failure, alveolar hemorrhage), renal involvement (glomerulonephritis: microscopic hematuria or red cell casts in the urinary sediment with either proteinuria >0.5 mg/day or serum creatinine >1.8 mg/dL; chronic renal), joint involvement (arthralgias or arthritis), cutaneous involvement (petechiae or purpura, cutaneous vasculitis, skin ulcers), ophthalmologic involvement (episcleritis, scleritis, amaurosis), neurologic involvement (peripheral: mononeuritis multiplex or cranial neuropathy, cranial vasculitis), cardiac involvement (cardiomyopathy), gastrointestinal involvement (intestinal perforation or bleeding). An organ or system was also deemed to be affected when a biopsy contained granulomatous inflammation or vasculitis or, in the case of the kidneys, segmental glomerular necrosis or pauci-immune extracapillary glomerulonephritis.

The extent of organ damage secondary to vasculitis was assessed by means of the Vasculitis Damage Index (VDI)[27], This score ranges from 0 to 64, with higher scores indicating more severe damage.

The classic therapeutic regimen with corticosteroids and imunossupressive agents was given to all patients. Cyclophosphamide was used either in an oral daily schedule of 2 mg/kg or every three weeks intravenous pulse therapy (doses ranging between 0.5 and 1.0 g/m$^2$). The choice between oral and parenteral treatment was based on access to medication and patient adherence to treatment. Oral prednisone, starting with 1mg/kg/day, was maintained for at least 2 months before gradual reduction for the next 6 months. In cases of immediate threat to either a critical organ or to the patient's life, corticosteroid was given as intravenous pulse therapy (methyl prednisolone 1 g + saline solution 0.9% 500 mL in 4 h, once day, three consecutive days) followed by the oral regimen described above. Other immunosuppressive agents such as methotrexate, azathioprine, and mycophenolate mofetil were used in selected cases due to intolerance to cyclophosphamide. Refractory patients received additional intravenous human immunoglobulin (2 g/kg). Cotrimoxazol (800+160 mg, twice per day, oral) was used in all patients.

**Statistical analysis.** Continues variables are shown as means plus standard deviation (SD) and categorical variables as percentages. Fisher's exact test was used for comparisons between both groups when applicable. The 95% confidence interval (95% CI) of percentage was calculated by a binomial distribution. $p$ values < 0.05 were considered to be statistically significant. Evaluation was performed using the computer program STATA version 7.0 software (STATA, College Station, TX, USA).

## Results

Eigtheen WG patients with SND were analyzed and matched for gender, age at WG diagnosis and duration of disease with 36 control subjects.

The demographic, clinical and laboratory features of all patients are shown in Table I. No difference was detected between the two groups in relation to WG form (limited form 0 *vs.* 8.3%; $p$=0.543), ethnicity (white, respectively, 83.3 *vs.* 86.1%; $p$=0.651) and laboratorial characteristics (cytoplasmatic ANCA, respectively, 72.2 *vs.* 55.6%; $p$=0.375). The VDI value was also similar to both groups (respectively, 6.3±2.0 *vs.* 6.3 ±2.5; $p$=0.966).

In general, constitutional symptoms and clinical manifestations were also similar in both groups, except for predominance of ROM (33.3 *vs.* 2.8%; $p$=0.004) and subglottic stenosis (22.2 *vs.* 2.8%; $p$=0.038) in patients with SND. In 6 out of 18 patients, ROM manifested prior to SND (Figure 1).

Therapy was also comparable in both groups and comprised glucocorticoid (100.0 *vs.* 94.5%; $p$=0.547) and cyclophosphamide (72.2 *vs.* 83.3%; $p$=0.475). Others drugs that were used include methotrexate (33.3 *vs.* 27.8%; $p$=0.756), azathioprine (16.7 *vs.* 19.5%; $p$=1.000), mycophenolate mofetil (27.8 *vs.* 8.3%; $p$=0.100), cotrimoxazol (77.8 *vs.* 55.6%, $p$=0.142) and human intravenous immunoglobulin (27.8 *vs.* 13.9%; $p$=0.273).

Comorbidities were also found equally in both groups consisting of systemic arterial hypertension (50.0 *vs. vs.* 33.3%; $p$=0.384) and non-glucocorticoid related diabetes mellitus (11.1 *v*s. 13.9%; $p$=1.000).

Both ROM (33.3 *vs.* 2.8%, $p$=0.004) and subglottic stenosis (22.2 *vs.* 2.8, $p$=0.038) were associated to SND on univariate analysis, while multivariate analysis, showed association only with ROM (Table II).

## Discussion

SND occurs in 10-25% of WG cases[9-13] and despite the importance of sinonasal findings in WG, relatively few studies have investigated the relationship between SND and other WG profiles. In the present study, a large retrospective analysis was conducted that found SND to be strongly associated with ROM in WG and therefore reinforcing the possibility of inflammatory extension from adjacent areas. Moreover, SND showed a tendency to manifest earlier than ROM.

Orbital mass is the most common form of ophthalmologic involvement later in the disease course and may be contiguous, secondary to spread of granulomatous disease from the nasal passages or paranasal sinuses, or focal, arising primarily within the orbit[2,9,18-24,28-33]. However, this hypothesis has not yet been verified in a large sample[31,33].

Rasmussem *et al*[9] analyzed the distribution of ENT involvement in a sample of 124 patients from the European vasculitis study group (EUVAS), but did not focus on their correlations. Cannady *et al*[11] observed sinonasal involvement in 89% of cases, manifesting as nasal crusts (56%), nasal obstruction (54%), epistaxis (50%), sinusitis (33%) and orbital lesions (2.5%). Woo *et al*[29] studied the main ophthalmologic manifestations in WG, and examined the simultaneous involvement of eyes and chronic sinusitis. However, these authors did not report the frequency of ROM or its relationship with other sinonasal manifestations. On the other hand, Kwan and Rose[33] reported a patient case with limited WG who developed an orbital inflammatory mass as a direct extension of nasal inflammatory disease through a rhinostomy formed during lacrimal drainage surgery.

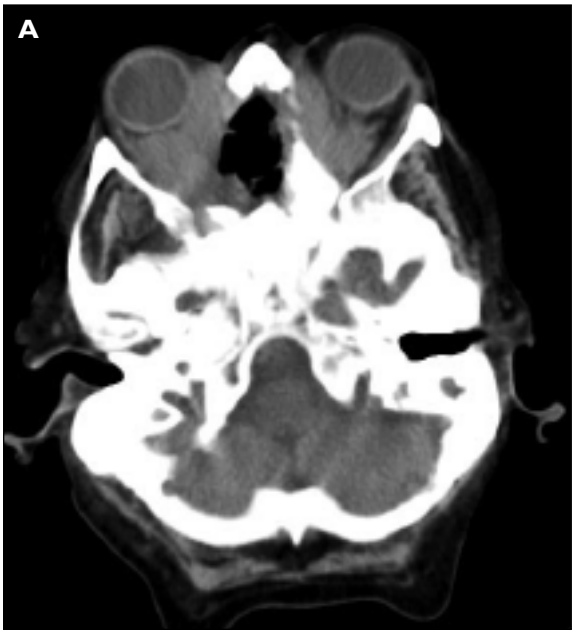
There is a significant difference in outcomes between orbital and sinonasal disease in WG[31]. The former often progresses in spite of systemic treatment and is generally acknowledged as one of the most refractory components of WG[31]. Orbital granulomas in WG present variable histopathology features of inflammation, fibrinoid necrosis, fibrosis and vasculitis[24]. During natural disease progression, fibrous tissue may replace areas of acute inflammation and necrosis. Consequently, granulomatous lesions in the orbit can diminish in response to immunosuppressive treatment but subsequently become fibrotic. Thus, early orbital disease diagnosis and its treatment may slow progression and reduce sequelae. In this context, it is important to identify laboratory and/or clinical features associated to orbital lesion to allow early intervention, for example with more aggressive drugs.

The association between SND and subglottic stenosis has not yet been described in the literature. This association was confirmed in the present study, but only on univariate analysis. Subglottic stenosis may arise either as a presenting feature or as a late-stage manifestation of the disease and it

**Table I. Demographic, clinical and laboratory features of Wegener's Granulomatosis patients**

| | Saddle nose+ (N=18) | Saddle nose- (N=36) | p |
|---|---|---|---|
| Mean age at onset WG diagnosis ± SD | 41.3±15.6 | 41.1 ±16.5 | 0.967 |
| Time duration of WG ± SD | 8.4±6.4 | 8.9±6.6 | 0.805 |
| Gender male (%) | 5 (27.8) | 16 (44.4) | 0.505 |
| Ethnicity white (%) | 15 (83.3) | 31 (86.1) | 0.651 |
| Limited form of WG (%) | 0 | 3 (8.3) | 0.543 |
| cANCA (%) | 13 (72.2) | 20 (55.6) | 0.375 |
| pANCA (%) | 3 (16.7) | 6 (16.7) | 1.000 |
| Constitutional symptoms (%) | 9 (50.0) | 17 (47.2) | 1.000 |
| Ophthalmologic involvement | | | |
| Episcleritis / escleritis (%) | 8 (44.4) | 12 (33.3) | 0.552 |
| Retro-orbital mass (%) | 6 (33.3) | 1 (2.8) | 0.004 |
| Ductal lacrimal obstruction (%) | 1 (5.6) | 2 (5.6) | 1.000 |
| Renal involvement | | | |
| Glomerulonephritis (%) | 10 (55.6) | 25 (69.5) | 0.372 |
| ENT involvement | | | |
| Sinusitis (%) | 14 (77.8) | 27 (75.0) | 1.000 |
| Rhinorrhea (%) | 12 (66.7) | 20 (55.6) | 0.560 |
| Epistaxis (%) | 12 (66.7) | 20 (55.6) | 0.560 |
| Subglottic stenosis (%) | 4 (22.2) | 1 (2.8) | 0.038 |
| Mastoiditis (%) | 1 (5.6) | 2 (5.6) | 1.000 |
| Hearing loss (%) | 2 (11.1) | 5 (13.9) | 1.000 |
| Pulmonar involvement | | | |
| Hemoptisis (%) | 5 (27.8) | 15 (41.7) | 0.381 |
| Alveolar hemorrhage (%) | 1 (5.6) | 5 (13.9) | 0.651 |
| Pulmonary infiltrate (%) | 2 (11.1) | 14 (38.9) | 0.057 |
| Pulmonary nodules (%) | 8 (44.4) | 12 (33.3) | 0.552 |
| Cavitations (%) | 5 (27.8) | 6 (16.7) | 0.475 |
| Cutaneous involvement | | | |
| Skin ulcers (%) | 2 (11.1) | 3 (8.3) | 1.000 |
| Purpura or petechiae (%) | 3 (16.7) | 8 (22.2) | 0.733 |
| Neurological involvement | | | |
| Peripherical (%) | 2 (5.6) | 3 (16.7) | 0.319 |
| Cranial (%) | 0 | 2 (11.1) | 0.107 |
| Central (%) | 0 | 0 | 1.000 |
| Cardiac involvement | | | |
| Cadiomyopathy (%) | 0 | 0 | 1.000 |
| Gastrointestinal tract involvement | | | |
| Intestinal bleeding (%) | 0 | 2 (2.8) | 1.000 |
| Intestinal perfuration (%) | 1 (5.5) | 3 (8.3) | 1.000 |
| Joint involvement | | | |
| Arthralgia or arthritis (%) | 2 (11.1) | 5 (13.9) | 1.000 |

ANCA: anti-neutrophil cytoplasmic antibody; ENT: eye, nose, throat; SD: standard deviation; WG: Wegener's granulomatosis



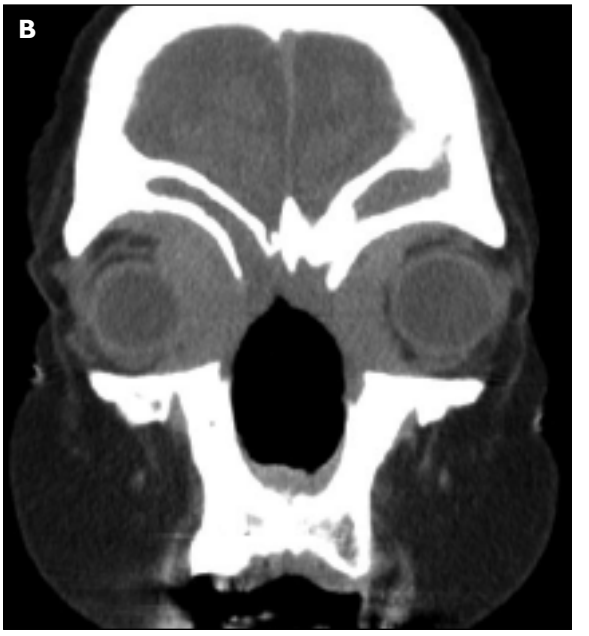




**Figure 1.** Wegener' s granulomatosis patient with retro-orbital mass formation and adjacent paranasal involvement (nasal septal destruction) at computed tomography

**Table II. Multivariate analysis**

| | OR | 95% CI |
|---|---|---|
| Sex (male) | 0.32 | 0.07-1.44 |
| Age | 1.02 | 0.98-1.06 |
| Retro-orbital mass | 17.15 | 1.11-265.52 |
| Subglottic stenosis | 2.14 | 0.11-41.13 |

CI: confidence interval; OR: *odds ratio.*

is an important complication occurring in 10-16% of WG[1,9,10,34-37]. In this case, an inflammatory process occurs in the walls of these structures causing air tract stenosis and subglottic stenosis, considered a catastrophic manifestation with acute respiratory insufficiency[34-37].

The possible association between ROM and subglottic stenosis has been previously described[30] only in small samples (6 out of 51 patients with WG). In this same study, it was reported the presence of SND in two patients with subglottic stenosis although ROM was not described.

In conclusion, SND was strongly associated to ROM and had a tendency to manifest earlier than did ROM in WG. This finding indicates a need for increased vigilance among this group of WG patients.

**Correspondence to**
Samuel Katsuyuki Shinjo
Av. Dr. Arnaldo, 455, 3° andar, Sala 3190,
CEP 01246-903, São Paulo, Brazil.
Phone: +55-11-3061-7492.
Fax: +55-11-3061-7490.
E-mail: samuel.shinjo@gmail.com

**References**

1. Godman GC, Churg J. Wegener´s granulomatosis: pathology and review of literature. Arch Pathol Lab Med 1954; 58: 533-553.
2. Hoffman GS, Kerr GS, Leavitt RY, et al. Wegener´s granulomatosis: an analysis of 158 patients. Ann Intern Med 1992; 116: 488-498.
3. Kornblut AD, Wolff SM, deFries HO, Fauci AS. Wegener´s granulomatosis. Laryngoscope 1980; 90: 1453--1465.
4. Nolle B, Specks U, Ludemann J, Rohrbach M, DeRemee RA, Gross WL. Anticytoplasmic autoantibodies: their immunodiagnostic value in Wegener granulomatosis. Ann Intern Med 1989; 111: 28-40.
5. Cotch MF, Hoffman GS, Yerg DE, Kaufman GI, Targonski P, Kaslow RA. The epidemiology of Wegener´s granulomatosis. Estimate of the five year prevalence, annual mortality and geographic disease distribution from population-based data sources. Arthritis Rheum 1996; 39: 87-92.
6. Bajema IM, Hagen EC, van der Woude FJ, Bruijin JA. Wegener´s granulomatosis: a meta-analysis of 349 literary cases reports. J Lab Clin Med 1997; 129: 17-22.

7. D´Cruz DP, Baguley E, Asherson RA, Hughes GR. Ear, nose and throat symptoms in subacute Wegener´s granulomatosis. BMJ 1989; 299: 419-422.
8. McDonald TJ, DeRemee RA. Head and neck involvement in Wegener´s granulomatosis. Adv Exp Med Biol 1993; 336: 309-313.
9. Rasmussen N. Management of the ear, nose and throat manifestations of Wegener granulomatosis: an otorhinolaryngologisti´s perspective. Curr Opin Rheumatol 2001; 13: 3-11.
10. Langford CA, Hoffman GS. Wegener´s granulomatosis. Thorax 1999; 54: 629-637.
11. Cannady S, Barra PS, Hoffman GS. Sinonasal Wegener Granulomatosis: A single institution experience with 120 cases. The Laryngoscope 2009; 119: 757-761.
12. McDonald T, DeRemee RA. Wegener´s granulomatosis. Laryngoscope 1983; 93: 220-231.
13. McDonald TJ, DeRemee RA, Kern EB, et al. Nasal manifestations of Wegener´s granulomatosis. Laryngoscope 1974; 84: 2101-1213.
14. Fauci AS, Wolff SM. Wegener´s granulomatosis: studies in eighteen patients and a review of the literature. Medicine (Baltimore) 1973; 52: 535-561.
15. O´Devaney K, Ferlito A, Hunter BC, et al. Wegener´s granulomatosis of the head and neck. Ann Otol Rhinol Laryngol 1998; 107: 439-445.
16. Pakrou N, Selva D, Leibovitch I. Wegener´s granulomatosis: ophthalmic manifestations and management. Semin Arthritis Rheum 2006; 35: 284-292.
17. Jabs DA. Ocular manifestations of the rheumatic diseases. In: Tasman W, Jeager EA, editors. Duane´s clinical ophthalmology. Philadelphia: Jb Lippincott. 1992; p. 1-33.
18. Fauci AS, Haynes BF, Katz P, Woff SM. Wegener´s granulomatosis: Prospective clinical and therapeutic experience with 85 patients for 21 years. Ann Intern Med 1983; 98: 76-85.
19. Haynes BF, Fishman ML, Fauci AS, Woff SM. The ocular manifestations of Wegener´s granulomatosis: Fifteen years of experience and review of the literature. Am J Med 1977; 63: 131-141.
20. Bullen CL, Liesegang TJ, McDonald TJ, DeRemee RA. Ocular complications of Wegener's granulomatosis. Q J Med 1993; 90: 279-290.
21. Thorne JE, Jabs DA.Ocular manifestations of vasculitis. Rheum Dis Clin North Am 2001; 27: 761-779.
22. Stavrou P, Deutsch J, Rene C, Laws DE, Luqmani RA, Murray PI. Ocular manifestations of classical and limited Wegener's granulomatosis Q J Med 1993; 86: 719-725.
23. Simmons JT, Leavitt R, Kornblut AD, Fauci AS. CT of the paranasal sinuses and orbits in patients with Wegener's granulomatosis. Ear Nose Throat J 1987; 66: 134-140.
24. Talar-Williams C, Sneller MC, Langford CA, Smith JA, Cox TA, Robinson MR. Orbital socket contracture: a complication of inflammatory orbital disease in patients with Wegener's granulomatosis. Br J Ophthalmol 2005; 89: 493-497.
25. Leavitt RY, Fauci AS, Bloch DA, et al. The American College of Rheumatology 1990 criteria for the classification of Wegener´s Granulomatosis. Arthritis Rheum 1990; 33: 1101-1107.
26. Rasmussen N. Consensus Therapeutic regimens for ANCA-associated systemic vasculitis: The European Community Systemic Vasculitis Study Group. Lancet 1997; 349: 1029-1030.
27. The WGET Research Group. Design of the Wegener´s granulomatosis Etanercept Trial. Control Clin Trials 2002; 23: 450-468.
28. Exley AR, Bacon PA, Luqmani RA, et al. Examination of disease severity in systemic vasculitis form the novel perspective of damage using the vasculitis damage index (VDI). Br J Rheumatol 1998; 37: 57-63.
29. Woo TL, Francis IC, Wilcsek GA, Coroneo MT, McNab AA, Sullivan TJ. Australasian orbital and adnexal Wegener´s granulomatosis. Ophthamol 2001; 108: 1535--1543.
30. Solans Laqué R, Bosh Gil J, Canela M, Lorente J, Pallisa E, Vilardell-Tarrés M. Clinical features and Therapeutic management of subglottic stenosis in patients with Wegener´s granulomatosis. Lupus 2008; 17: 832--836.
31. Juri J, Neda S. Review and new insights on Wegener granulomatosis. Coll Antropol 2005; 29: 159-162.
32. Fechner FP, Faquin WC. Wegener´s granulomatosis of the orbit: a clinicopathological study of 15 patients. The Laryngoscope 2002; 112: 1945-1950.
33. Kwan ASL, Rose G. Orbital Wegener's granuloma resulting from direct extension of nasal disease through a surgical rhinostomy. Br J Ophthalmol 1998; 82: 198.
34. Waxman J, Bose WJ. Laryngeal manifestations of Wegener's granulomatosis: case report and review of the literature. J Rheumatol 1986; 13: 408-411.
35. Langford CA, Sneller MC, Hallahan CW, et al. Clinical features and therapeutic management of subglottic stenosis in patients with Wegener's granulomatosis. Arthritis Rheum 1996; 39: 1574-1560.
36. Gluth MB, Shinners PA, Kasperbauer JL. Subglottic stenosis associated with Wegener's granulomatosis. Laryngoscope 2003; 113: 1304-1307.
37. McAdam LP, O'Hanlan MA, Bluestone R, Pearson CM. Relapsing polychondritis: prospective study of 23 patients and a review of the literature. Medicine (Baltimore) 1976; 55: 193-215.

# BACK PAIN DURING PREGNANCY: A LONGITUDINAL STUDY

C. Quaresma[*], C. Silva[**], M. Forjaz Secca[*,***], J. Goyri O'Neill[*,****], J. Branco[***,*****]

## Abstract

**Objective:** The goal of the present study was to evaluate the prevalence of back pain during four different periods of pregnancy and its action on each woman during this stage.
**Methods:** The sample comprises of a group of 49 pregnant women aged between 20 and 39 years. The presence of back pain symptoms and severity were evaluated at 12, 20, 32 and 37 weeks of gestation in each woman, using one question of the NIH Record Activity (ACTRE).
**Results:** The ANOVA for repeated measures was used to compare the four moments of evaluation (12 weeks, 20 weeks, 32 weeks and 37 weeks) in relation to back pain. A significant difference between the pain scores over the four moments were observed, being that higher pain scores were noted at 12, 32 and 37 weeks of gestation. We also verified that at 12 weeks of gestation 71.4% of women had back pain, while at 20 weeks only 16.3% confirmed pain. At 32 weeks 91.7% of women reported pain and at 37 weeks, 98% reported the same.
**Conclusion:** We found that back pain is prevalent during pregnancy and its intensity varies throughout this period.

**Keywords:** Women; Pregnancy; Back pain

## Introduction

Pregnancy is a state during which severe physiological changes occur in the muscle and skeletal system, physical and emotional life of the woman whose body adapts to the general and local modifications that take place throughout this period[1].

Back pain is a considerable problem in the general population[2], and it is thought to be even more common among pregnant women. Back pain is a common symptom in normal pregnant women and studies have reported that between 35 and 76% of pregnant women experience back pain[3]. Although many women experience back pain during pregnancy, it has not been considered an important health problem[3].

A Swedish survey reports that 66% of women between the ages of 38 and 64 experience back pain[4]. Interestingly, the majority of these women reported that their first episode of back pain occurred at a certain time during their pregnancy[5,6]. Several other studies also indicate that women with severe pain during pregnancy are at extremely high risk for developing a new episode of severe pain during a subsequent pregnancy as well as later in life[7-10].

Pregnancy is considered a normal physiological condition and the pregnant woman is expected to go on with her life and work as usual[11]. However, back pain in pregnancy is a significant problem given its significant negative impact on how women function and their well-being during pregnancy[3,12]. Previous studies reported that back pain affects the pregnant woman's daily activities. Mens *et al.*[13] reported that more than 80% of pregnant women with back pain experience discomfort in daily activities and difficulties in housework, child-rearing and job performance[3]. Many women report that back pain not only compromises their ability to work during pregnancy but also interferes with activities of daily living[14].

Not only does the problem persist well beyond pregnancy in a significant number of women, but many women with chronic back pain link its onset to pregnancy[14].

In order to identify the causes of that pain in an attempt to develop effective intervention programs targeted at the different stages of pregnancy it is im-

*Cefitec, Departamento de Física, Faculdade de Ciências e Tecnologia, Universidade Nova de Lisboa, Monte de Caparica, Portugal
**Escola Superior de Saúde do Alcoitão, Portugal
***Ressonância Magnética – Caselas, Lisboa, Portugal
****Faculdade de Ciências Médicas, Universidade Nova de Lisboa", Portugal
*****Maternidade Dr Alfredo da Costa, Lisboa, Portugal

portant to bear in mind the above mentioned facts, as well as understand the action of back pain during pregnancy in each woman. Thus, the aim of this study was to identify the prevalence of back pain in four different stages of pregnancy: 12, 20, 32 and 37 weeks of gestation.

## Materials and Methods

This study is part of a broader project which seeks to identify both the biomechanical changes of the spine that occur throughout pregnancy and the factors correlated with these changes. The one aspect that was discussed and accordingly presented as an independent study was the prevalence of back pain during pregnancy.

The study was approved by the Portuguese Ethics Committees of the Faculty of Medical Sciences of New University of Lisbon ("*Comissão de Ética da Faculdade de Ciências Médicas da Universidade Nova de Lisboa*"), the Maternity Hospital Dr Alfredo da Costa (*"Maternidade Dr. Alfredo da Costa"*) and the Regional Health Administration of Lisbon and Vale do Tejo ("*Administração Regional de Saúde de Lisboa e Vale do Tejo*").

All the data was collected between October 2008 and January 2010, and our sample comprises of pregnant women that were being followed at the obstetric services at the Health Institution Center of Sete Rios, in Lisbon, Portugal ("*Centro de Saúde de Sete Rios*").

Each subject was previously informed about the procedures and objectives of the study and signed an informed consent form. The NIH Activity Record (ACTRE) for evaluating the existence or lack of back pain and the intensity of the same in pregnant women during the four stages of pregnancy was used: 12, 20, 32 and 37 weeks of gestation in the same woman.

In this article, the questions of that instrument that address back pain were analyzed. They cover four possible answers, presented in a Likert scale, from which the subject must indicate the answer closer to her degree of concordance. The subjects evaluated the intensity of each symptom experienced during the moment of evaluation. Each response, which ranges from a minimum of 1 (without) a maximum of 4 (very), was added to the total score.

The sample comprised of 49 pregnant women with no associated pathology. Their ages ranged from 20 to 39 years. Table I shows additional characteristics of the sample: race; status and qualifications.

### Statistical Analysis

The statistical data was obtained through the use of the 17.0 version of the SPSS *(Statistical Package for Social Sciences)* program.

The ANOVA for repeated measures was used to compare the four moments in relation to back pain

**Table I. Characteristics of the sample: race; status and qualifications**

| | **Min= 19<br>Average = 30,61** | **Max=40<br>Standard Deviation = 5,46** |
|---|---|---|
| | **Freq.** | **%** |
| Race | | |
| Caucasian | 43 | 87,8 |
| Biracial | 5 | 10,2 |
| Status | | |
| Married | 40 | 81,6 |
| Single | 8 | 16,3 |
| Divorced | 1 | 2,0 |
| Qualifications | | |
| 1st stage of basic education (1st - 4th year) | 1 | 2,0 |
| 3rd stage of basic education (7th - 9th year) | 6 | 12,2 |
| Secondary Education (10th - 12th year) | 21 | 42,9 |
| Higher Education | 21 | 42,9 |

Table I: Sample Characteristics (N =49)

**Table II. ANOVA Repeated samples: comparison of 4 assessment moments regarding this variable**

| Back Pain | Average | Standard Deviation | N | ANOVA SAMPLE REPETIDAS | Observed Power* |
|---|---|---|---|---|---|
| Moment 1 12 weeks of gestation | 1,81 | ,56 | 49 | | |
| Moment 2 20 weeks of gestation | 1,23 | ,46 | 49 | F(3) = 55,343 | 1,00 |
| Moment 3 32 weeks of gestation | 2,12 | ,47 | 49 | p = 0,000 | |
| Moment 4 37 weeks of gestation | 2,21 | ,48 | 49 | | |

*Calculated for an alpha 0,05

(12 weeks, 20 weeks, 32 weeks and 37 weeks). The feasibility of this parametric test results from the presence of a normal distribution at different moments of evaluation was obtained with the use of normality tests: Shapiro-Wilk and Kolmogorov-Smirnov test. It was also important to examine the observed power of the test in association with the ANOVA. The power represents the probability of correctly rejecting H0 (i.e. when H0 is false). Thus, the greater the observed power, the greater the degree of confidence in the conclusion obtained. If the observed power of the test is low (less than 0.80) the results must be interpreted with caution (Maroco 2003). ANOVA revealed a significant result at $p \leq 0.001$ which indicates the existence of differences between the different periods, and the excellent power of the test (above 0.80). In order to identify the distinct moments, the Bonferroni test was used.

## Results

The first analysis of the ANOVA revealed a significant result at $p \leq 0.001$ which indicates the existence of differences between the different periods, thus the power of the test was considered excellent (above 0.80).

Significant differences between the four stages of evaluation: 12. 20, 32 and 37 weeks of gestation, were observed. Table II shows that the standard deviation in the 1st moment of evaluation is 0.56, the 2nd moment is 0.46, whereas in the 3rd and 4th moments the standard deviation points are 0.47 and 0.48, respectively.

A significant decrease of the pain score (1.23) was observed at 20 weeks of gestation and (1.81) at 12 weeks (Figure 1). This score tends to increase again at 32 weeks (2.12) and remain almost the same throughout the 3rd trimester of pregnancy.

During the four stages of data collection, it was possible to establish that the maximum and minimum scores of the following pain values varies in each period: 12 weeks - 3.50 and 1.00, and 1.00 - 3.00 20 weeks, 32 weeks - 3, 50, and 1.00, and 1.36 -3.56 37 weeks.

All women reported pain in the lumbar region and it was also ascertained that the pain score tends to increase later in the day.

The Bonferroni test (Table III) was used in order to identify the different moments.

The Bonferroni test confirmed that there is a significant decrease in back pain during the first and second moments of evaluation (from 1.81 to 1.21, $p \leq 0.001$), with a significant increase during the third moment (from 1.23 to 2.12, $p \leq 0.05$), indicating a stabilization of the level of back pain

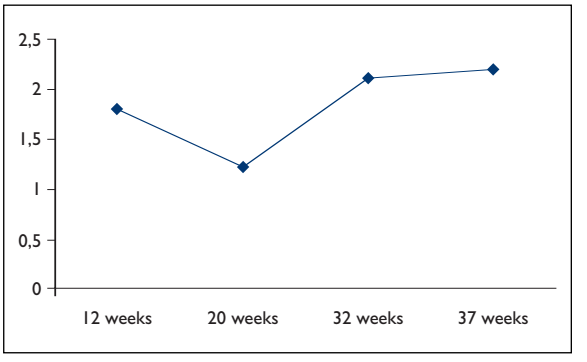



**Figure 1.** Back Pain at the 12, 20, 32 and 37 weeks of gestation

**Table III. Bonferroni test (Post-Hoc ANOVA): multiple comparisons of the 4 time periods regarding the Back Pain variable**

| Bonferroni Test | 2nd Moment 20 Weeks X = 1,23 | 3rd Moment 32 Weeks X = 2,12 | 4th Moment 37 Weeks X = 2,21 |
|---|---|---|---|
| 1st Moment 12 Weeks X = 1,81 | Difference in Averages = 0,58 p = 0,000*** | Difference in Averages = -0,31 p = 0,015* | Difference in Averages = -0,40 p = 0,000*** |
| 2nd Moment 20 Weeks X = 1,23 | – | Difference in Averages = -0,89 p = 0,000*** | Difference in Averages = -0,98 p = 0,000*** |
| 3rd Moment 32 Weeks X= 2,12 | – | Difference in Averages = -0,09 p = 1,000 (n.s) | |

(*significant $p \leq 0,05$, *** significant $p \leq 0,001$, n.s : not significant)

from the 3rd to the 4th moment of assessment (from 2.12 to 2.21 ns). The pain is lower in the second stage of evaluation (at 20 weeks) and significant differences were recorded in regards to all the other periods.

Subsequently, during the four moments of assessment it was possible to examine the percentage of pregnant women that reported permanent back pain, those that reported the onset of back pain for the first time (in any of the four moments), those that ceased to have back pain and those that continued to have no pain (Table IV).

At 12 weeks of gestation 39 women (71.4%) reported having their first back pain while 16 women (28.6%) remained without pain.

In regards to the 20th week of gestation, only seven women (14.3%) reported back pain, 27 women (55.1%) ceased to have pain, 14 reported no pain and only one woman reported having pain for the first time during her pregnancy.

At 32 weeks, 36 women (75%) reported having back pain, whilst 8 (16.7%) reported unremitting back pain and 4 women (6.3%) remained pain free and no longer felt any pain at this moment of the assessment.

At 37 weeks of gestation, 44 women (91.7%) reported having back pain**.** Three women (6.3%) reported their first signs of pain at this moment, whereas one woman (2.1%) did not refer to permanent pain, and actually showed no sings of this symptom during this period.

Observation of the collected data revealed that only 1 (2.1%) woman never had back pain during pregnancy, whereas 7 (14.3%) women reported having pain during every moment of the evaluation. 10 (20.4%) women reported pain only in the 3rd

**Table IV. The percentage of pregnant women that reported permanent back pain, those that reported the onset of back pain for the first time , those that ceased to have back pain and those that continued to have no pain**

| Differences Between ↓ | Maintained Back Pain | Onset of Back Pain | Stopped having back Pain | Remains without Back pain |
|---|---|---|---|---|
| 12 Weeks Vs 20 Weeks | 14,3% (7) | 2% (1) | 55,1% (27) | 28,6% (14) |
| 20 Weeks Vs 32 Weeks | 16,7% (8) | 75% (36) | 0% (0) | 6,3% (4) |
| 32 Weeks Vs 37 Weeks | 91,7% (44) | 6,3% (3) | 0% (0, ) | 2,1% (1) |

quarter.

We analyzed the prevalence of pain in only one of the moments of evaluation and noted that only two (4.1%) women suffered from this condition; referring to pain only at 37 weeks of gestation.

Data analysis revealed that the percentage of pregnant women with back pain varies greatly throughout pregnancy. We observed that at 12 weeks of gestation 71.4% of women had back pain, whereas at 20 weeks only 16.3% reported pain. However, at 32 weeks 91.7% of women reported pain, and at 37 weeks, 98 % mentioned pain.

## Discussion

The purpose of this longitudinal study was to identify the levels of back pain during pregnancy. For that purpose the NIH Activity Record was applied to each woman in four differences moments of pregnancy: 12, 20, 32 and 37 weeks of gestation.

Several studies in different parts of the world have reported a high incidence of back pain during pregnancy, and it is predicted that approximately half of all pregnant women suffer from back pain at some point in their pregnancy – a large number of them severely enough to hinder their normal activities[1].

Data analysis revealed that the prevalence of back pain varies significantly throughout pregnancy and that this difference is more apparent during the 2nd (20 weeks) and 3rd trimesters (32 and 37 weeks). This result is contrary to the results obtained by Carvalho whose study did not establish a significant relationship between trimesters[15].

It was also possible to establish that at 12 weeks of gestation 71.4% of women had back pain, whereas at 20 weeks only 16.3% reported pain. At 32 weeks, 91.7% of women reported pain and at 37 weeks, 98% mentioned this symptom.

This data is not in accordance with studies that indicate a prevalence of 80% for back pain during pregnancy[16] in view of the fact that our study indicates that over 90% of pregnant women suffer from back pain in the third trimester (32 and 37 weeks).

Kilstrand *et al.* report a 20% increase of back pain in pregnant women. These authors also state that this increase may result from the greater concern regarding the quality of life in the present day, especially concerning the welfare of pregnant women. This factor has produced more detailed and objective research on the diagnosis[17].

Our results point to a greater prevalence of pain during the 1st and 3rd quarters. This result is contrary to the results obtained by Sihvonen *et al.*, who ascertained that the highest incidence was not in those trimesters[18].

We also verified that the higher incidence of back pain occurs during the third quarter which is contrary to the study by Martins and Silva[16] who established that pain was more common in early pregnancy.

According to Orvieto *et al.*, women in their last month of pregnancy reported higher incidences of back pain[19].

This study is in agreement with others published in medical literature as it also concluded that musculoskeletal pain is frequent symptom during pregnancy[20,21].

The results revealed a considerable decrease in the number of pregnant women who have back pain during the second stage of evaluation (20 weeks of gestation). This finding is contrary to data that indicates a higher incidence of back pain between the 5th – 7th months of pregnancy. This factor represents a common reason for sick leave[10].

In contrast to the existing literature that indicates that back pain mainly occurs mainly during the first 5–7 months of pregnancy, we determined that back pain may be occur any time during pregnancy.

Nearly 30% of the women with back reported that they had to discontinue at least one daily activity because of back pain. For all other daily activities, they reported mild-to-severe degrees of difficulty because of back pain[11].

This study revealed that back pain is not a stationary aspect but rather a condition that undergoes alterations during gestation. It was also established that back pain decreases at 20 weeks of gestation and increase again during the 3rd trimester.

As the structure of society changes, back pain in pregnancy extends its negative impact across many areas of women's daily lives, including work, household responsibilities, leisure activities, and sleep[11].

This specific pain has an impact not only on the individual woman but also adversely affects those she cares for by limiting her daily activities, as well as adversely influencing her work productivity. We call upon researchers to contribute to the improvement of women's health through research focu-

sed on the prevention and treatment of lower back pain during pregnancy.

In conclusion, the data clearly indicates that back pain during pregnancy is a common problem that should not be ignored.

We consider it imperative that health professionals become familiar with the frequency and characteristics of these complaints, because a greater awareness of this problem will help minimize its consequences on the one hand and, possibly reduce its prevalence, on the other[16]. Thus, we suggest that further studies verify the effectiveness of different treatments available in order to help solve or decrease its impact on the welfare of pregnant women and allow for their integration in more homogeneous activities, domestic and professional[16].

**Acknowledgments**

C. Quaresma would like to acknowledge «*Fundação Ciência e Tecnologia*» (FCT) for the grant (SFRH/BD/44042/2008).

This research was supported in part by FCT project POCTI/0068/2003.

**Correspondence to**

Claudia Quaresma
Cefitec, Departamento de Física,
Faculdade de Ciências e Tecnologia,
Universidade Nova de Lisboa,
Monte de Caparica, Portugal
Tel: +351 212948576
Fax: +351212948549
E-mail: q.claudia@fct.unl.pt

**References**

1. Sant'ana P, Freire S, Alves A, Silva D. Caracterização da dor lombar em gestantes atendidas no Hospital Universitário de Brasília. Universitas: Ciências da Saúde, 2006;4: 37-48.
2. Walter BF. The prevalence of low back pain in Australian adults. A systematic review of the literature from 1966-1998. Asia-Pac J Public Health 1999;11: 45-51.
3. Shim, Mi-Jung; Lee, Young-Sook, Oh, Hyun-Ei, Kim, Jin-Sun. Effects of a Back-pain-reducing program during pregnancy for Korean women: a non-equivalent control-group pretest-posttest study. International Journal of Nursing Studies 2007;44: 19-28.
4. Biering-Sorensen F. Low back trouble in a general population of 30-, 40-, 50-, and 60-year-old men and women: study design, representativeness, and basic results. Dan Med Bull 1982; 29: 289 – 299.
5. Svensson HO, Andersson GB, Hagstad A, Jansson PO. The relationship of low-back pain to pregnancy and gynecologic factors. Spine 1990; 15 :371–375.
6. Berg G, Hammar M, Moller-Nielsen J, Linden U, Thorblad J. Low back pain during pregnancy. Obstet Gynecol 1988; 71: 71–75.
7. Ostgaard HC, Andersson GB. Previous back pain and risk of developing back pain in future pregnancy. Spine 1991;16:432– 436.
8. Ostgaard HC, Zetherstrom G, Roose-Hansson E. Back pain in relation to pregnancy: a 6-year follow-up. Spine1997; 22: 2945–2950.
9. Noren L, Ostgaard S, Johansson G, Ostgaard HC. Lumbar back and posterior pelvic pain during pregnancy: a 3-year follow-up. Eur Spine J 2002; 11: 267–271.
10. Shu-Ming Wang , Peggy Dezinno, Inna Maranets et al. Low Back Pain During Pregnancy: Prevalence, Risk Factors, and Outcomes Obstetrics & Gynecology 2004:104; 65-70.
11. Olsson C, Nilson–Wikmar L. Health -related quality of life and physical ability among pregnant women with and without back pain in late pregnancy. Acta Obstet Gynecol Scand 2004; 83: 351-357.
12. Perkins J, Hammer R, Loubert P. Identification and management of pregnancy-related low back pain. Journal of Nurse-Midwifery 1998; 43: 331-340.
13. Mens JMA, Vleeming A, Stoeckart R, Stam HJ, Snijders CJ. Understanding peripartum pelvic pain. Implications of a patient survey. Spine 1996; 21:1363–1370.
14. Cecin HA, Bichuetti JAN, Daguer MK, Pustrelo MN. Lombalgia e gravidez. Rev Bras Reumatol 1992;32:45--50.
15. Carvalho YBR, Caromano FA. Alterações morfofisiológicas relacionadas com lombalgia gestacional. Arquivos de Ciências da Saúde da Unipar 2001; 5: 267--272.
16. Martins R, Silva J. Prevalência de dores nas costas na gestação. Ver. Assoc. Med Bras 2005;51: 144-147.
17. Khilstrand M, Stenman B, Nilsson S, Axelsson O. Water gymnastics reduced the intensity of back/low pain in pregnant women. Acta Obstet Gynecol Scan 1999;78:180-185.
18. Sihvonen T, Huttunen M, Makkanen A, Airaksinen O. Functional changes in back muscle activity correlate with pain intensity and prediction of low back pain during pregnancy. The Archives of Physical Medicine and Rehabilitation 1998; 79: 1210-1212.
19. Orvieto R, Achiron A, Bem-Rafael Z, Gelernter I, Achiron R. Low back pain of pregnancy. Acta Obstetricia Et Gynecologica Scandinavica 1994; 73: 209-214.
20. Dumas GA, Reide JG, Wolfe LA, Griffin MP, McGrath MJ. Exercise, posture and back pain during pregnancy: Part 2 Exercise and Back pain. Clinical Biomechanics 1995; 10: 104-109.
21. Fast A, Shapiro D, Ducommun EJ, Friedmann LW, Bouklas T, Floman Y. Low-back pain in pregnancy. Spine 1987; 12: 368 -371.

# NÍVEIS SÉRICOS DE VITAMINA D EM PORTUGUESES COM FRACTURAS DE FRAGILIDADE

Lígia Silva[*], Joana M. Freitas[**], Luzia Sampaio[*], Georgina Terroso[*], José A. Pinto[***], Vitorino Veludo[****], Abel T. Cabral[*****], Francisco S. Ventura[******]

## Resumo

**Objectivos:** A osteoporose é uma «epidemia silenciosa», multifactorial, com factores causais e de risco, cujas prevalências dependem de particularidades populacionais. Os autores propõem-se caracterizar alguns destes elementos, dando especial atenção aos níveis de vitamina D (vitD), numa população portuguesa, de risco, seleccionada com base na história de fractura de fragilidade prévia.
**Material e Métodos:** Os participantes foram seleccionados da listagem computorizada de todas as altas de internamento num Hospital Central do Porto, ente as datas de 1/1/2002 e 31/12/2004, com o diagnóstico de fractura do punho de baixo impacto. Foram convidados a participar numa reavaliação do seu risco de fractura, passados 5 a 7 anos daquele evento. Para cada um, foi preenchido um protocolo, incidindo em parâmetros clinico-epidemiológicos, analíticos, radiológicos e densitométricos.
**Resultados:** Nesta população, como seria de esperar, verificou-se uma alta taxa de factores associados a osteoporose, que podem explicar a também elevada taxa de fracturas osteoporóticas subsequentes. Entre outros, destacam-se a menopausa precoce, baixo aporte de cálcio e proteínas, níveis globalmente insuficientes de vitD, e o baixo índice de tratamento de osteoporose.
**Discussão:** A insuficiência generalizada de vitD, descrita noutras populações, maioritariamente de países nórdicos, foi também aqui constatada, suportando a suspeita de que também em Portugal pode haver défice, apesar da suposta exposição solar regular. Esta e outras observações desta casuística, a serem comprovadas em estudos dirigidos, deverão fazer aumentar os índices de sensibilização da comunidade, mas sobretudo dos profissionais de saúde e responsáveis por políticas de saúde pública, numa questão com tão forte impacto na saúde individual e colectiva no País.

**Palavras-chave:** Vitamina D; Factores de risco; Osteoporose; Fractura; Portugal.

## Abstract

**Objectives:** Osteoporosis is a «silent epidemic», resulting from a combination of many possible causal and risk factors, which prevalence depend on particular features of the population. The authors propose to characterize some of these elements, with special attention to vitamin D (vitD) levels, in a Portuguese population at risk, selected on the basis of a history of prior fragility fracture.
**Methods:** Participants were selected from the computerized list of discharges from all hospitalized patients in a Central Hospital in Oporto, between the dates 1/1/2002 and 31/12/2004, with the diagnosis of low-impact fracture of the wrist. They were invited to a reassessment of their risk of fracture, after 5 to 7 years from that event. For each one, a protocol was completed, focusing on clinical, epidemiological, laboratorial, radiological and densitometric parameters.
**Results:** In this population, as expected, there was a high rate of osteoporosis risk factors, which may explain the also high rate of subsequent osteoporotic fractures. Among others, early menopause, low intake of calcium and protein, levels of vitD generally inadequate and low frequency of osteopo-

*Interna Complementar de Reumatologia nos Serviços de Reumatologia do Hospital de São João e da Faculdade de Medicina da Universidade do Porto
**Interna Complementar de Ortopedia no Serviço de Ortopedia do Hospital de São João
***Assistente Hospitalar Graduado de Reumatologia no Hospital de São João
****Assistente Hospitalar de Ortopedia no Hospital de São João
*****Director do Serviço de Ortopedia do Hospital de São João
******Director dos Serviços de Reumatologia do Hospital de São João e da Faculdade de Medicina da Universidade do Porto.
Serviços de Reumatologia e de Ortopedia do Hospital de São João e da Faculdade de Medicina da Universidade do Porto

rosis treatment were noticed.
**Discussion:** The widespread insufficiency of vitD, described in other populations, mostly from the Northern countries, was also found here, supporting the suspicion that also in Portugal low vitD levels could be prevalent, despite the supposed regular sun exposure. These and other observations in this series, to be proven in directed studies, should, meanwhile, raise the levels of awareness of the community, but particularly health professionals and policymakers of public health, in a matter with a strong impact on individual and collective health in the country.

**Keywords:** Vitamin D; Risk factors; Osteoporosis; Fracture; Portugal.

## Introdução

A vitD ou calciferol, é o nome genérico referente a um grupo de compostos lipossolúveis com papel fulcral na prevenção da osteoporose e também de fracturas, pela sua acção privilegiada na mineralização óssea, e na manutenção funcional neuromuscular, aumentando a força e equilíbrio, diminuindo as quedas[1-4]. Mais recentemente, têm surgido fortes indícios da sua intervenção em outros mecanismos celulares, com efeitos imunomoduladores e antiproliferativos, associados, por exemplo, à diminuição da prevalência de algumas neoplasias[1,5,6].

Inúmeros estudos, maioritariamente reflectindo a realidade de países nórdicos, documentam a insuficiência dos níveis de vitD, não apenas em populações de risco (Tabela I), mas também na população geral[2,7]. São múltiplos os factores implicados, sendo a escassa e irregular exposição solar, apontada como causa maior, já que a principal fonte de vitD é a sua síntese na pele exposta a radiação solar ultravioleta-B[1,2]. Se este facto pode explicar, pelo menos parcialmente, os défices nestes países, desconhece-se a realidade de outros com maior índice de exposição solar, como é o caso de Portugal. Alguns relatos clínicos sugerem que também aqui prevalece a insuficiência[8,9], o que poderá dever-se a questões sociais e culturais, que aumentam os níveis de protecção solar, ou mesmo mitos, que desviam a atenção dos profissionais de saúde e autoridades de saúde pública, menos sensibilizados para a necessidade de suplementação terapêutica individual, ou alimentar, no âmbito comunitário[1,9,10].

Face ao exposto, pretendemos aqui avaliar os níveis séricos de vitD de uma amostra de indivíduos da região do Porto, em Portugal, que pela história de fractura de fragilidade prévia, apresentam elevado risco fracturário. A caracterização incidiu ainda em outros parâmetros, clínicos, analíticos, radiológicos e densitométricos, associados a esta realidade.

## Material e Métodos

A avaliação transversal dos níveis séricos de vitD (e do risco fracturário) numa população portuguesa considerada de alto risco, implicou a realização de um protocolo incidindo numa série de características clínico-laboratoriais[11-17], radiológicas[18,19] e densitométricas[20,21], amplamente documentadas na literatura internacional.

**Tabela I. Causas de défice de Vitamina D**

| | |
|---|---|
| Diminuição da fotoisomerização cutânea | • Défice de exposição solar (vestuário, creme solar, latitude > 37ºN e < 37ºS, Outono-Inverno)<br>• Maior pigmentação cutânea<br>• Idosos |
| Diminuição da hidroxilação hepática/ renal | • Doença hepática severa<br>• Insuficiência renal crónica (cl cr < 30 mL/min) |
| Diminuição da absorção | • Baixa ingestão de ergocalciferol (ovos, peixes gordos)<br>• Síndromes de mal-absorção (Doença Celíaca, D. de Crohn, Fibrose Cística, Insuficiência pancreática, D. hepática colestática) |
| Alteração do metabolismo ou diminuição da biodisponibilidade | • Obesidade<br>• Fármacos (fenitoína, carbamazepina, heparina, rifampicina, isoniazida, colestiramina, corticosteróides, teofilina) |

O estudo foi aprovado pela Comissão de Ética do Hospital de São João do Porto, e decorreu no período de Julho a Outubro de 2009.

Foram incluídos nesta casuística indivíduos adultos, que estiveram internados no Serviço de Ortopedia do Hospital de São João no Porto, no período de 1/1/2002 a 31/12/2004, por fractura de fragilidade do punho (queda da própria altura).

Os participantes foram contactados telefonicamente, sendo-lhes explicados, de forma sumária, os objectivos e procedimentos. Foi-lhes solicitada comparência no Hospital, na posse de eventuais exames auxiliares de diagnóstico efectuados previamente, para avaliação numa primeira consulta. Nesta consulta foram requisitados exames que constavam do protocolo: análises séricas (hemograma, transaminases, gamaglutamiltransferase, fosfatase alcalina, cálcio, fósforo, magnésio, creatinina, paratormona intacta, 25-hidroxivitamina $D_3$ (25-vit$D_3$), hormona tireoestimulante, anticorpo anti-transglutaminase IgA, e no caso do sexo masculino, também testosterona livre, prolactina e hormona adrenocorticotrófica), na urina de 24 horas (creatinina, cálcio e fósforo), radiografias (em perfil da coluna dorsal centrada em D7 e lombar centrada em L2), e densitometria óssea (DEXA-*dual energy x-ray absorptiometry*). Na segunda (e última) consulta, em conformidade com a avaliação global, registada no protocolo, foram orientados clinicamente, com aconselhamento de estilos de vida, eventual terapêutica farmacológica, e monitorização pelo seu médico assistente.

## Resultados

De um total de 139 doentes que o registo hospitalar computorizado indicava, não foi possível contacto com 80 doentes (57,5%) (em 13 casos, os familiares reportaram a sua morte; nos restantes 67, o contacto telefónico já não se encontrava atribuído), e 17 doentes recusaram participar, maioritariamente por limitações na mobilidade (12 à partida, telefonicamente, e 5 após a primeira consulta).

Os 42 participantes no estudo, todos portugueses do distrito do Porto, de raça branca, tinham média de idade de 64 ± 10,2 anos, com idades compreendidas entre os 35 e 85 anos. 39 (92,8%) eram do sexo feminino, com média de idade de 64,3 anos, e 3 do sexo masculino com média de 59,7 anos. De referir que a população inicial de 139 doentes internados, teria hoje a média de idade de 69,1 anos, sendo que 13 doentes falecidos teriam média de 76,9 anos, 67 não contactáveis, 71,4 anos, e 17 que recusaram participação, têm em média 66,8 anos.

O valor médio de 25-vit$D_3$ foi de 25,6 ng/mL; 26,2% dos indivíduos apresentavam níveis ≥ 30 ng/mL, 45,2% apresentaram insuficiência (com valores de entre 20-29 ng/mL), 23,8% apresentavam défice (25-vit$D_3$ entre 8-20 ng/mL), e défice severo (25-vit$D_3$ < 8 ng/mL) em 4,8% dos casos[2,22]. Para mais fácil percepção dos resultados, os 42 participantes foram distribuídos por intervalos de idade (Tabela II).

A Tabela III mostra, resumidamente, resultados de outros parâmetros, clínicos, analíticos, radiológicos e densitométricos, avaliados.

A Tabela IV expõe os factores de risco de fractura e causas secundárias de osteoporose, que foram avaliados neste estudo[11,15,16]. Relativamente aos factores de risco *major*, em média 2 por participante, a fractura prévia de fragilidade foi a mais prevalente, e esta refere-se não apenas à fractura do punho

**Tabela II. Distribuição etária dos níveis de 25-hidroxivitamina $D_3$ (25-vit$D_3$), e dos valores médios do índice de massa corporal (IMC)**

| Idade actual (anos) | Nº de doentes (n) | 25-Vit$D_3$ (ng/mL) | | | | | Supl. vitD (n) | IMC médio (kg/m²) |
|---|---|---|---|---|---|---|---|---|
| | | Média | ≥ 30 (n) | 20-29 (n) | 8-20 (n) | < 8 (n) | | |
| < 40 | 1 | 40 | 1 | – | – | – | – | 32 |
| 40-50 | 2 | 16,5 | – | – | 2 | – | – | 25,3 |
| 51-60 | 13 | 27,9 | 4 | 7 | 2 | – | 6 | 28,1 |
| 61-70 | 15 | 26,2 | 4 | 7 | 4 | – | 3 | 28,7 |
| 71-80 | 10 | 24,5 | 2 | 5 | 2 | 1 | 3 | 25,7 |
| > 80 | 1 | 3 | – | – | – | 1 | – | 25,1 |
| TOTAL | 42 | 25,6 | 11 | 19 | 10 | 2 | 12 | 27,6 |

**Tabela III. Resultados clinico-analíticos, radiológicos e densitométricos**

| Idade | n | Nº de factores de risco de fractura (média) | | Nº de causas 2árias deOP (média) | Nº de novas fracturas (n) | | | T score (média) | |
|---|---|---|---|---|---|---|---|---|---|
| (anos) | | *Major* | *Minor* | | Punho | Anca | Vertebral | Fémur | Lombar |
| < 40 | 1 | 1 | 1 | 1 | – | – | 1 | +1,5 | +1,7 |
| 40-50 | 2 | 1 | 2 | 1 | – | – | 4 | -0,8 | -1,9 |
| 51-60 | 13 | 1,7 | 1,2 | 0,8 | 1 | – | 7 | -1,1 | -1,5 |
| 61-70 | 15 | 1,9 | 1 | 0,7 | 4 | – | 8 | -0,4 | -1,9 |
| 71-80 | 10 | 2,8 | 0,8 | 0,7 | 5 | 1 | 1 | -1,7 | -1,5 |
| > 80 | 1 | 2 | 1 | – | 1 | – | 1 | -1,6 | -1,9 |
| Total | 42 | 2 | 1,1 | 0,7 | 11 | 1 | 21 | -0,9 | -1,6 |

Legenda: Número de doentes (n), 2árias (secundárias), OP (osteoporose).

**Tabela IV. Causas secundárias de osteoporose e factores de risco de fractura**

| | |
|---|---|
| Causas secundárias de osteoporose | • Hipertiroidismo<br>• Hiperparatiroidismo<br>• Malnutrição/Malabsorção<br>• Doença hepática crónica<br>• Diabetes mellitus insulinotratada<br>• Osteogenesis imperfecta<br>• Hipogonadismo/ Menopausa precoce (< 45 anos) |
| Factores de risco *major* de fractura | • Idade > 65 anos<br>• Fractura de fragilidade prévia<br>• Fractura da anca de um progenitor<br>• Corticoterapia ≥3meses, equivalente a prednisolona >5 mg/dia<br>• Quedas frequentes (> 2 no último ano) |
| Factores de risco *minor* de fractura | • Artrite reumatóide<br>• Terapêutica crónica com anti-epiléptico/ heparina<br>• Baixo aporte de cálcio<br>• Tabagismo<br>• Consumo excessivo de álcool (≥3 unidades/dia)<br>• IMC< 19 kg/m2/ diminuição do peso >10% (relativo ao peso aos 25 anos)<br>• Imobilização prolongada |

inicial, mas também a novas fracturas (vertebrais morfométricas[18,19] em 21 doentes, do punho em 11, e da anca em 1 caso), que foram contabilizadas para cada doente, em conjunto, como 1 factor de risco apenas. No período subsequente à fractura do punho inicial, só 18 dos 42 participantes não apresentaram nova(s) fractura(s).

Dos factores de risco *minor*, presentes em média 1,1 por doente, o mais prevalente foi o baixo aporte de cálcio. 28 doentes referiram que, por «escassez de recursos» ou «não gostarem», não ingeriram produtos lácteos até a idade adulta. Destes 28, 12 continuavam a não ingerir lácteos à data da avaliação, e destes 12, apenas 2 faziam suplementos de cálcio. Do total de 42 participantes, apenas 12 faziam suplementos de cálcio e vitD; ainda assim, 5 destes apresentaram níveis de 25-vit$D_3$ < 30 ng/mL.

Apenas uma doente apresentou índice de massa corporal inferior a 19 kg/$m^2$ (todos os outros ti-

nham valor superior ou igual a 21).

O tabagismo, em 4 casos, foi factor comum aos 3 indivíduos do sexo masculino, e 5 participantes referiram ingestão excessiva de álcool, de longa data.

Apesar de não contabilizados como factores de risco, 16 participantes referiram escassa ingestão proteica até a idade adulta, e o sedentarismo teve grande expressão; apenas 8 participantes referiram a prática regular de exercício físico «desde sempre», e dos restantes 34, apenas 6 passaram a fazer exercício regular (caminhada) desde que fracturaram o punho, 5 a 7 anos antes.

Relativamente a causas secundárias de osteoporose, em média 0,7 por participante, as mais prevalentes foram a menopausa precoce (< 45 anos) em 15 mulheres, 4 casos de hipertiroidismo (documentados à data da fractura do punho), 4 de hiperparatiroidismo (em 3 casos, primário, e 1 secundário a insuficiência renal crónica), 4 de doença hepática crónica, e 2 casos de doença inflamatória intestinal (doença de Crohn e colite ulcerosa).

Do ponto de vista densitométrico, o índice T médio no colo do fémur e coluna lombar, enquadrou-se, globalmente, em valores de osteopenia[20].

No que concerne a terapêutica farmacológica de osteoporose instituída (em todos os casos após a fractura inicial do punho), apenas 12 faziam suplementação com cálcio e vitD, 12 estavam medicados com bifosfonato, e 1 com ranelato de estrôncio.

## Discussão

A alta prevalência de osteoporose e fracturas, o seu forte impacto na saúde individual (reflectindo-se em incapacidade funcional e mortalidade), e o crescente peso em saúde pública, são factos amplamente conhecidos[10,15,21]. Vários estudos apontam a fractura de fragilidade do punho como factor de risco de novas fracturas[15,23,24], e estima-se que a taxa de mortalidade 1 ano após fractura da anca, é de 10-20%.[10] Para avaliar factores de risco de fractura osteoporótica numa população de alto risco, optámos por incluir nesta casuística doentes com história de internamento hospitalar por fractura de fragilidade do punho (grave, a justificar a necessidade de cirurgia e internamento) e não da anca, já que a menor média de idades possibilitaria aceder a uma maior percentagem de doentes, 5 a 7 anos depois. Ainda assim, a história de fractura prévia e a média de idade dos doentes (superior no caso dos «não participantes»), podem explicar, por si só, a impossibilidade de contacto de 80, e a recusa na participação por 17 dos 139 indivíduos internados 5 a 7 anos antes. Isto é corroborado pelas causas apontadas para a não participação; muitos deles falecidos, institucionalizados, ou com défices de mobilidade e autonomia. Também o facto de apenas uma participante ter tido fractura da anca, pode indiciar um viés de participação. Por tudo isto, a alta taxa de «não participação» sugere fortemente que os «não participantes» teriam índices de saúde global (e taxa de factores de risco de fracturas e de insuficiência de vitD) se não idênticos, ainda menos favoráveis, comparativamente à população avaliada, não alterando o sentido dos resultados obtidos. Os resultados, relativos aos vários parâmetros analisados, vêm na direcção dos dados publicados[1,2,8,9,10,12].

A revisão bibliográfica *on-line* (*PubMed, UpToDate*), confirmou a escassez de dados relativos aos níveis de vitD em países considerados de alto índice de exposição solar. Neste estudo, a alta taxa de insuficiência de vitD, apesar de se tratar de uma população com exposição solar regular (nenhum institucionalizado ou impossibilitado de sair de casa), e de os doseamentos terem sido realizados nos meses de Julho-Outubro/2009, aproxima-se de valores registados nos países nórdicos. O mito do sol nos países do sul, pode ter contribuído para a eventual excessiva protecção da radiação solar[1], por um lado, e a menor sensibilização dos profissionais de saúde na suplementação (terapêutica individual e suplementos alimentares). A esta falha, associa-se a fraca adesão à suplementação, não só por falta de motivação dos doentes pelos clínicos, mas também porque se trata de uma patologia (geralmente) assintomática, crónica, em indivíduos frequentemente polimedicados, e de não raras vezes ser relatada intolerância gastro-intestinal às formulações com cálcio associado[1,15,25]. Em paralelo, apesar da indicação indiscutível e amplamente estabelecida nas recomendações nacionais e internacionais para tratar os doentes com fractura de fragilidade (inclusive aqueles com osteopenia densitométrica, já que este parâmetro é apenas mais um de entre muitos outros marcadores de risco de fractura)[11,15,16,26,27], continuamos a verificar o não tratamento da maioria dos doentes com fracturas osteoporóticas[10,23,28]. Os resultados revelam ainda outros factores preocupantes, que deverão alertar para eventuais especificidades da população idosa portuguesa. São exemplos a elevada taxa

de hiperparatiroidismo, défices nutricionais reportados à sua juventude, e a alta taxa de menopausa precoce não tratada, que nos devem fazer agir de imediato, para proteger estes grupos, à partida fragilizados, perante um futuro que tende a agravar-se, dado o envelhecimento da população[10,12,29].

**Correspondência para**
Lígia Silva
Serviço de Reumatologia do Hospital de São João,
Alameda Professor Hernâni Monteiro
4202-451 Porto, Portugal
E-mail: ligia1silva@yahoo.com

**Referências**

1. Holick M. High prevalence of vitamin D inadequacy and implications for health. Mayo Clin Proc 2006; 81:353-373.
2. Agus Z, Drezner M. Causes of vitamin D deficiency and resistance. In: UptoDate, Schur P (Ed), UpToDate, 2010. Acedido em 22 Janeiro de 2010.
3. Cameron ID, Murray GR, Gillespie LD et al. Interventions for preventing falls in older people in nursisng care facilities and hospitals. Cochrane Database SYst Rev 2010; 20(1):CD005465.
4. Adami S, Giannini S, Bianchi G et al. Vitamin D status and response to treatment in post-menopausal osteoporosis. Osteoporos Int 2009; 20:239-244.
5. Bouillon R, Carmeliet G, Verlinden L et al. Vitamin D and Human Health: Lessons from Vitamin D Receptor Null Mice. Endocr Rev 2008; 29:726-776.
6. Melamed ML, Michos ED, Post W, Astor B. 25-hydroxyvitamin D levels and the risk of mortality in the general population. Arch Intern Med 2008; 168:1629-1637.
7. Ovesen L, Andersen R, Jakobsen J. Geographical differences in vitamin D status, with particular reference to European countries. Proc Nutr Soc 2003; 62:813-821.
8. Canhão H, Fonseca JE, Queirós MV. Avaliação de hábitos alimentares e estilos de vida numa população portuguesa- factores de risco e de protecção para a osteoporose. Acta Reum Port 2006; 31:331-339.
9. Lucas R, Costa L, Barros H. Ingestão de cálcio e vitamina D numa amostra urbana de mulheres Portuguesas. Arquivos de Medicina 2005; 19:7-14.
10. Branco J, Felicíssimo P, Monteiro J. A epidemiologia e o impacto sócio-económico das fracturas da extremidade proximal do fémur- uma reflexão sobre o padrão actual de tratamento da osteoporose grave. Acta Reum Port 2009; 34:475-485.
11. Compston J, Cooper A, Cooper C et al, on behalf of the National Osteoporosis Guideline Group (NOGG). Guidelines for the diagnosis and management of osteoporosis in postmenopausal women and men from the age of 50 years in the UK. www.iofbonehealth.org/osteofoud/download/concensus-guidelines/nogg-pocket-guide-for-helthcare-professionals.pdf. Acedido em 10 Janeiro de 2010.
12. René Rizzoli. Atlas of Postmenopausal Osteoporosis-third edition. London: Current Medicine Group 2010: 4-5, 26-34, 83-86.
13. Kanis JA, Oden A, Johnell O. The use of clinical risk factors enhances the performance of BMD in the prediction of hip and osteoporotic fractures in men and women. Osteoporos Int 2007; 18:1033-1046.
14. Briot K, Cortet B, Trémollières F et al. Osteoporose masculine: démarche diagnostique. Identification des hommes à risque de fracture et identification des patients nécessitant un traitement. Revue du Rhumatisme 2009; 76:216-221.
15. Kanis JA, Burlet N, Cooper C et al on behalf of the European Society for Clinical and Economic Aspects of Osteoporosis (ESCEO). European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int 2008; 19:399-428.
16. Tavares V, Canhão H, Gomes JA et al. Recomendações para o diagnóstico e terapêutica da osteoporose. Acta Reum Port 2007; 32:49-59.
17. Kanis JA, Reginster JY. European guidance for the diagnosis and management of osteoporosis in postmenopausal women- what is the current message for clinical practice? Pol Arch Med Wewn 2008; 118:538-540.
18. Genant HK, Wu CY, van Kuijk C, Nevitt MC. Vertebral fracture assessment using a semiquantitative technique. J Bone Miner Res 1993; 8:1137-1148.
19. Genant HK, Jergas M. Assessment of prevalent and incident vertebral fractures in osteoporosis research. Osteoporos Int. 2003; 14:43-55.
20. Kanis JA, McCloskey EV, Johansson H, Oden A, Melton LJ 3rd, Khaltaev N. A reference standard for the description of osteoporosis. Bone 2008; 42:467-475.
21. Orientação Técnica para a utilização da absorsiometria radiológica de dupla energia (DEXA). Direcção-Geral da Saúde. Abril de 2008. http://www.dgs.pt/upload/membro.id/ficheiros/i009644.pdf
22. Dawson-Hughes B. Treatment of vitamin D deficient states. In: UptoDate, Schur P (Ed), UptoDate, 2010. Acedido em 22 Janeiro de 2010.
23. Kurup H, Andrews G. Secondary prevention of osteoporosis after Colles fracture: Current practice. Joint Bone Spine 2008; 75:50-52.
24. Hodsman AB, Leslie WD, Tsang JF, Gamble GD. 10-year probability of recurrent fractures following wrist and other osteoporotic fractures in a large clinical cohort: an analysis from the Manitoba Bone Density Program. Arch Intern Med 2008;168:2261-2267.
25. Rosen H. Calcium and vitamin D supplementation in osteoporosis. In: UpToDate, Schur P (Ed), UptoDate, 2010. Acedido em 22 Janeiro de 2010.
26. Geusens P, Roux C, Reid D et al. Drug insight: choosing a drug treatment stategy for women with osteoporosis- an evidence-based clinical perspective. Nature Clinical Practice Rheumatology 2008. doi:10.1038/ncprheum0773.
27. Brown JP, Josse RG, Scientific Advisory Council of the Osteoporosis Society of Canada. 2002 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada. CMAJ 2002; 167:1-34.
28. Gong H, Oh W, Chung M, Oh J, Lee Y, Baek G. Patients with Wrist Fractures are less likely to be evaluated and managed for osteoporosis. J Bone Joint Surg Am 2009; 91:2376-2380.
29. Reginster JY, Burlet N. Osteoporosis: a still increasing prevalence. Bone 2006;38:4-9.

# REMITTING SERONEGATIVE SYMMETRICAL SYNOVITIS WITH PITTING OEDEMA SYNDROME, ASSOCIATED WITH PROSTATE ADENOCARCINOMA: A CASE REPORT

Gonçalo Marto*, Zoya Klitna*, Maria C. Biléu*, Anabela Barcelos**

## Abstract

Remitting seronegative symmetrical synovitis with pitting oedema (RS3PE) of the dorsum of the hands and/or feet can be observed in different inflammatory rheumatic diseases as well as in haematological and solid malignancies. McCarty *et al,* described this syndrome for the first time more than twenty years ago. Underlying malignancy should always be excluded in patients with RS3PE syndrome.

**Keywords:** RS3PE; Prostate Adenocarcinoma; Elderly.

## Introduction

Remitting seronegative symmetrical synovitis with pitting oedema (RS3PE) is a rare inflammatory type of arthritis that occurs predominantly in elderly men with clinical manifestations of acute onset pitting oedema of hands. Is usually characterized by a rapid-onset symmetrical synovitis; presence of pitting oedema of joints involved, especially the dorsum of hands; seronegativity of rheumatoid factor; absence of joint erosion; good response to low dose steroids with long term remission after withdrawal. In spite of appearing a well-characterized condition, subsequently research has shown that it is not a specific entity but rather a syndrome that can in fact represent the first manifestation of various types of rheumatic diseases and neoplastic conditions, usually of the elderly. In the last years, some reports described the RS3PE syndrome as paraneoplastic syndrome, exemplified in patients with distal extremity with swelling pitting oedema as the first manifestation of haematological and solid malignancies. Herein we report a case of pitting oedema on hands in a patient with prostate adenocarcinoma.

## Case report

E.S., a 74-year-old male Caucasian patient, was admitted into the Rheumatology Clinic of our institution (Hospital Infante D. Pedro, E.P.E.) in the first week of January 2009 with pain and swelling of both hands with severe disability started suddenly during the two weeks before. The patient also had complaints of weight loss of 2kg in 15 days, epigastric pain and nocturia. His complaints did not decrease with nonsteroidal antiinflammatory drugs. No preceding history of major trauma, headache, fever, skin changes, anorexia, cough or intestinal disorders. His past medical history included two prostate surgical procedures, blood hypertension with no alcohol or tobacco abuse. The physical examination revealed swelling of both hands with pitting oedema noted over the dorsum (Figures 1 and 2) with inflammation of flexor tendon sheaths of the hands and swelling of knee joints. Laboratory data showed an erythrocyte sedimentation rate (ESR) of 130 mm/h and a C-reactive protein (CRP) level of 15.51 mg/dL. The haematological values and biochemical markers were found to be normal except for haemoglobin (10.6 g/dL) and albumin (2.6 g/dL). Rheumatoid factor (RF), anticitruline (anti-CCP), hepatitis B and C antibodies were negative. Serum prostate-specific antigen (PSA) level was raised (10.10 ng/dL with normal values under 4,0 ng/dL). Radiological examination of the hands showed soft tissue swelling and did not reveal any erosions. Chest radiograph and endoscopy of upper gastrointestinal system were normal. The diagnosis of remitting seronegative symmetrical synovitis with pitting oedema (RS3PE syndrome) was

*Internal Medicine Department, Hospital Infante D. Pedro, E.P.E., Aveiro
*Rheumatology Department, Hospital Infante D. Pedro, E.P.E., Aveiro

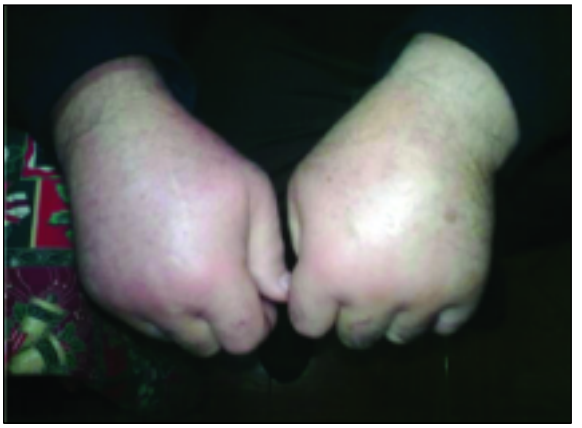


**Figure 1.** Pitting oedema of Dorsum of Hands before treatment

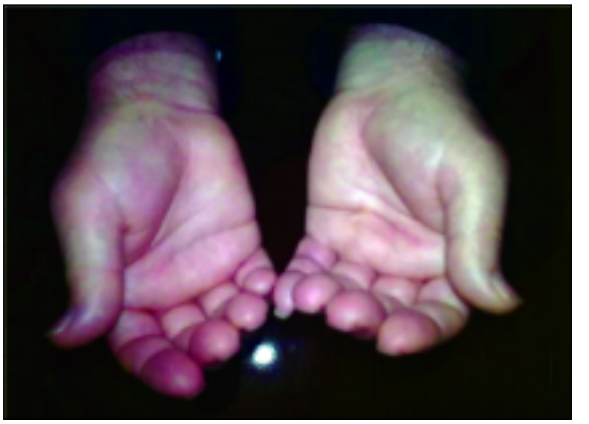


**Figure 2.** Oedema of Palm of Hands before treatment

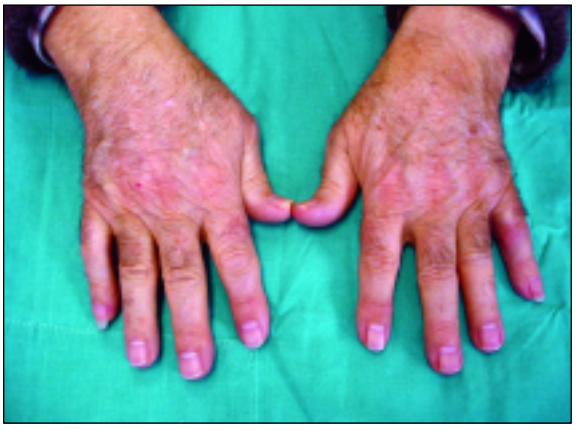


**Figure 3.** Dorsum of Hands after Treatment

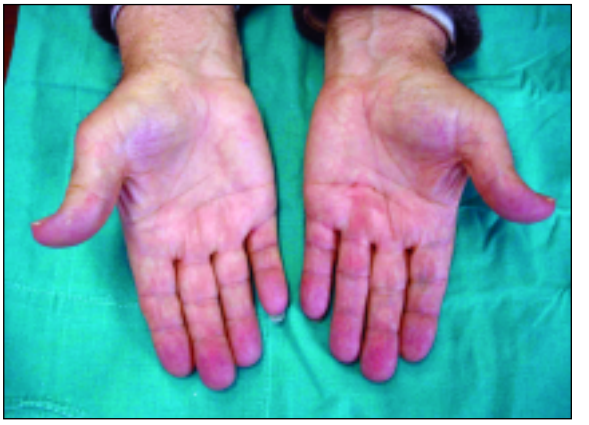


**Figure 4.** Palm of Hands after Treatment

suggested and, considering the possibility of an underlying malignancy, a prostate biopsy was performed. The patient was treated with oral diclofenac 150 mg/day and oral prednisolone 20 mg/day with an improvement of the hands oedema. Meanwhile prostate biopsy showed an adenocarcinoma and the patient underwent antiandrogenic therapy. There was remission of clinical findings (Figure 3 and 4) and improvement in laboratory parameters (Hb 12.4 mg/dL). The patient became independent in daily living activities.

## Discussion

In 1985, McCarthy *et al*[1] described a specific type of arthritis, with a sudden onset bilateral symmetrical synovitis of upper and/or lower limbs associated with a marked pitting oedema of the dorsum of the hands ("boxing-glove" hand) and/or feet, especially affecting the elderly males and with an excellent prognosis. Etiology of the RS3PE syndrome is unknown but infectious agents or environmental factors are known to have impact in the development of this disease[1]. Serologic testes, like rheumatoid factor (RF) are negative and radiographic joint destruction is not seen[1]. The clinical findings originally described for RS3PE syndrome had also been observed in other diseases such as rheumatic diseases and neoplastic conditions of the elderly[2]. In fact, clinical findings of RS3PE syndrome were described in conditions like acute sarcoidosis[3], and in other rheumatic diseases: polymyalgia rheumatica[4,5], spondylarthropathies[2,6], rheumatoid arthritis[7] and psoriatic arthritis[8]. Several articles have reported patients with distal extremity swelling with pitting oedema as the first manifestation of haematological and solid tumors[9]. Prostate, stomach and colon seem to be the most frequently in-

volved organs[9], but association with non-Hodgkin lymphoma[10], chronic lymphoid leukemia, T lymphoma[11], hepatocellular carcinoma[12], endometrial adenocarcinoma[13] or undifferentiated lung carcinoma[14] was also reported.

Patients with idiopathic RS3PE syndrome showed an excellent response to low doses of corticosteroids compared to the poor response of the RS3PE patients with associated neoplasia. However, in some reported cases RS3PE was relieved with steroid treatment before treatment of malignancy[15]. In our case, the patient received corticosteroids and hormone therapy almost in the same time. Therefore, the efficacy of steroids treatment should be questioned. A higher frequency of systemic signs and symptoms (fever, anorexia and weight loss) have been observed in patients with an underlying malignancy[14].

In the clinical setting of RS3PE syndrome, the rheumatologist should consider malignancies in the absence of other associated rheumatic diseases, in the presence of systemic signs and symptoms and if the response to corticosteroids is poor[5].

**Correspondence to**
Gonçalo Marto
Internal Medicine Department
Hospital Infante D Pedro, E.P.E.
Avenida Artur Ravara
3814-501 Aveiro, Portugal
Telephone: +351 234 378 300
Fax: 234 378 395
E-mail: marto.goncalo@gmail.com

### References

1. McCarthy DJ, O'Duffy JD, Pearson L, Hunter JB: Remitting Seronegative Symmetrical Synovitis with Pitting Edema: RS3PE syndrome. JAMA 1985; 254: 2763--2767.
2. Schaeverbeke T, Fatout E, Marce S, et al. Remitting seronegative symmetrical synovitis with pitting oedema: disease or syndrome? Ann Rheum Dis 1995; 54:681-684.
3. Cantini F, Niccoli L, Olivieri I, et al. Remitting distal lower extremity swelling with pitting oedema in acute sarcoidosis. [Letter]. Ann Rheum Dis 1997;56:565--566.
4. Olivieri I, Padula A, Favaro L, Oranges GS, Ferri S. 1. RS3PE syndrome with unilateral involvement. [Letter]. J Rheumatol 1994;21:372.
5. Salvarani C, Gabriel S, Hunder GG. Distal extremity swelling with pitting edema in polymyalgia rheumatica. Arthritis Rheum 1996;39:73-80.
6. Olivieri I, Padula A, Pierro A, Favaro L, Orange GS, Ferri S. Late onset undifferentiated seronegative spondylarthropaty. J Rheumatol 1995;22:899-903.
7. Bhakta BB, Pease CT. Late-onset rheumatoid arthritis: is pitting oedema of the hands at onset a good prognostic indicator? Br J Rheumatol 1997;36:214--219.
8. Olivieri I, Salvarani C, Cantini F. Remitting distal lower extremity swelling with pitting edema: a distinct syndrome or a clinical feature of different inflamatory rheumatic diseases? J Rhematol 1997;24:249-252
9. Olivieri I, Salvarani C, Cantini F. RS3PE Syndrome: An overview. Clin Exp Rheumatol 2000;18:53-55.
10. Goldenberg K, Rozenbaum M, Rosner I, Naschitz J, Kotler C. Remitting symmetric seronegative synovitis with pitting edema (RS3PE) secondary to non-Hodgkin's lymphoma. Clinic Exp Rheumatol 1998;16:767-768.
11. A del Blanco J, Pons M, Vaquero M, Tena X. The clinical spectrum of remitting seronegative symmetrical synovitis with pitting edema. The Catalán Group for the Study of RS3PE. J Rheumatol 1997;24:333-336.
12. Nakashima H, Tanaka Y, Shigematsu H, Kanaya S, Otsuka T, Hayashida K, Horiuchi T, Niho Y. Remitting seronegative symmetrical synovitis with pitting edema syndrome associated with cryptogenic hepatocellular carcinoma. Clin Exp Rheumatol 1999;17:390--391.
13. Olivo D, Mattace R. Concurrence of benign edematous polysynovitis in the elderly (RS3PE synrome) and endometrial adenocarcinoma. Scand J Rheumatol 1997;26:67-68.
14. Cantini F, Salvarani C, Olivieri I. Paraneoplastic remitting seronegative symmetrical synovitis with pitting edema. Clin and Exp Rheumatol 1999;17:741--744.
15. Cobeta-Garcia JC, Domingo-Morera JA, Martinez--Burgui J. RS3PE syndrome and chronic lymphoid leukaemia. Clin Exp Rheumatol 1999;17:266.

# DIAGNOSIS OF JUVENILE SYSTEMIC LUPUS ERYTHEMATOSUS IN ADOLESCENTS WITH HASHIMOTO'S THYROIDITIS: TWO CASE REPORTS

Crésio Alves*, Teresa Cristina Vicente Robazzi**, Manuela Fragomeni***

## Abstract

**Objectives:** To report the unusual diagnosis of juvenile systemic lupus erythematosus (JSLE) in two adolescents with a previous diagnosis of Hashimoto's thyroiditis (HT).

**Case reports:** Case # 1: An 11 year-old girl was diagnosed with HT. One year later, she presented with generalized edema, pericardial and pleural effusion, positive ANA, thrombocytopenia, increased anti-cardiolipin IgG and nephritis, being diagnosed with JSLE. (Case # 2): A 13 year-old girl was diagnosed with HT at the age of 10 years. Two years later, she presented with weight loss, knee and elbow arthritis, alopecia, leukopenia, and positive ANA and dsDNA autoantibody confirming the diagnosis of JSLE. The first patient was treated with prednisone and cyclophosphamide, and the second with prednisone and hydroxychloroquine with both achieving relief of the lupic symptoms.

**Conclusion:** In spite of the known association between autoimmune diseases and thyroid disorders, the occurrence of JSLE in patients with a previous diagnosis of HT is rare. It is important to bear in mind this possibility when following patients with HT in order to not delay the diagnosis and treatment of a serious systemic autoimmune disease such as JSLE.

**Keywords:** Adolescent; Hashimoto's Thyroiditis; Systemic Lupus Erythematosus.

*Professor of Pediatrics, Chief of the Pediatric Endocrinology Service, Hospital Universitário Professor Edgar Santos, Faculty of Medicine, Universidade Federal da Bahia

**Professor of Pediatrics, Chief of the Pediatric Rheumatology Service, Hospital Universitário Professor Edgar Santos, Faculty of Medicine, Universidade Federal da Bahia

*** Pediatrician, Hospital Universitário Professor Edgar Santos, Faculty of Medicine, Universidade Federal da Bahia

## Introduction

The autoimmune diseases can be classified as systemic or organ-specific[1]. Hashimoto's thyroiditis (HT) is an organ-specific autoimmune disease in which production of thyroid antibodies occurs along with thyroid lymphocytic infiltration. Systemic lupus erythematosus (SLE) is an autoimmune systemic disease, characterized by autoantibodies and deposition of immune complexes in several organs and tissues. The diagnosis of autoimmune thyroid disease in patients with SLE is well-known, especially in adults, with few case reports involving children and adolescents[2]. However, the literature is scarce in studies showing the opposite, that is, the occurrence of SLE in previously diagnosed HT patients[3-5].

As there is little data about this theme, the authors describe two adolescents who developed SLE one year after the diagnosis of Hashimoto's thyroiditis.

## Case Report

### Patient #1

An 11 year-old girl was diagnosed with HT at the age of 10 years-old, based on free thyroxine [FT4]: 0.22 ng/dL (0.75–1.80), thyrotropin [TSH]: 135 mIU/mL (0.3–5.0); antiperoxidase antibody (TPO): 263 IU/mL (< 35) and antithyroglobulin antibody: 51 IU/mL (< 40). One year later, she presented with generalized edema, mucosal bleeding and hematuria. Physical examination showed: T 36.5 °C (97.7 °F); HR: 108 bpm; RR 26 ipm; BP: 136/95 mmHg; height: 121 cm; weight: 30.2 Kg and absence of arthritis or butterfly rash. Laboratory evaluation (reference values in parenthesis) demonstrated: hemoglobin: 7.1 g/dL, leukocytes: 8,800/mm$^3$, platelets 4,800/ /mm$^3$ (145,000–450,000), BUN: 54.2 mg/dL (6-20), creatinine: 1.2 mg/dL (0.4 – 1.1), sodium: 138 mEq/ /L (136–148), potassium: 6.1 mEq/L (3.5–5.5), albu-

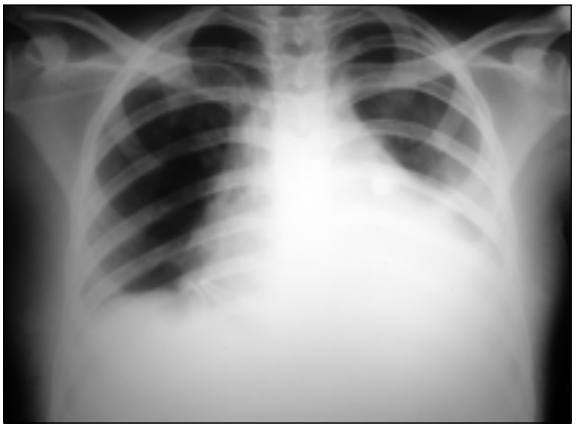


**Figure 1.** Chest X-ray revealing bilateral pneumonia, right pleural effusion and pericardial effusion

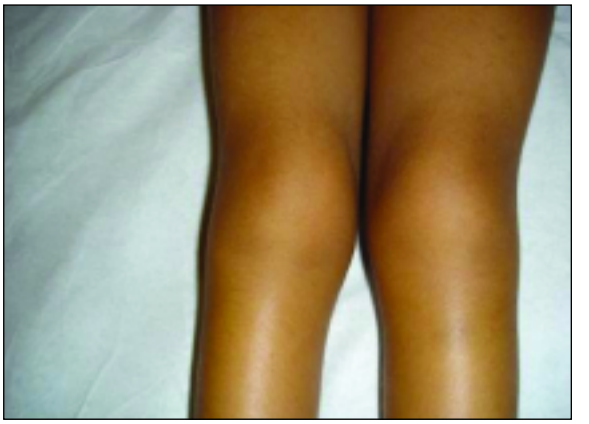


**Figure 2.** Bilateral knee arthritis

min: 2.5 g/dL (3.5–5.0), aspartate aminotransferase: 15 U/dL (15–37) and alanine aminotransferase: 18 U/dL (30–65). Urine analysis revealed proteinuria and hemoglobinuria. Renal sonogram identified cortex-medullar alterations bilaterally. Chest X-ray revealed bilateral pneumonia, right pleural effusion and pericardial effusion (Figure 1). Myelogram was normal. Serologies were negative to HIV, HTLV and cytomegalovirus. Rheumatologic studies showed: C3: 31 mg/dL (90–207), C4: 1.6 mg/dL (17–52), CH-100: undetected, ANA staining pattern: mixed pattern (homogeneous and speckled), with titles of 1:320 e 1:5.120, extractable nuclear antigens (Ro/SSA, La/SSB, SM), anti dsDNA, P-ANCA and C-ANCA autoantibodies and VDRL were negative. Anti-cardiolipin IgM reactiveness was negative, and the corresponding IgG was moderate reactive. Renal biopsy was compatible to Class IV lupus nephritis. The diagnosis of JSLE was confirmed through the American College of Rheumatology criteria[6]. As there was not a satisfactory response with oral prednisone, intravenous methylprednisolone and cyclophosphamide were added with edema regression, normalization of diuresis and blood pressure levels. She was discharged medicated with cyclophosphamide, prednisone, captopril, levothyroxine and omeprazole.

### Patient # 2

A 13 year-old girl was diagnosed with HT at 10 year--old, confirmed by: FT4: 1.38 ng/dL; TSH: 29.72 IU/mL; TPO: 220 UI/mL and antithyroglobulin antibody: 71 UI/mL. Two years later, she developed fatigue, weight loss, arthralgia of the wrists, knee and ankles arthritis and alopecia. Physical examination showed: T: 36,5º C (97.7 °F); HR: 84 bpm; RR: 20 ipm; TA: 85/60 mmHg; height: 166 cm; weight: 44 kg and arthritis in both knees and ankles (Figure 2). Laboratory studies demonstrated: hemoglobin: 9.4 g/dL, leukocytes: 2,800/mm$^3$, platelets 250,000/mm?, ESR: 71 mm/1$^{st}$ hour (< 20). Renal and liver function tests, electrolytes, proteins, serum lipids, hemoglobin, electrophoresis, urine analysis, echocardiogram, renal ultrasonography and chest X-ray were without abnormalities. Rheumatologic studies showed: C3: 80mg/dL (90-207), C4: 12 mg/dL (17-52), CH-100: 44 mg/dL (> 60); ANA staining pattern: mixed pattern (homogeneous and speckled), with titles of 1:320 e 1:620 and positive dsDNA antibody. The Ro/SSA, La/SSB, anti-SM, anti-cardiolipin IgM and IgG, P-ANCA and C-ANCA autoantibodies, Rheumatoid Factor and VDRL were negative. The diagnosis of JSLE was confirmed by the American College of Rheumatology criteria[6]. The patient was treated with prednisone and hydroxychloroquine with a good clinical response.

Table I summarizes the main clinical and laboratory data of the two patients.

## Discussion

There is a consensus about a higher prevalence of autoimmune thyroid diseases and thyroid antibodies among SLE patients[2-7]. Although elevated thyroid antibodies prevalence can be evidenced in some SLE series, the presence of thyroid dysfunction is rare. Blich *et al.*, reported a 4.3 to 21.4 per-

**Table I. Overview of clinical and laboratory findings**

| Variables | | Case report # 1 | Case report # 2 |
|---|---|---|---|
| Age at HT diagnosis | | 10 year-old | 10 year-old |
| Age at SLE diagnosis | | 11 year-old | 13 year-old |
| Thyroid Function Tests | TSH (0.3-5.0 IU/mL) | 135 | 29,72 |
| | FT4 (0.75-1.80 ng/dL) | 0.22 | 1.38 |
| | Antiperoxidase antibody (< 35 IU/mL) | 263 | 220 |
| | Antithyroglobulin antiboby (< 40 IU/mL) | 51 | 71 |
| Work-up for SLE diagnosis | C3 (90-207 mg/dL) | 31 | 80 |
| | C4 (17-52 mg/dL) | 1.6 | 12 |
| | CH-100 (> 60 mg/dL) | Undetected | 44 |
| | ANA (Negative) | Positive | Positive |
| | sdDna antibody (Negative) | Negative | Positive |
| | Anti-cardiolipin IgG (Negative) | Moderate Reactiveness | Negative |
| | Ro/SSA (Negative) | Negative | Negative |
| | La/SSB (Negative) | Negative | Negative |
| | Anti-Sm (Negative) | Negative | Negative |
| | P-ANCA (Negative) | Negative | Negative |
| | C-ANCA (Negative) | Negative | Negative |
| Systemic manifestations | Pancytopenia | + | – |
| | Arthritis/Arthralgia | + | + |
| | Renal failure | + | – |
| | Thrombocytopenia | + | – |
| | Serositis | + | – |

Legend: (HT): Hashimoto's thyroiditis; (SLE): systemic lupus erythematosus; (FT4): free thyroxine; (TSH): thyrotropin; (C): complement; (ANA) antinuclear antibody.

cent prevalence rate of thyroid abnormalities among SLE patients when compared to a 1 percent prevalence rate in the general population[1]. Some studies demonstrated a higher frequency of thyroid abnormalities in children, whereas others did not[8].

However, the current knowledge is limited about if there is a higher prevalence of SLE in autoimmune thyroid disease patients. Besides few case reports, we found two large studies connecting these two conditions: a study from Gaches *et al.* indicated a 13.7 percent prevalence rate of systemic autoimmune diseases among HT patients, particularly SLE and Sjögren's syndrome[9]; and a study by Biró *et al.* demonstrated a 6.5 percent prevalence rate of SLE among patients with HT, compared to 0.05-0.1 percent for the general population[4].

Tektonidou *et al.* suggest as a feasible explanation to the association between HT and systemic autoimmune diseases a polyclonal autoimmune response against organ-specific autoantigens[5]. Biró *et al.* demonstrated the association of HLA-DQA1*0301/DQB1*0401/DRB1*0405 haplotypes with these syndromes, as well as with thyroid autoantibodies cross reaction with several tissues and organs, besides an unbalanced proinflammatory cytokine setting[3]. Picco *et al.* proposed a role of the pubertal hormonal changes in triggering the outburst of these diseases[4]. In their study, the authors revealed a positive ANA two years before overt clinical SLE. However, Eberhard *et al.* mentioned that 30% of the children diagnosed with autoimmune thyroiditis had a positive ANA, although only some of them presented SLE[8]. In the study of Picco *et al.*, similar to the patient presented in the first case, anti-dsDNA and anti-Sm were negatives at the SLE diagnosis[4]. Kramer *et al.* alleged a higher prevalence of hyperprolactinemia among LES patients, which must be considered among the causes of immunologic imbalance[10]. Furthermore, hyper-

prolactinemics patients have a higher prevalence of thyroid antibodies, evidencing an interrelationship among these three syndromes.

It is important to be alert to the unusual possibility of SLE developing in patients with a previous diagnosis of autoimmune thyroiditis. Cohorts studies must be designed in order to clarify the risk factors and the causality between thyroid dysfunction and SLE. For instance: if Hashimoto's thyroiditis and systemic autoimmune diseases share a polyclonal autoimmune response against organ-specific autoantigens, if thyroid autoantibodies cross react with several tissues and organs, and the role of pubertal hormonal changes in triggering the outburst of these diseases.

**Correspondence to**
Crésio Alves
Rua Plínio Moscoso, 222/601.
CEP: 40-157-190. Salvador, Bahia, Brazil.
Phone: (55) (71) 9178-4055.
E-mail: cresio.alves@uol.com.br

**References**

1. Blich M, Rozin A, Edoute Y. Systemic lupus erithematosus and thyroid disease. IMAJ 2004; 6:218-220.
2. Scott JJX, Raghupathy P. Presence of thyroid antibodies in a child with systemic lupus erythematosus. Indian Pediatr 2005; 42:191-193.
3. Biró E, Szekanecz Z, Czirják L, et al. Association of systemic and thyroid autoimmnune diseases. Clin Rheumatol 2006; 25:240-245.
4. Picco P, Gattorno M, Buoncompagni A, et al. Autoimmune thyroiditis developing into systemic lupus erithematosus in a 15-year-old girl. Clin Exp Rheumatol 1996; 14:348-349.
5. Tektonidou MG, Margarita A, Vlachoyiannopoulos P, Moutsopoulos HM. Presence of systemic autoimmune disorders in patients with autoimmune thyroid diseases. Ann Rheum Dis 2004; 63:1159-1161.
6. Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982; 25:1271-1277.
7. Miller FW, Moore GF, Weintraub BD, Steinberg AD. Prevalence of thyroid disease and abnormal thyroid function test results in patients with systemic lupus erythematosus Arthritis Rheum 1987; 30:1124-1131.
8. Eberhad BA, Laxer RM, Eddy AA, Silverman ED. Presence of thyroid abnormalities in children with systemic lupus erithematosus J Pediatrics 1991; 119:277--279.
9. Gaches F, Delaire L, Ndalon S, Loustaud-Ratti V, Vidal E. Frequency of autoimmune diseases in 218 patients with autoimmune thyroid pathologies. Rev Med Intern 1998; 19:173-179.
10. Eisenbarth GS, Gottlieb PA. Autoimmune polyendocrine syndromes N Engl J Med 2004; 350:2068--2079.

# ACENOCUMAROL E VASCULITE – UM CASO CLÍNICO RARO

Pedro Abreu, Cátia Duarte, Armando Malcata*


## Resumo

Os autores apresentam o caso de um homem de 62 anos de idade que acorre ao Serviço de Urgência por lesões cutâneas purpúricas, de instalação insidiosa com três semanas de evolução. O exame físico revelou múltiplas lesões purpúricas de conformação redonda e confluentes envolvendo todo o corpo, incluindo as áreas palmo-plantar. Os exames laboratoriais realizados não apresentaram alterações. Durante o internamento foi realizada biópsia cutânea. Após exclusão de outras causas de lesões purpúricas foi suspenso o acenocumarol e as lesões desapareceram, espontaneamente, numa semana. A púrpura foi atribuída à administração de acenocumarol, dada a resolução das lesões, apesar da cronicidade com que o doente já tomava este medicamento. Este caso ilustra uma rara associação de vasculite e acenocumarol.


**Palavras-Chave:** Acenocumarol; Cumarínico; Vasculite de pequenos vasos; Anticoagulação.


## Abstract

The authors present a case of a man with 62 years of age who comes to the emergency room by purple skin lesions affecting the whole body, including palmar-plantar involvement, with insidious installation, with three weeks of development. Physical examination revealed multiple purple-shaping round and confluent lesions involving the entire body. Laboratory tests performed were all normal. During the admission a skin biopsy was performed. After exclusion of other causes for the purpuric lesions, the acenocoumarol was interrupted and the lesions disappeared, spontaneously, in a week. The purple was attributed to the administration of acenocoumarol, given the resolution of lesions, despite the chronicity of therapy. This case illustrates a rare association between vasculitis and acenocoumarol.


*Serviço de Reumatologia – Hospitais da Universidade de Coimbra

**Keywords:** Acenocoumarol; Cumarinic; Small-vessel vasculitis; Anticoagulation.

## Introdução

O acenocumarol é um anticoagulante oral cumarínico largamente utilizado para profilaxia de doenças tromboembólicas. A hemorragia é o efeito adverso mais frequentemente relatado deste fármaco[1]. A necrose cutânea, «*purple toes syndrome*» (descrito inicialmente em 1961 e caracterizado por aparecimento súbito e bilateral de lesões purpúricas, dolorosas, nos dedos dos pés e que não desaparecem à digito pressão; surgindo 3 a 8 semanas após início de terapêutica anti-coagulante), erupções maculopapulares ou vesiculares urticariformes também têm sido descritas[2]. A vasculite associada à terapêutica com acenocumarol é muito raramente encontrada na literatura.

## Caso clínico

Doente do sexo masculino, de 62 anos de idade, caucasiano, reformado, natural e residente em Penacova. Recorre ao Serviço de Urgência dos Hospitais da Universidade de Coimbra referindo história de lesões cutâneas purpúricas afectando todo o corpo, incluindo envolvimento palmo-plantar, de instalação insidiosa com três semanas de evolução (Figuras 1 e 2). Associadamente referia artralgias dos cotovelos de ritmo mal definido. Negava perdas hemáticas visíveis. Não tinha história de alergia a fármacos e negava também consumo de produtos de ervanária.

Nos antecedentes pessoais, salientava-se história de fenómeno de *Raynaud* completo com aproximadamente 37 anos de duração e história de isquémia crónica do membro inferior esquerdo de grau IV (classificação de Fontaine) com necrose do 1º dedo do pé esquerdo e parésia sensitivo-motora que motivou realização, em 1996, de *bypass* femuro-poplíteo, sendo seguido, desde então, na

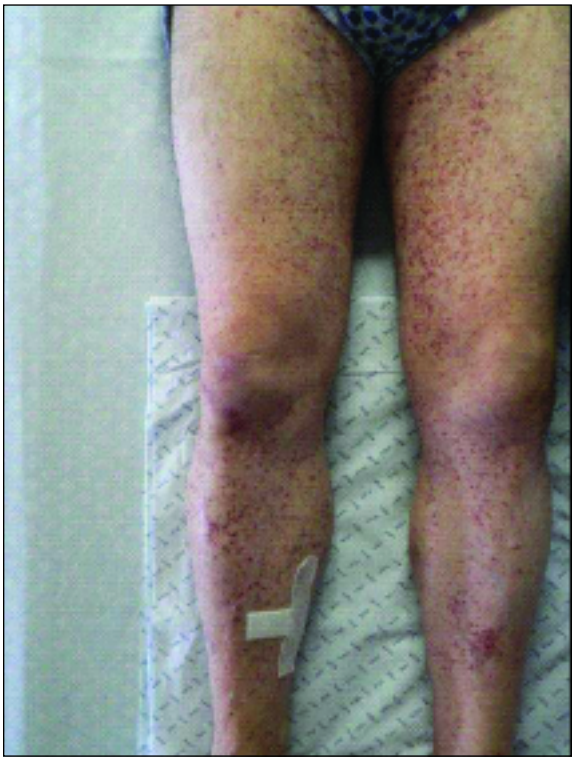


**Figura 1.** Lesões purpúricas de pequenas dimensões nos membros inferiores.

consulta de Cirurgia Vascular do mesmo Hospital. Estava medicado com acenocumarol desde 1998; sem outros fármacos. Fumador de 90 unidades-maço/ano, tendo suspendido há 11 anos. Hábitos alcoólicos ligeiros.

O exame físico evidenciou múltiplas lesões purpúricas arredondadas e confluentes envolvendo todo o corpo, incuindo envolvimento palmo-plantar, que não desapareciam à digito pressão. O palato apresentava lesões eritematosas. Não se detectaram alterações na avaliação cardio-pulmonar, abdominal ou do foro otorrinolaringológico.

Analiticamente, apresentava hemoglobina 17.1 g/dL, contagem leucocitária total $9.0x10^3/mm^3$ (2% eosinófilos), plaquetas $270x10^3/mm^3$, provas hepáticas normais com excepção de gama-glutamil transpeptidase (GGT) 64 U/l (<50 U/L) , creatinina 1.0 mg/dL, ureia 17 mg/dL, albumina 4.9 mg/dL, proteína C reactiva (PCR) 3.22 mg/dL (<0.5 mg/dL), velocidade de sedimentação (VS) 19 mm/1ª hora e proteinograma com imunoelectroforese dentro dos valores normais. No estudo de coagulação a taxa de protrombinémia, aPTT e INR (*International Normalized Ratio*) foi 18%, 48.8 seg. e 3.77, respectivamente. D-dímeros 1.61 µg/mL (0-0.6 µg/mL) e fibrinogénio 4.4 g/dL (2.0-5.0 g/dL). As hemoculturas e uroculturas efectuadas foram negativas. Estudo das fracções do complemento (C3 e C4) normal e pesquisa de autoanticorpos foi positivo para os autoanticorpos nucleares (ANAs) - título 1:320 – com um padrão granular fino denso, mas negativo para a pesquisa de anticorpos anti-neutrófilos citoplasmáticos (ANCAs). Factor reumatóide (FR), serologias virais (hepatite B, C), citomegalovírus, *Epstein-Barr* vírus, *Herpes simplex* vírus (1+2), toxoplasma e *Ricketzia* negativos. Pesquisa de imunocomplexos foi negativa. O exame sumário de urina revelou proteinúria (20 mg/dL) e eritrocitúria 108.9/µL. Foi realizada determinação de proteinúria nas 24 horas cujo valor foi 345.8 mg (50-80 mg/24h). Realizou capilaroscopia que não mostrou alterações com excepção de uma área de trombose do 5º dedo direito.

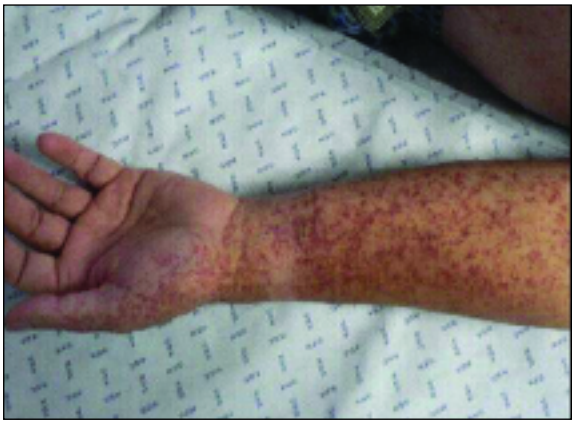


**Figura 2.** Envolvimento palmar e do membro superior das lesões purpúricas.

Imagiologicamente não apresentava alterações na radiografia torácica, ecografia abdominal ou prostática.

A biópsia cutânea, realizada ao 4º dia de internamento não demonstrou haver vasculopatia, nem infiltrado inflamatório significativos.

O tratamento com acenocumarol foi suspenso depois de descartadas outras hipóteses diagnósticas, nomeadamente causa infecciosa e vasculite sistémica. As lesões cutâneas resolveram espontaneamente nos 7 dias seguintes. Verificou-se, também, nesse período, normalização do sedimento urinário. Teve alta com indicação de reiniciar acenocumarol. No dia seguinte, recorre, ao Serviço de Reumatologia por reaparecimento das lesões cutâneas, sendo reinternado. Foi novamente suspen-

so acenocumarol, com melhoria espontânea nos 7 dias seguintes. Foi efectuado o diagnóstico de vasculite de pequenos vasos, secundária a fármaco, e iniciou antiagregação oral com ticlopidina 250mg bid que mantém até hoje e sem intercorrências associadas a este medicamento.

## Discussão

O presente caso mostra um caso de vasculite de pequenos vasos, secundária à toma de um anticoagulante oral cumarínico – acenocumarol.

Os fármacos estão associados a aproximadamente 10-15% de todas as lesões dermatológicas do tipo vasculítico[3,4]. As drogas mais frequentemente envolvidas são a penicilina, as sulfonamidas, as quinolonas, o tamoxifeno, os anticoncepcionais, a fenotiazina, o alopurinol e retinóides[4,5]. O acenocumarol pertence à família dos anticoagulantes cumarínicos e é prescrito frequentemente para o tratamento e profilaxia de doenças arteriais ou venosas tromboembólicas. A hemorragia é o principal efeito adverso. Entre os demais efeitos adversos cutâneos decorrentes da terapêutica anticoagulante, são frequentes a «*purple toes syndrome*» e a necrose cutânea[6,7]. Esta última situação tem sido bem documentada apesar de ser mais frequente com a varfarina[4,8]. Ocorre habitualmente entre o 3º e 8º dia de terapêutica, embora possa aparecer mais tardiamente[9]. É mais frequente em mulheres e atinge sobretudo as zonas onde abunda tecido celular subcutâneo adiposo: mamas, coxas e regiões glúteas. Histopatologicamente, caracteriza-se por trombose microvascular nas zonas cutâneas afectadas[6,9]. A vasculite induzida por fármacos cumarínicos é muito rara. Surge mais tarde e é acompanhada por um infiltrado inflamatório. A sua localização é diferente e o tratamento é baseado na descontinuação do fármaco e na administração de corticóides[6].

Outros efeitos adversos têm sido relatados com o acenocumarol: equimoses, erupções maculopapulares e fotossensibilidade[2,4].

Os autores definiram o diagnóstico de associação de vasculite secundária ao acenocumarol dados os seguintes factos: a relação temporal entre a suspensão do fármaco e a resolução dos sinais de vasculite e posteriormente o reaparecimento de lesões com a sua reintrodução, bem como a ausência de outra causa medicamentosa ou outra etiologia associada - infecciosa, neoplásica ou inflamatória. Apesar dos antecedentes do doente – quadro neuropático do membro inferior em consequência patologia vascular isquémica grave, a ser seguido em consulta de Cirurgia Vascular, por fenómeno de Raynaud idiopático – ficou evidente, após a realização de história clínica apurada, a inexistência de sintomas constitucionais, assim como sinais ou sintomas compatíveis com quadro de conectivite ou vasculite sistémica, nomeadamente envolvimento articular, muscular, pulmonar, cardíaco ou gastrointestinal. Dada a limitação das lesões à pele (vasculite cutânea), não se realizou angiografia. A biópsia cutânea, de importância fundamental para o diagnóstico, e ainda que efectuada na fase inicial da doença, não revelou, contudo, processo inflamatório significativo.

Apenas 3 casos se encontram descritos na literatura médica relatando relação entre acenocumarol e vasculite: um, numa mulher de 62 anos[4]; outros dois, em indivíduos do sexo masculino de 54 anos[6] e de 61 anos[10], respectivamente. Dessa forma, este será o quarto caso descrito de vasculite induzida pelo acenocumarol. Tal facto ilustra uma rara associação de vasculite e acenocumarol. Os clínicos deverão estar alerta para este potencial efeito adverso e recomendar a suspensão do fármaco se houver relação entre o desaparecimento das lesões e a suspensão definitiva do mesmo.

**Correspondência para**
Pedro Abreu
Serviço de Reumatologia dos Hospitais da Universidade de Coimbra,
Praceta Mota Pinto
3000-075 Coimbra
Email: pmabreu@aeiou.pt

**Referências**

1. Hirsh J, Dalen JE, Deykin D, Poller L, Bussey H. Oral anticoagulants. Mechanism of action, clinical effectiveness, and optimal therapeutic range. Chest 1995; 108:231-246.
2. Gallerani M, Manfredini R, Moratelli S. Non-haemorrhagic adverse reactions of oral anticoagulant therapy. Int J Cardiol 1995; 49:1-7.
3. Fiorentino DF. Cutaneous vasculitis. J Am Acad Dermatol 2003; 48:311-340
4. Aouam K, Gassab A, Khorchani H, et al. Acenocoumarol and vasculitis: a case report. Pharmacoepidemiology and Drug Safety 2007; 16:113-114.
5. Dubost JJ, Tournadre A, Sauvesie B. Vascularites médicamenteuses. Rev Rhum 2002; 69:370-375.
6. Jiménez-Gonzalo FJ, Medina-Pérez M, Marín-Martín J. Acenocoumarol-induced leukocytoclastic vasculitis. Haematologica 1999; 84:462-463.

7. Sallah S, Thomas DP, Roberts HR. Warfarin and heparin-induced skin necrosis and the purple toe syndrome: infrequent complications of anticoagulant treatment. Thromb Haemostasis 1997; 78:785-90.
8. Valdivielso M, Longo I, Lecona M, Lazaro P. Cutaneous necrosis induced by acenocoumarol. J Eur Acad Dermatol Venereol 2004; 18:211-215.
9. Essex DW, Wynn SS, Jin DK. Late-onset warfarin induced skin necrosis: case report and review of the literature. Am J Hematol 1998; 57:233-237.
10. Vizoso MR, Sureda MF, Martí SG, García JS. Vasculitis leucocitoclástica y acenocumarol. Med Clin (Barc) 2008; 130:399.

# 32nd American Society for Bone and Mineral Research Annual Meeting

**Toronto, Canada**
**15 a 19 de Outubro 2010**

# VI Jornadas de Reumatologia e Medicina Familiar do Algarve

**Vilamoura, Portugal**
**22 a 23 de Outubro 2010**

# EPITHELIOID HEMANGIOENDOTHELIOMA PRESENTING AS A VERTEBRAL FRACTURE

Nuno Neves*, Francisco Lima-Rodrigues**, Manuel Ribeiro-Silva*, Pedro Cacho-Rodrigues*, Catarina Eloy***, Maria Emília Paiva***, Rui Pinto*

## Abstract

Epithelioid hemagioendothelioma (EH) is a rare vascular tumor with an intermediate biological behavior between hemangioma and angiosarcoma. Vertebral location is even more rare, and because the number of reported cases of EH is small and the follow-up periods short, the best surgical treatment, the role of radiotherapy and chemotherapy, as well as the definitive prognosis are still not established.

The authors report a case of EH which presented as a vertebral fracture with neurological impairment, where a percutaneous biopsy was inconclusive. Treatment included vertebrectomy, with complete excision of the lesion, spinal canal decompression and vertebral stabilization. Anatomopathological study revealed an epithelioid vascular neoplasm with low mitotic index, and tumor cells reactive to vimentin, CD31 and CD34, leading to the diagnosis of Grade I Epithelioid Hemangioendothelioma. Because of the wide resection achieved and the low aggressiveness of the lesion, no adjuvant radio or chemotherapy was undertaken, and at 6 years follow-up there are no signs of recurrence or metastasis.

**Keywords:** Epithelioid Hemagioendothelioma; Vertebral Tumor.

## Introduction

Epithelioid hemangioendothelioma (EH) is a rare vascular soft tissue tumor of intermediate malignancy[1]. Although initially described as most common in the soft tissues of the extremities, other locations are possible, namely bone. Reported cases of spinal involvement are extremely rare and follow-up periods have been too short, so the best management and prognosis for these lesions is still not clear.

## Case Report

MMDE, female, 51 years old, presented with a 2 months history of low back pain and progressive paraplegia. There was no trauma history or relevant general symptoms. Imaging studies, including X-Rays, CT-Scan and MRI (Figures 1, 2, 3), revealed a L1 pathological fracture with vertebral collapse and significant spinal compression. A percutaneous biopsy was performed but was inconclusive. Primary occult neoplasm studies were negative and inflammatory markers were only marginally increased (ESR: 20 mm, CRP: 0,7).

Due to the neurologic deterioration a staged surgical treatment was decided aiming at spinal canal decompression and vertebral stabilization. Through an anterior approach a L1 corpectomy was done, with placement of a vertebral spacer (Synex, Synthes Spine) and lateral plate fixation (Z-plate, Medtronic). Two weeks later T10-L4 pedicle instrumentation and fusion was performed (CD Horizon, Medtronic) (Figure 4).

Histological study of the lesion revealed a mesenchymal tumor with vessels formation composed by epithelioid cells forming cords or in solid areas, surrounded by a condroid-like stroma. Mitotic index was low and no necrosis was observed. Immunohistochemical study revealed that the tumor cells were reactive to vimentin, CD31 and CD34, leading to the diagnosis of Epithelioid Hemangioendothelioma (Figure 5).

In face of the extensive resection and the nature of the lesion it was decided not to proceed with other treatments such as radiotherapy or chemotherapy.

The patient remained asymptomatic for 5 years af-

*Spine Group, Orthopedic Department, Hospital de São João, Porto Medical School
**Orthopedic Department, ULSAM, Viana do Castelo
***Pathology Department, Hospital de São João, Porto

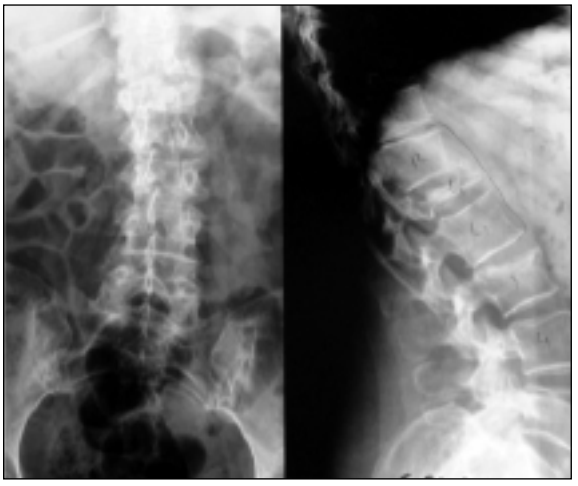


**Figure 1.** X-Rays showing a L1 burst fracture with nearly complete vertebral collapse

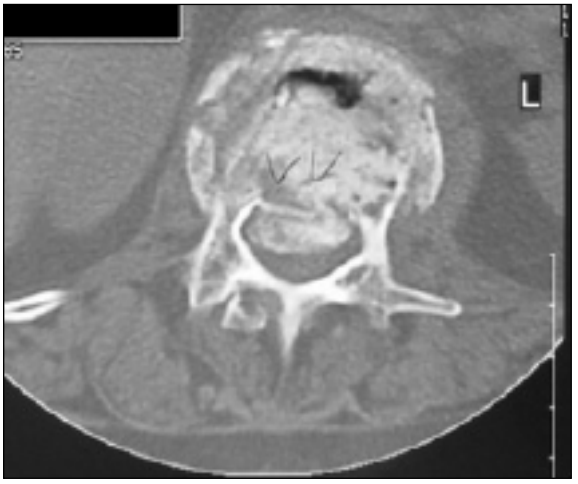



**Figure 2.** CT-scan revealed significant compromise of canal diameter

ter surgery, when she consulted again for progressive anterior imbalance. Radiographic study showed junctional kyphosis above the fused segment. It was decided to perform multiple Smith-Peterson osteotomies and extend the instrumentation to T4 to correct the deformity. The evolution was positive, and an asymptomatic balanced spine was achieved.

At present, more than 6 years after surgery, there is no evidence of recurrence or metastasis (Figure 6).

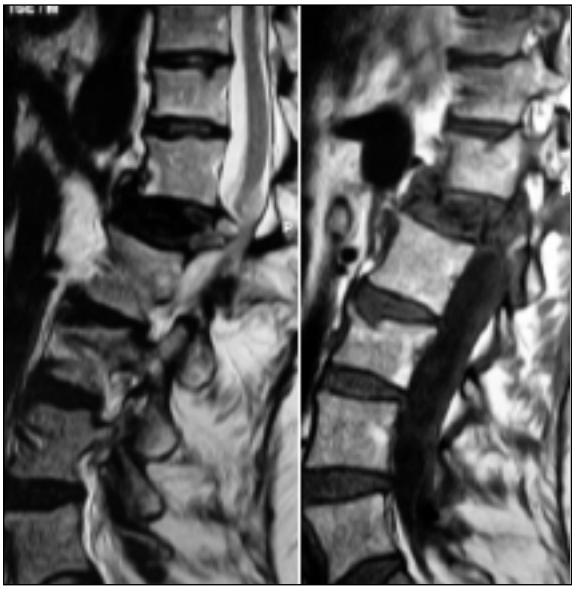


**Figure 3.** MRI: both on T1 and T2 weighted sequences severe neural compromise is observed; the lesion is confined to L1, which is significantly collapsed, with no adjacent reaction

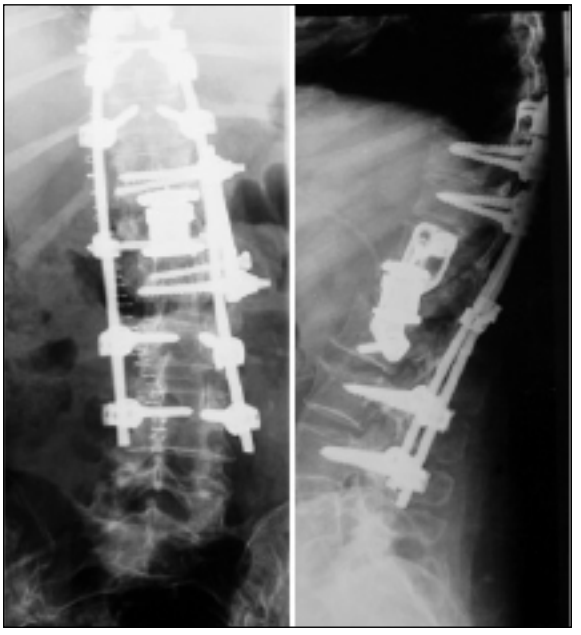


**Figure 4.** Post op of staged double approach vertebrectomy, with complete excision of the lesion, spinal canal decompression and vertebral stabilization

## Discussion

Vascular tumors account for less than 1% of all bone tumors[2]. Malignant primary vascular tumors of bone are even more rare and include angiosarcoma and hemangioendothelioma. EH was first described by Weiss and Enzinger in 1982 as a rare vascular lesion with an epithelioid appearance[1].

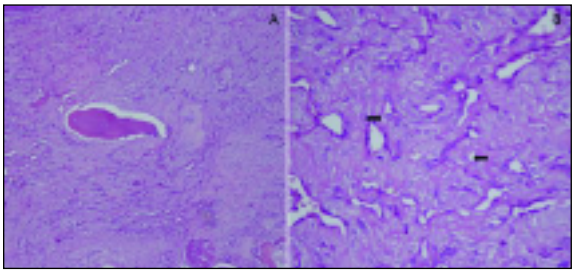


**Figure 5.** Histological aspect of epithelioid hemangioendotelioma involving bone (A – HE, 100x), consisting of cells with intracytoplasmatic vascular lumina (arrows), or delimiting vascular spaces (B – HE, 200x)

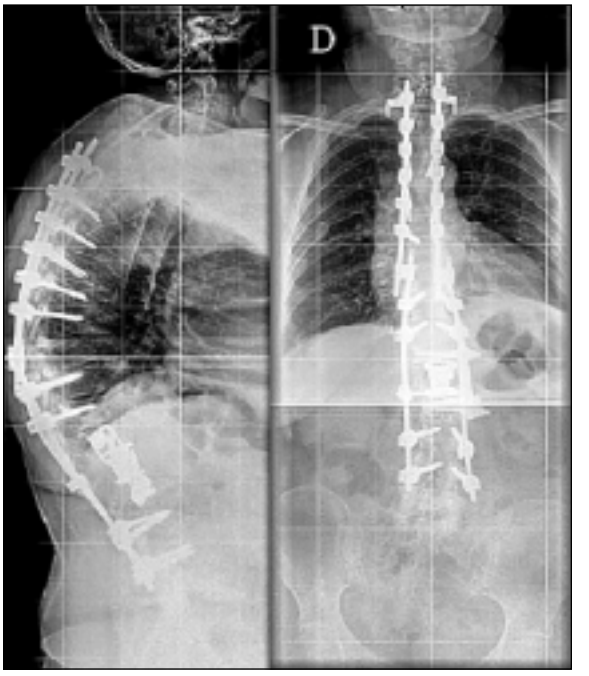



**Figure 6.** At 6 years follow-up, after surgical correction of anterior imbalance, there is no evidence of recurrence or metastasis

The tumor is composed of a discrete population of epithelioid endothelial cells arranged to resemble primitive capillaries with an intermediate biological behavior between hemangioma and angiosarcoma[1,3,4]. EH represents 1% of all vascular neoplasms and is locally aggressive. Although initially described as being most common in the soft tissues of the extremities, other reported sites of occurrence include the liver, lung, breast, meninges, brain and long bones[5-8].

Osseous EH is an extremely rare lesion. Commonly affected bones include tibia (25%), femur (20%), metatarsals (15%), fibula (10%) and humerus (10%). Vertebrae represent only 10% of all reported cases[3,9]. Multiple lesions may be present either in the same bone (particularly the tibia and fibula), in adjacent bones in the same limb, in widely separated bones, or in nearby or distant soft tissues[3,9].

There seems to be no gender predilection, although some authors consider it to be more frequent in males[3,9]. The highest incidence occurs in the third and fourth decades[10,11]. Recently a rare association with neurofibromatosis type I has been reported[12].

Clinically, osseous EH presents with pain and swelling, especially if the affected bone is superficial, or as an enlarging mass (most are smaller than 5 cm.), and pathological fractures can occur in nearly 10% of the patients[3,9]. If the spine is involved, the lesion may cause radicular symptoms or paraplegia, as in the present case, indicating urgent intervention[9,13].

Radiographically, EH appears as an expansive, osteolytic lesion well demarcated if small (1-2 cm) or poorly demarcated if large[3,9,11]. It has a distinctive soap-bubble matrix with a sclerotic margin like that found in benign vascular tumors, with no periostal reaction. Lesions with ill-defined margins and loss of trabeculae are considered more aggressive[9]. Radiographic findings may be nonspecific and differential diagnosis should include osteomyelitis, aneurismal bone cyst, giant cell tumor, osteolytic sarcomas, lymphomas and metastasis[3].

On CT-scan these lesions enhance with contrast media, and though nondiagnostic, it may outline the extent of bone destruction and help distinguish EH from hemangioma, which has a characteristic CT appearance[9].

MRI findings are nonspecific. In T1-weighted contrast sequences, bone tumors of vascular origin show higher intensities than skeletal muscles but lower intensities than fat; in pulse sequences emphasizing a T2 contrast, signal intensities of vascular bone tumors are considerably higher than intensities of muscle and fat[3,9].

On gross pathology examination EH present as reddish-brown lobulated masses, well demarcated with irregular scalloped borders and a bright red hemorrhagic appearance. Microscopically, the tumor is characterized by anastomosing cords, solid nests, or short strands of round to slightly spindled eosinophilic neoplastic endothelial cells embedded in a chondroid-like or hyalinized stroma[9,14],

as can be observed in the present case. Rarely large and distinct vascular channels are identified in the center of the tumor, as contrasted with the periphery of the lesion, and mitotic activity seldom is identified in these tumors[13]. In some instances osteoclastic giant cells can be observed, and in others these tumors show atypical histological features such as marked nuclear atipia, higher mitotic activity, spindling of the neoplastic cells and necrosis, which are associated with a more aggressive course[9,15].

Immunohistochemical analysis reveals that the tumor cells are positive for vimentin and endothelial markers such as factor VIII-related antigen, ulex europaeus lectin, CD31 and CD34[9]. Histological differential diagnosis mainly includes metastatic carcinoma in bone in which immunohistochemical demonstration of keratin and epithelial membrane antigen identifies the adenocarcinoma cells in the absence of reactivity for endothelial markers[9].

Campanacci *et al.* classified EH in 3 grades of malignancy, based on the morphology and differentiation of angioblasts, being treatment and prognosis grade-dependent[16]. According to these criteria the present case could be classified as Grade I EH.

Treatment can vary from simple curettage for grade I lesions to vertebrectomy with preoperative embolization for grade III tumors[9,16]. *En bloc* resection, following oncologic surgical principles, significantly improves results and should be attempted whenever possible[17]. Radiation seems beneficial and safe for treating surgically inaccessible tumors, and has also been proposed as adjuvant therapy after surgical excision[9,17]. Although there may be a place for chemotherapy in the management of EH, precise indications and regimens have not yet been established[3,13].

The prognosis is often favorable, particularly for low-grade lesions where complete excision is performed. However local recurrence or even metastasis are possible[13,18,19]. In the present case, because of the wide resection achieved and the low aggressiveness of the lesion no adjuvant therapy was decided, and 6 years after there are no signs of recurrence or metastasis.

Nevertheless, since the number of reported cases of EH is small and the follow-up periods short, the best surgical treatment, the role of radiotherapy and chemotherapy, as well as the definitive prognosis are still not established.

**Correspondence to**
Nuno Neves
Serviço de Ortopedia
Hospital de São João
Al. Prof. Hernâni Monteiro
4200 Porto
E-mail: nsmneves@gmail.com

**References**

1. Weiss SW, Goldblum JR (eds). Hemangioendothelioma: vascular tumors of intermediate malignancy. In: Enzinger and Weiss's Soft Tissue Tumors. Ed 4. St. Louis:Mosby 2001;891-915.
2. Dorfman HD, Steiner GC, Jaffe HC. Vascular tumors of bone. Hum Pathol 1975;3:349-376.
3. Boutin RD, Spaeth HJ, Mangalik A, Sell JJ. Epithelioid hemangioendothelioma of bone. Skeletal Radiol 1996;25:391-395.
4. Rosai J, Gold J, Landy R. The histiocytoid hemangiomas. A unifying concept embrassing several previously described entities of skin, soft tissue, large vessels, bone, and heart. Hum Pathol 1979;10:707-730.
5. Bevelaqua FA, Valensi Q, Hulnick D. Epithelioid hemangioendothelioma: A rare tumor with variable prognosis presenting as a pleural effusion. Chest 1988;93:665-666.
6. Dietze O, Davies SE, Williams R, Portmann B. Malignant epithelioid hemangioendothelioma of the liver: A clinicopathological and histochemical study of 12 cases. Histopathology 1989;15:225-237.
7. Chow LT, Chow W, Fong DT. Epithelioid hemangioendothelioma of the brain. Am J Surg Pathol 1992;16: 619-625.
8. Larsson SE, Lorentzon R, Bouquist L. Malignant hemangioendothelioma of the bone. J Bone Joint Surg Am 1975;57:84-89.
9. Themistocleous GS, Papagelopoulos PJ, Petraki KD, Stilianessi EV, Partsinevelos AA, Sapkas GS. A 23-year-old woman with complete paraplegia and anesthesia below the T8 level. Clin Orthop Rel Res 2005;430:258-265.
10. Wold LE, Unni KK, Beabout JW, Ivins JC, Bruckman JE, Dahlin DC. Hemangioendothelial sarcoma of bone. Am J Surg Pathol. 1982;6:59-70.
11. Tsuneyoshi M, Dorfman HD, Bauer TW. Epithelioid hemangioendothelioma of bone: a clinicopathologic, ultrastructural, and immunohistochemical study. Am J Surg Pathol 1986;10:754-764.
12. Reis C, Carneiro E, Fonseca J, et al. Epithelioid hemangioendothelioma and multiple thoraco-lumbar lateral meningoceles: two rare pathological entities in a patient with NF-1. Neuroradiol 2005;47:165-169.
13. Aflatoon K, Staals E, Bertoni F, et al. Hemangioendothelioma of the spine. Clin Orthop 2004;418:191-197.
14. Weiss SW, Enzinger FM. Epithelioid hemangioendothelioma: a vascular tumor often mistaken for a carcinoma. Cancer 1982;50:970-981.
15. Tsuji M, Ozaki T, Tsutsumi A. Epithelioid heman-

gioendothelioma with osteoclast-like giant cells. Pathol Res Pract 2002;198:501-505.
16. Campanacci M, Boriani S, Giunti A. Hemangioendothelioma of bone: a study of 29 cases. Cancer 1980;46:804-814.
17. Aquilina K, Lim C, Kamel MH, Marks CJ, O'Sullivan MG, Keohane C. Epithelioid hemangioendothelioma of the spine. J Neurosurg Spine 2005;3:393-399.
18. Ranty ML, Michot C, Le Pessot F, Simonet J, Defives T, Metayer J. Hémangiome épithélioide osseux récidivant. Ann Pathol 2003;23:173-176.
19. Chau YP, Chan ACL, Wong CC. Lytic lesion in a vertebra of a 17-year-old adolescent girl. Arch Pathol Lab Med 2001;125:1611-1612.

# XXXI Curso de Reumatologia dos Hospitais da Universidade de Coimbra

**Coimbra, Portugal**
**22 a 23 de Outubro 2010**

# 74th American College of Rheumatology Annual Meeting

**Atlanta, EUA**
**7 a 11 de Novembro 2010**

# HAND INVOLVEMENT IN OLLIER DISEASE AND MAFFUCCI SYNDROME: A CASE SERIES

Diogo Casal*, Carlos Mavioso**, Maria-Manuel Mendes**, Maria-Manuel Mouzinho***

## Abstract

Ollier Disease and Maffucci Syndrome are two rare diseases that can cause tumors in several organs, having a special predilection for the hand. However, there have been very few reports in the literature focusing on hand manifestations of these diseases.

We report the cases of three female patients: one with Ollier Disease, and two other with Maffucci Syndrome. All patients had hand involvement as their initial primary complaint. The Ollier Disease patient developed chondrosarcomas of two digits and had to have these fingers amputated. One of the Maffucci patients died one year after presentation from a brain glioblastoma.

These cases emphasize the importance of early diagnosis of Ollier Disease and Maffucci Syndrome, as these two conditions are associated not only to crippling hand deformity, but also to a significant risk of chondrosarcoma, and other malignant tumors.

**Keywords:** Ollier Sisease; Multiple Enchondromatosis; Chondrosarcoma; Maffuci Syndrome; Hand.

## Introduction

First described by Ollier in 1900[1], Ollier disease is a rare, nonfamilial disorder characterized by multiple enchondromas and areas of dysplastic cartilage[2-3]. The estimated prevalence of Ollier disease is one in 100 000[4]. Maffucci syndrome is an even rarer condition that was described for the first time in 1881[5], being characterized by the association of enchondromatosis and hemangiomas[6]. Hemangiomas can affect skin, mucosal surfaces and internal organs[7]. There are only slightly over of 200 cases of Maffucci syndrome reported in the literature worldwide[8-9].

The ability to identify these two diseases is crucial, as they are associated with a significant risk of chondrosarcomas and other malignant tumors, that have a better prognosis if treated early[4].

## Case Series

### Case 1

A 48-year-old right-handed female appointed at the Department of Plastic Surgery at our hospital complaining of functional and aesthetic problems with her left hand and foot caused by soft tissue swellings since she was 14 years old. She mentioned that the lesions in the third and fourth digits of her left hand had started to increase in size in the previous month and that, since then, she suffered from an ever growing pain in those digits (Figure 1A).

Radiographs of the hand revealed features suggestive of enchondromas, but with signs of possible malignant transformation (Figure 1B). The diagnosis of Ollier disease was established. Biopsies of the finger nodules were performed, revealing only evidence of enchondromas. As the patient continued to complain of pain, the nodules were excised, preserving the fingers (Figure 2A). However, as histopathological analysis of the nodules revealed chondrosarcomas in both fingers, amputation of the third and fourth digits was performed. Further histological analysis of the amputated fingers revealed complete excision of the tumors. One year after surgery, the patient showed no signs of recurrence and had acceptable left hand function (Figure 2B).

### Case 2

A 33-year-old right-handed female came to the

*Resident at Department of Plastic and Reconstructive Surgery, São José Hospital
**Consultant at Department of Plastic and Reconstructive Surgery, São José Hospital
***Consultant at Department of Plastic and Reconstructive Surgery, São José Hospital; Head of the Hand Clinic at São José Hospital
Centro Hospitalar de Lisboa Central, Lisbon, Portugal

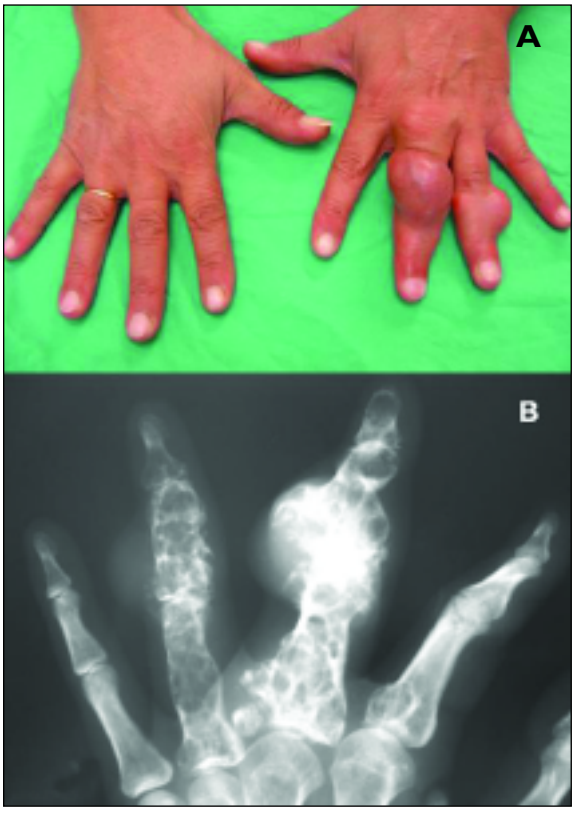



**Figure 1.** Patient with Ollier disease and signs of malignant transformation
A photograph of the hands (**1A**) shows large subcutaneous nodules in the third and fourth fingers of the left hand, corresponding to enchondromas.
A radiograph of the left hand (**1B**) shows, at the base of the proximal phalanx of the second finger, an oval, radiolucent, and homogenous lesion with a well-defined bony margin. This radiographic presentation is highly suggestive of enchondroma. In contrast, at the level of the third and fourth digits, there are multiple cystic-like lesions, with various radiographic signs of malignant transformation, namely: cortical bone erosion, extension of the tumor into the soft tissues, margin irregularity and uneven pattern of mineralization[2,5]

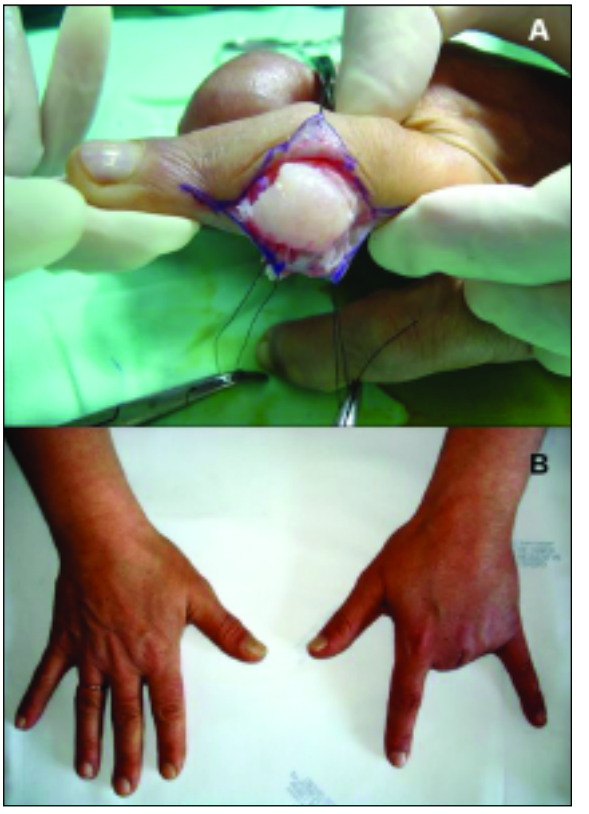



**Figure 2.** Treatment of a patient with Ollier disease
(**2A**) Surgical dissection of the nodule in the third finger of the left hand of the patient depicted in Figure 1 reveals a light-grey oval-shaped cartilaginous lesion within the osseous portion of the middle phalanx
**(2B)** As the nodules in the third and fourth fingers proved to be chondrosarcomas, proximal digital amputation was performed. One year after amputation, the patient had a reasonable hand function

Hand Clinic complaining of insidious growth of several small nodules in her hands since she was 13 years old. In the previous fifteen years she also noticed the progressive development of areas of bluish discoloration scattered through her upper limbs that bleached with pressure (Figures 3A and 3B). Radiographs of the hands revealed the presence of multiple enchondromas and phlebolits (Figure 3C). The patient was diagnosed with Maffucci syndrome. Even though surgery was offered to excise some of the enchondromas, and several options were presented to treat the hemangiomas, the patient declined any procedure for the time being, and continues to be followed regularly in the Hand Clinic.

## Case 3

A 28-year-old right-handed female was referred to the Hand Clinic because of multiple continuously growing nodules in both her hands since she was 8 years old (Figures 4A and 4B). The patient also presented multiple hemangiomas all over her body since that time. She was diagnosed with Maffucci syndrome. An arteriography of both her hands was performed (Figure 4C) revealing the classical pattern of hand hemangiomas. She was submitted to excision of the nodules that had been growing most rapidly. Microscopical analysis of the surgical specimens was consistent with the diagnosis of en-

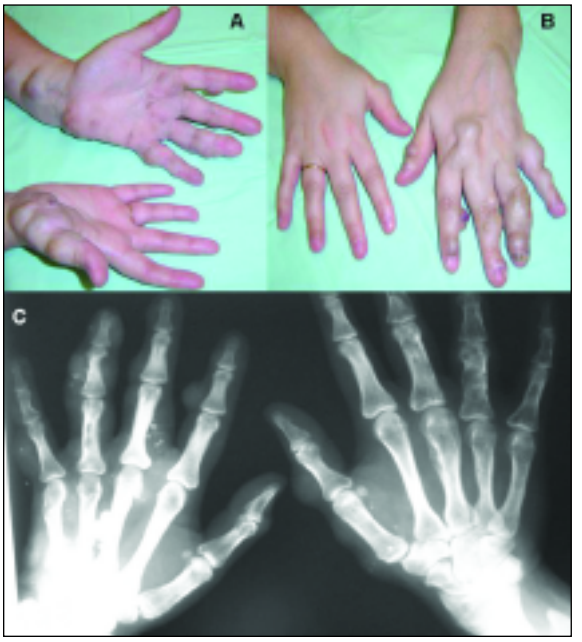



**Figure 3.** Hands of a patient with a moderate form of Maffucci Syndrome
Photographs of the palmar (**A**) and dorsal (**B**) regions show multiple hard subcutaneous nodules in both forearms and hands, compatible with multiple enchondromas. There are also several areas of bluish discoloration consistent with hemangiomas.
Radiograph of the hands (**C**) shows multiple small, radiolucent, and homogenous lesions, with a well-defined bony boundary visible, corresponding to enchondromas. In addition, there are multiple small round calcifications in the surrounding soft tissues, suggestive of phleboliths, which are typical of cavernous hemangiomas

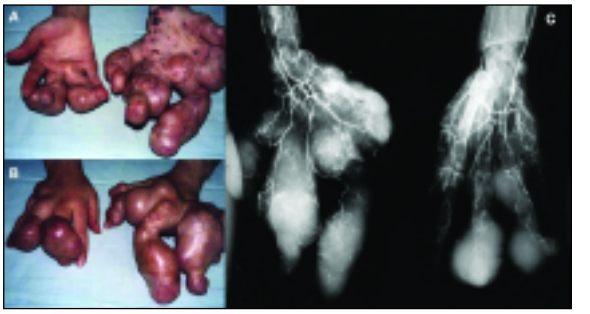



**Figure 4.** Hands of a patient with an extreme form of Maffucci Syndrome
Photographs of the palmar (**A**) and dorsal (**B**) regions show multiple large enchondromas in both hands, which not only cause great deformity, but also significantly hamper the function of both the involved segments and of the uninvolved digits close to them. In the left hand, subcutaneous vessels are dilated and tortuous, and several hemangiomas are visible.
Hand arteriography (**C**) shows anomalous hand vasculature in both hands. Terminal vessels originate a fine mesh of small vessels that supply round or ovoid areas of hypervascularity. These represent hemangiomas. Multiple lytic lesions are distributed centrally and eccentrically in the phalanges and metacarpal bones of both hands, representing enchondromas

chondromas. One year after her initial consultation, she died of a rapidly expanding brain glioblastoma.

## Discussion

Ollier disease and Maffucci syndrome are two rare diseases that can be diagnosed relatively easily solely on clinical grounds and taking into account a few simple ancillary tests, namely radiographs and, occasionally, arteriography[2-4].

In these diseases, the most frequent locations of enchondromas are the small bones of the hands and feet, the long tubular bones, and also the flat bones like the pelvis[2,4]. The trunk is usually spared[2,4,6] .

Even though Ollier disease and Maffucci syndrome have been said to be two manifestations of the same mesenchymal dysplasia[10], it is of clinical interest to differentiate the two, as the risk of sarcomatous change is much higher in patients with Maffucci syndrome, ranging from 17% to 50% of the cases to an astounding 100% after prolonged follow-up[2]. In Ollier disease, on the contrary, sarcomatous transformation occurs only in 25–30% of cases[11].

Skeletal lesions that enlarge or become painful without prior trauma are suspected of having undergone malignant degeneration and need to be biopsied without delay[2]. Similarly, suspicious radiological lesions, should merit prompt biopsy[4].

In the absence of clinical symptoms or problems, no treatment is needed[2,4]. Surgery is indicated only in the case of complications, such as pathological fractures, growth defects and malignant transformation[2,4]. The goals of surgery are to remove the tumor mass and to allow the histological diagnosis. This could reveal lesions possibly requiring adjunctive therapies (e.g., chondrosarcomas)[2]. Sclerotherapy, irradiation, laser therapy and surgery for the vascular lesions in Maffucci syndrome have also been described[8].

In conclusion, Ollier disease and Maffucci syndrome are two rare diseases whose hand ma-

nifestations are considered pathognomonic[11]. Their timely diagnosis is of paramount importance, as these two conditions are associated not only to crippling hand deformity, but also to a significant risk of chondrosarcoma, and other malignant tumors[4].

**Correspondence to**
Maria Manuel Mouzinho
Serviço de Cirurgia Plástica e Reconstrutiva
Hospital de São José; Rua José António Serrano
1150-199, Lisboa; Portugal.
E-mail address: mmmouzinho@sapo.pt

**References**

1. Ollier L. De la dyschondroplasie. Bull Soc De Chir de Lyon 1900;3:22.
2. D'Angelo L, Massimi L, Narducci A, Di Rocco C. Ollier disease. Childs Nerv Syst 2009;25:647-653.
3. Costa J, Bogas M, Ribeiro A, Alcino S, Araujo D. Multiple enchondromatosis: Ollier's disease. Acta Reumatol Port 2008;33:473-474.
4. Pannier S, Legeai-Mallet L. Hereditary multiple exostoses and enchondromatosis. Best Pract Res Clin Rheumatol 2008;22:45-54.
5. Lewis RJ, Ketcham AS. Maffucci's syndrome: functional and neoplastic significance. Case report and review of the literature. J Bone Joint Surg Am 1973;55:1465-1479.
6. Ribeiro C, Fernandes P, Reis FC. The Maffucci syndrome with axial bone lesions. A rare cause of low back pain. Acta Med Port 1998;11:559-562.
7. Laskaris G, Skouteris C. Maffucci's syndrome. Report of a case with oral hemangiomas. Oral Surg Oral Med Oral Pathol 1984;57:263-266.
8. Collins PS, Han W, Williams LR, Rich N, Lee JF, Villavicencio JL. Maffucci's syndrome (hemangiomatosis osteolytica): a report of four cases. J Vasc Surg 1992;16:364-371.
9. Kaplan RP, Wang JT, Amron DM, Kaplan L. Maffucci's syndrome: two case reports with a literature review. J Am Acad Dermatol 1993;29:894-899.
10. Mellon CD, Carter JE, Owen DB. Ollier's disease and Maffucci's syndrome: distinct entities or a continuum. Case report: enchondromatosis complicated by an intracranial glioma. J Neurol 1988;235:376-378.
11. Zwenneke Flach H, Ginai AZ, Wolter Oosterhuis J. Best cases from the AFIP. Maffucci syndrome: radiologic and pathologic findings. Armed Forces Institutes of Pathology. Radiographics 2001;21:1311-1316.

# 5th European Workshop on Immune-mediated Inflammatory Diseases

## Sitges, Espanha
## 1 a 3 de Dezembro 2010

# ESTENOSE TRAQUEAL POR COMPRESSÃO EXTRÍNSECA: UM CASO DE OSTEOFITOSE CERVICAL ANTERIOR HIPERTRÓFICA

M. Coutinho*, S. Freitas**, A. Malcata***

## Resumo

A Osteofitose Cervical Anterior Hipertrófica (OCAH) é uma entidade clínica decorrente de alterações degenerativas da coluna vertebral[1,2], podendo, igualmente, ser encontrada na Hiperostose Vertebral Idiopática Difusa[1-3], na Espondilite Anquilosante[4] e em situações de osteofitogénese pós-traumática[1]. Numa minoria de casos, pode conduzir a compromisso do tracto digestivo e, menos comummente, do tracto respiratório[1].

Os autores descrevem o caso clínico de um doente de 75 anos de idade, seguido em consulta de Reumatologia por gota tofácea crónica, com antecedentes de doença pulmonar obstrutiva crónica (DPOC), que se apresentou com agravamento progressivo da habitual dispneia, associado a disfagia ligeira para sólidos e à sensação de corpo estranho na região cervical. Apresentava, ao exame objectivo geral, uma auscultação pulmonar com um murmúrio vesicular globalmente diminuído e com ligeiro prolongamento do tempo expiratório, bilateralmente, sem outras alterações. Ao exame reumatológico, apresentava uma limitação moderada da mobilidade da coluna cervical em todos os planos, crepitações grosseiras à flexão dos joelhos e múltiplos tofos gotosos em ambas as mãos. A radiografia da coluna cervical (AP e perfil) identificou a presença de osteófitos anteriores volumosos ao nível de C4 e C5. A videobroncofibroscopia documentou a presença de um abaulamento da parede posterior da traqueia, no seu terço superior, por compressão extrínseca, alterações corroboradas pela Tomografia Axial Computorizada (TAC) cervical, a qual viria a comprovar a presença de um desvio anterior do esófago por osteofitose cervical anterior exuberante. A videofluoroscopia esofágica documentou a presença de uma contracção paradoxal do músculo cricofaríngeo. O doente foi medicado com um anti-inflamatório não-esteróide (AINE) e um relaxante muscular, com melhoria da disfagia, embora mantendo as queixas respiratórias. Apesar da indicação para a remoção cirúrgica dos osteófitos hipertróficos, o doente recusou a referida terapêutica, mantendo-se, contudo, sob vigilância clínica regular.

**Palavras-chave:** Osteofitose Cervical Anterior Hipertrófica; Compressão Traqueal.

## Abstract

Anterior Cervical Hypertrophic Osteophytosis (ACHO) is a clinical entity caused by degenerative changes of the cervical spine[1,2]. ACHO may also be found in Diffuse Idiopathic Skeletal Hyperostosis (DISH)[1-3], Ankylosing Spondylitis[4] and Post-traumatic Osteophytogenesis[1]. In a minority of cases it may lead to oesophagical manifestations and less commonly, to respiratory complaints[1].

The authors report the case of a 75-year-old male with a personal history of chronic tophaceous gout and chronic obstructive lung disease. The patient presented with a history of progressive worsening of dyspnoea and dysphagia (for solid food) as well as foreign body sensation at the cervical level. On general examination, the patient presented with slightly diminished breath sounds and an increased expiratory time. On rheumatologic examination, the patient had moderate limitation of all cervical movements, crepitating knees and multiple gout tophi in both hands. Cervical plain radiographs showed large anterior osteophytes at the level of C4 and C5. Flexible videobronchoscopy was also performed, showing an angle of distortion in the upper third of the tracheal wall, caused by extrinsic compression. These changes were confirmed by cervical CT scan which also documented an

*Interna do Internato Complementar de Reumatologia, serviço de Reumatologia dos Hospitais da Universidade de Coimbra
**Assistente Hospitalar de Pneumologia, serviço de Pneumologia dos Hospitais da Universidade de Coimbra
***Chefe de Serviço, serviço de Reumatologia dos Hospitais da Universidade de Coimbra

anterior sliding of the oesophagus due to large anterior cervical osteophytes. Videofluoroscopic swallow study revealed the presence of paradoxal contraction of the cricopharyngeal muscle.

The patient was treated with a non-steroidal anti-inflammatory drug (NSAID) and a skeletal muscle relaxant. Dysphagia improved but not the respiratory symptoms. Although there was indication for surgical removal of the hypertrophic osteophytes, the patient refused surgery and continues to be followed-up regularly at our outpatient clinic.

**Keywords:** Anterior Cervical Hypertrophic Osteophytosis; Tracheal Compression.

## Introdução

A Osteofitose Cervical Anterior Hipertrófica (OCAH) é uma entidade clínica decorrente de alterações degenerativas da coluna vertebral[1,2], podendo, igualmente, ser encontrada na Hiperostose Embainhante Idiopática Difusa (HEDI)[1-3], na Espondilite Anquilosante[4] e em situações de osteofitogénese pós-traumática[1]. A maioria destes indivíduos é assintomática[1]. Contudo, numa minoria dos casos, podem surgir sintomas decorrentes do compromisso do tracto digestivo, nomeadamente disfagia[1,5-7]e, menos comummente, do tracto respiratório[1], tais como dispneia (aguda ou crónica)[2,5], tosse e engasgamento durante a ingestão alimentar[3], disfonia[3,6] e sensação de corpo estranho na região cervical[3,8]. Situações de pneumonia decorrente de aspiração pulmonar também têm sido relatadas[8]. Em doentes sintomáticos, a disfagia é o sintoma mais frequente[5], sendo que a sua incidência varia de 0.2 a 28%, consoante as séries[9-11]. A dispneia é de ocorrência rara, sendo escasso o número de casos relatados na literatura[2,8,13].

Diversos mecanismos têm sido defendidos como estando implicados na ocorrência de disfagia em doentes com OCAH, nomeadamente os seguintes: compressão esofágica mecânica (causando obstrução do lúmen do esófago), compressão esofágica por osteófito estrategicamente localizado ao nível do ponto de fixação do esófago (ao nível da cartilagem cricóide), reacção inflamatória dos tecidos periesofágicos com edema associado (por irritação faringo-esofágica provocada pelos osteófitos hipertróficos), espasmo do músculo crico-faríngeo (devido à pressão dos osteófitos sobre o esófago) e combinação de diferentes mecanismos[2,5,7,8]. A inflamação dos tecidos periesofágicos e o edema associado, causados pela irritação crónica associada à compressão mecânica, podem ser efectivos de modo directo ou indirectamente, neste último caso por diminuição do peristaltismo esofágico como consequência da inflamação crónica e do espasmo do músculo cricofaríngeo[6].

A ocorrência de dispneia, como sintoma adicional ou isolado, é muito rara, devido à ausência de contiguidade anatómica entre a coluna cervical e o eixo laringo-traqueal, por interposição do esófago. Desta forma, quando presente, associa-se, habitualmente, à presença de osteófitos de grandes dimensões[5]. A dispneia pode variar de episódica e ligeira (com resolução espontânea) até situações de dispneia grave, com necessidade de terapêutica invasiva urgente. Os mecanismos implicados na sua génese são os seguintes: compressão extraluminal (provocando obstrução), irritação crónica da face posterior da cartilagem cricóide (resultando em inflamação crónica e edema, com posterior obstrução da laringe), infecção sobreposta e parésia ou paralisia uni ou bilateral das cordas vocais[2,5]. O mecanismo exacto que conduz à imobilização das cordas vocais permanece desconhecido, muito embora alguns autores defendam as seguintes hipóteses: parésia de fibras nervosas da porção terminal da laringe, traumatismo dos músculos crico-aritnoideus (lateral e posterior) e envolvimento directo da articulação cricoaritnóide. Todos estes mecanismos pressupõem um efeito mecânico directo da fricção repetida da laringe sobre uma hiperostose óssea[2].

Nas situações clínicas associadas à ocorrência de disfonia, a restrição dos movimentos da cartilagem aritnóide (como resultado do contacto directo do osteófito com a região pós-cricóide) e a compressão do nervo laríngeo inferior, são os mecanismos habitualmente implicados[6].

## Caso clínico

M.S., sexo masculino, de 75 anos de idade, sob seguimento clínico em consulta de Reumatologia por gota tofácea crónica poliarticular. Antecedentes de Doença Pulmonar Obstrutiva Crónica (DPOC), Hipertensão Arterial (HTA), Obesidade e Gonartrose bilateral.

Em Novembro de 2008 iniciou agravamento progressivo da habitual dispneia, disfagia ligeira para sólidos e sensação de corpo estranho na re-

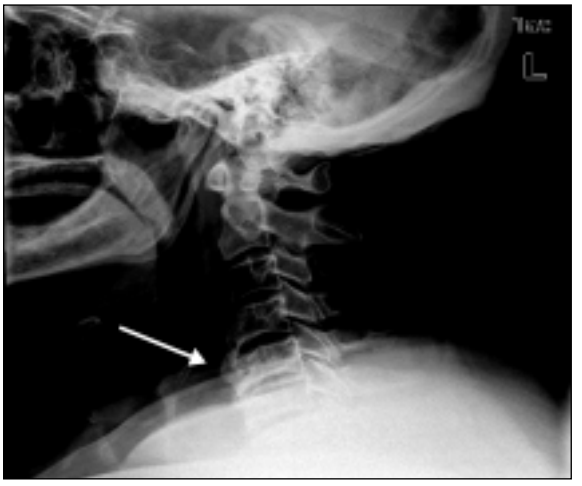


**Figura 1.** Radiografia da coluna cevical (perfil): osteófitos anteriores hipertróficos em C4 e C5 (seta)

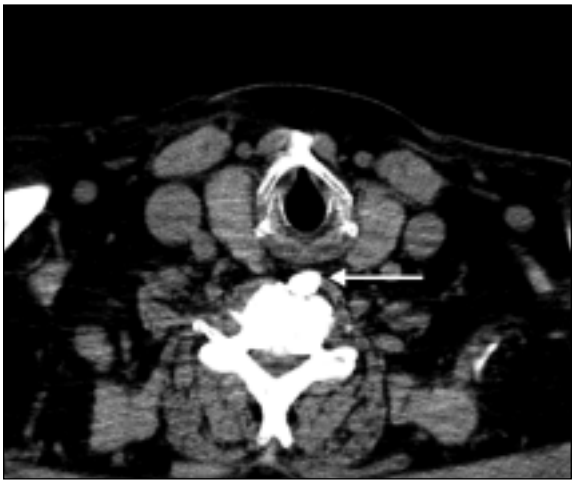


**Figura 2.** TAC cervical: osteófito hipertrófico ao nível de C4-C5 (seta)

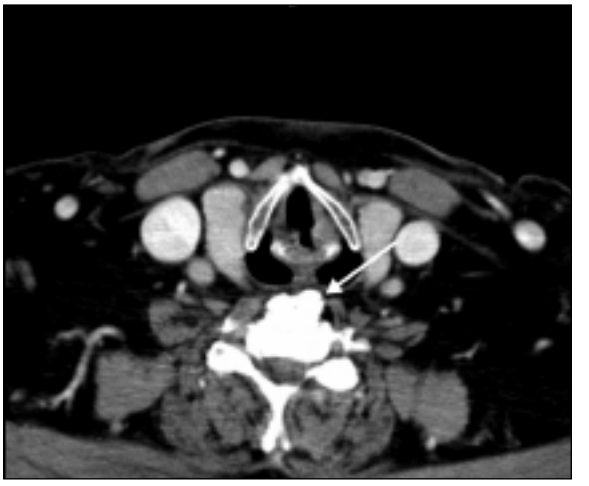


**Figura 3.** TAC cervical: osteófito hipertrófico ao nível de C4-C5, exercendo compressão sobre as estruturas adjacentes (seta)

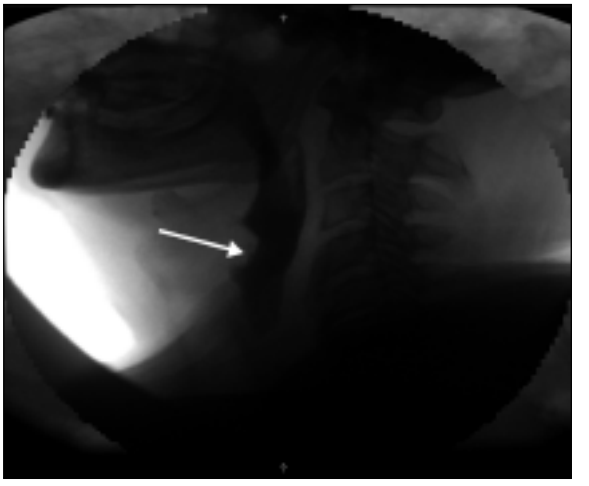


**Figura 4.** Videofluoroscopia esofágica: contracção do músculo cricofaríngeo (seta)

gião cervical. Ao exame objectivo geral, apresentava um IMC de 32 kg/m2 e uma auscultação pulmonar com um murmúrio vesicular globalmente diminuído e com prolongamento do tempo expiratório bilateralmente (sem outras alterações relevantes). Ao exame reumatológico, apresentava uma limitação moderada da mobilidade da coluna cervical (em todos os planos), crepitações grosseiras à flexão de ambos os joelhos e múltiplos tofos gotosos localizados às pequenas articulações das mãos, sem evidência de articulações tumefactas ou de outras alterações no referido exame. O estudo laboratorial de rotina (hemograma e bioquímica) documentava a presença de hipercolesterolémia (colesterol total 320 mg/dl), sem outras alterações. A radiografia da coluna cervical (ântero-posterior e perfil) revelou a presença de osteófitos anteriores volumosos ao nível de C4 e, sobretudo, de C5 (Figura 1), sendo que a radiografia de tórax (AP) não apresentava alterações relevantes. Foi solicitada uma consulta de Pneumologia (devido ao agravamento das habituais queixas respiratórias), a partir da qual realizou videobroncofibroscopia, que viria a documentar a presença de um abaulamento da parede posterior da traqueia, ao nível do terço superior, por compressão extrínseca, sem outras alterações identificáveis, nomeadamente da mucosa. A Tomografia Axial Compu-

torizada (TAC) da região cervical viria a comprovar a presença de compressão da parede posterior da traqueia e o desvio anterior do esófago por osteofitose cervical anterior exuberante (Figuras 2 e 3). A endoscopia digestiva alta revelou-se normal e a videofluoroscopia esofágica documentou a presença de um entalhe na parede faringo-esofágica, sugestivo de contracção paradoxal do músculo cricofaríngeo (Figura 4). O doente iniciou terapêutica com ibuprofeno 600 mg (2id) e com tizanidina 6 mg (id), com moderada melhoria da disfagia, muito embora sem benefício clínico relativamente às queixas respiratórias. Apesar da indicação para a remoção cirúrgica dos osteófitos hipertróficos, o doente recusou a referida terapêutica, mantendo-se, contudo, sob vigilância clínica regular, face ao risco de agravamento clínico progressivo e de falência respiratória aguda.

## Discussão

Neste caso clínico, a presença de agravamento das queixas respiratórias num doente com patologia respiratória crónica e o início de queixas de disfagia, num doente idoso, exigiu o despiste de diversas patologias, nomeadamente de patologia neoplásica do tracto respiratório (laringe, brônquios e pulmão) e digestivo (faringe ou esófago). Associadamente, impunha-se a exclusão de outras causas de disfagia, nomeadamente de estenoses esofágicas benignas, de acalásia ou mesmo de compromisso da deglutição decorrente de patologia do foro neurológico. A normalidade da endoscopia digestiva alta (EDA) permitiu afastar a hipótese de patologia esofágica intrínseca. A videobroncofibroscopia não revelou a presença de qualquer lesão laríngea ou endotraqueal, documentando, contudo, um abaulamento da parede posterior da traqueia, decorrente de compressão extrínseca. A radiografia da coluna cervical evidenciou a presença de osteófitos anteriores volumosos ao nível de C4 e de C5, alterações corroboradas pela TAC cervical, a qual concluiu pela compressão traqueal extrínseca efectuada pelos referidos osteófitos hipertróficos. A videofluoroscopia esofágica representa um instrumento valioso na avaliação do mecanismo da deglutição, sendo particularmente importante no despiste de causas neuromusculares de disfagia[3,5]. No presente caso clínico, foi detectada apenas a presença de uma contracção do músculo cricofaríngeo como resultado da irritação crónica causada pelos osteófitos hipertróficos sobre a parede esofágica. Esta situação, tal como anteriormente descrito, representa um dos mecanimos defendidos como estando implicados na origem de disfagia nestes doentes. A terapêutica conservadora com um relaxante muscular e um AINE permitiu um alívio moderado da disfagia, havendo, contudo, manutenção das queixas respiratórias. Devido à presença de compressão da via aérea, com progressão gradual da dificuldade respiratória, foi proposta a remoção cirúrgica dos osteófitos hipertróficos. O doente recusou a terapêutica cirúrgica, mantendo-se sob seguimento clínico regular em consulta de Pneumologia e de Reumatologia.

A diferente localização dos osteófitos hipertróficos na coluna cervical pode associar-se a diferentes padrões de disfagia. Mathew *et al.*[1], num estudo retrospectivo efectuado em 10 doentes com OCAH e com sintomatologia digestiva (com ou sem sintomatologia respiratória associada) documentaram que as localizações mais frequentes dos osteófitos hipertróficos foram C3-C4 e C4-C5 (78% dos casos), seguidas das localizações C5-C6 (56% dos casos). No mesmo estudo, verificou-se que os osteófitos localizados à face anterior de C3-C4 ou de C4-C5 se associaram à ocorrência de aspiração de líquidos durante a deglutição (por redução da mobilidade da epiglote e compromisso do encerramento da laringe). Por outro lado, os osteófitos localizados à face anterior de C5-C6 ou C6-C7 interferiam com a deglutição de sólidos ao nível da faringe (por indentação da parede) e, em alguns casos, com a elevação da laringe durante a deglutição, situação que resultaria na retenção faríngea de alimentos, com a consequente possibilidade de aspiração pós-deglutição.

Em doentes com OCAH, diversas perturbações da deglutição poderão ser encontradas. Através da videofluoroscopia esofágica poder-se-ão identificar situações de aspiração, a penetração de líquidos no espaço supraglótico (devido a uma protecção incompleta do *aditus* da laringe por parte da epiglote), perturbação da elevação da laringe e do seu movimento anterior, com retenção de alimentos no seio piriforme, redução dos movimentos peristálticos da faringe (acima e ao nível do osteófito, a qual dificulta o transporte de alimentos sólidos), estenoses esofágicas ou divertículos da faringe[3]. Apesar da realização de EDA, nestes casos, ainda ser controversa, devido ao risco de perfuração da parede esofágica posterior, fragilizada pela

irritação crónica associada aos osteófitos, a sua realização permite a exclusão de causas de disfagia decorrentes de patologia esofágica intrínseca, o que lhe confere uma enorme importância na investigação desta situação clínica[5,7].

A terapêutica médica conservadora é, na maioria dos casos, suficiente no controlo da sintomatologia ligeira a moderada[1,12]. Em doentes com queixas de disfagia, é recomendada a modificação da consistência dos alimentos e a adequada mastigação dos mesmos, com recurso, se necessário, a terapia da deglutição. As medidas farmacológicas visam a diminuição da inflamação muscular e a melhoria do relaxamento, reduzindo, desta forma, o edema muscular e o espasmo. É recomendado o uso de relaxantes musculares, sedativos, terapêutica anti-refluxo, AINE´s, corticosteróides e, na presença de infecção sobreposta, de antibioterapia[1-3,5,7,8]. A dispneia, como resultado de compressão e consequente obstrução da via aérea, associa-se, habitualmente, a doença avançada, pelo que a terapêutica conservadora é frequentemente ineficaz[1].

A remoção cirúrgica dos osteófitos hipertróficos (osteofitectomia) deve ser reservada para doentes com sintomatologia grave ou refractária à terapêutica conservadora[1,2,6,8]. A abordagem cirúrgica extra-faríngea tem demonstrado resultados mais favoráveis do que a abordagem faríngea transoral, pois permite a manutenção da integridade da mucosa e da fáscia faringo-basilar, diminuindo o risco de contaminação e facilitando a mobilidade da parede faríngea no pós-operatório, por diminuição da formação de aderências e de cicatrizes[1]. Contudo, apresenta um risco acrescido de formação de hematomas, fístulas, perfuração esofágica e paralisia das cordas vocais por lesão do nervo laríngeo recorrente[3]. O recurso a alimentação por sonda nasogástrica para alívio da disfagia, bem como a traqueostomia para alívio da dispneia, têm sido reservados para doentes com sintomatologia grave e com elevado risco cirúrgico ou com esperança de vida reduzida[1].

**Correspondência para**
Margarida Coutinho
Hospitais da Universidade de Coimbra
Serviço de Reumatologia
Praceta Prof. Mota Pinto
3000 – 075 Coimbra
Telef: 239 400 439
E-mail: margarida.coutinho@portugalmail.pt

**Referências**

1. Matthew L. Carlston, David J. Archibald, Darlene E. Graner, Jan L. Kasperbauer. Surgical management of dysphagia and airway obstruction in patients with prominent ventral cervical osteophytes. Disphagia Published Online First: 23 January 2010. DOI: 10.1007/s00455-009-9264-6.
2. Roland Giger, Pavel Dulguerov and Michael Payer. Anterior cervical osteophytes causing dysphagia and dyspnea: an uncommon entity revisited. Dysphagia 2006; 259-263
3. T. O. Seidler, J. C. Pèrez. Àlvarez, K. Wonneberger, T. Hacki. Dysphagia caused by ventral osteophytes of the cervical spine: clinical and radiographic findings. Eur Arch Otorhinolaryngol 2009; 266: 285-291
4. Wilfredo E. de Jesus Monge, Elsie I. Cruz-Cuevas. Dysphagia and lung aspiration secundary to anterior cervical osteophytes: a case report and review of the literature. Ethn Dis 2008; 18: 137-140
5. Francesco Maiuri, Lucio Stella, Luigi Sardo, Simona Buonamassa. Dysphagia and dyspnea due to an anterior cervical osteophyte. Arch Orthop Trauma Surg 2002; 122: 245-247
6. Ayla Akbal, Aydan Kurtaran, Barin Selcuk, Aysel Gurcan, Murat Ersoz, Mufit Akyuz. The development of dysphagia and dysphonia due to anterior cervical osteophytes. Rheumatol Int 2009; 29: 331-334
7. Salih Ozgocmen, Adem Kiris, Ercan Kocakoc, Ozge Ardicoglu. Osteophyte-induced dysphagia: report of three cases. Joint Bone Spine 2002; 69: 226-229
8. Pinho M. M., Alonso V. O. Osteófitos cervicais - um incomum caso de paralisia de pregas vocais. Revista Brasileira de Otorrinolaringologia 1998; vol. 64, 2ª edição: 177-180
9. Resnick D, Shaud SR, Robins J. M. Diffuse idiopathic skeletal hyperostosis (DISH): Forestier´s disease with extraspinal manifestations. Radiology 1975; 115: 513--524
10. Nemours-Auguste S., Barag N. Dysphagia caused by cervical arthrosis. Presse Med 1960; 25: 2295-2297
11. Saffouri H. H., Ward PH. Surgical correction of dysphagia due to cervical osteophytes. Ann Otol Rhinol Laryngol 1974; 83: 65-70
12. Sobol SM, Rigual NR. Anterolateral extrapharyngeal approach for cervical osteophyte-induced dysphagia. Literature review. Ann Otol Rhinol Laryngol 1984; 93: 498-504
13. Anthony J. Matan, Jack Hsu, Bruce A. Fredrickson. Management of respiratory compromise caused by cervical osteophytes: a case report and review of the literature. The Spine Journal 2, 2002; 456-459

# EpiReumaPt Protocol – Portuguese epidemiologic study of the rheumatic diseases

Sofia Ramiro*, Helena Canhão**, Jaime C. Branco***

## Abstract

Rheumatic diseases (RDs) are among the most common diseases. In the developed world, they are the leading cause of disability and consume a large amount of health and social resources. Therefore, it is crucial to assess the impact of RDs on the general population in what refers to their prevalence, and repercussion on quality of life and function. However, no nationwide epidemiological studies on RDs have ever been performed in Portugal. With this research project we aim to estimate the prevalence of different RDs in Portugal, as well as to determine the burden of RDs, more specifically their impact on quality of life and functional and work capacity. A cross-sectional study will be performed, using a random sample of the Portuguese population. RDs will be screened through a structured interview, and subjects with a positive screening will be examined by a trained rheumatologist to establish the final diagnosis. The knowledge of the prevalence of RDs will contribute to the development of specific health plans for the current and future management of these diseases.

**Keywords:** Rheumatic Diseases; Prevalence; Epidemiologic Studies; Cost of Illness.

*Serviço de Reumatologia, Hospital Garcia de Orta, EPE
Maastricht University Medical Center, Maastricht, the Netherlands
**Unidade de Investigação em Reumatologia, Instituto de Medicina Molecular, Faculdade de Medicina da Universidade de Lisboa (FMUL), Serviço de Reumatologia, CHLN, EPE / Hospital de Santa Maria, Lisboa, Harvard Medical School, Boston, USA
***Centro de Estudos de Doenças Crónicas (CEDOC) – Faculdade de Ciências Médicas da Universidade Nova de Lisboa
Serviço de Reumatologia, CHLO, EPE / Hospital Egas Moniz
Coordenador do Programa Nacional Contra as Doenças Reumáticas (PNCRD)

## Background

Rheumatic diseases (RDs) can be defined as systemic diseases affecting the connective tissue (including joint components) and other medical disorders of the musculoskeletal system. Clinically, they are characterized by pain and/or stiffness and disability, and in some cases, inflammation. They may or may not be accompanied by involvement of other organs and systems. RDs are among the most common diseases managed at the primary health care level, as well as the leading cause of disability in the developed world, and consume a large amount of health and social resources[1-3].

Prevalence of RDs needs to be assigned to specific populations, as different populations with different genetic and environmental backgrounds show different rates. Furthermore, in the context of increasing treatment costs, economic constraints and managed care, specific local data on the prevalence and local major determinants of different diseases might help healthcare systems develop specific plans for the care of a given disease. At a national level, knowledge of the most important RDs and their consequences is essential for planning the needs of healthcare professionals, infrastructures, and resources. In Portugal, the prevalence of RDs is ill-defined. A nationwide epidemiological study is the only way to fulfill this need, and it is also a specific objective of the National Program Against Rheumatic Diseases ("Programa Nacional Contra as Doenças Reumáticas"). Furthermore, the knowledge of the burden of RDs will raise public awareness on their importance and impact in our society.

Well-designed and consistent RDs epidemiological studies have not been performed in Portugal, as opposed to what has happened in several other European countries, such as Spain and Greece[4, 5]. No population-based studies have been done on the prevalence of any of the rheumatic symptoms or RDs in the Portuguese population. Furthermo-

re, the impact of RDs on quality of life and on function has never been assessed at a population level, despite the fact that quality of life is the most important indicator of the burden of this group of diseases[6]. Thus, it is crucial to assess the impact of rheumatic diseases on the general population in terms of their prevalence, effect on quality of life, and function.

An epidemiologic study of RDs has long been necessary in Portugal, but it has been repeatedly postponed due to financial constraints. Herein we are presenting a project where we hope to have finally met all the minimum requirements to develop and undertake an epidemiological study determinant for the future of Portuguese rheumatology and of patients with RDs.

## Objectives

### Primary Objective

Estimate the prevalence of the different RDs in Portugal;

### Secondary Objectives:

1. Estimate the prevalence of the different RDs according to socio-demographic characteristics;
2. Identify socio-demographic and clinical variables associated with the diagnosis of some RDs;
3. Estimate the frequency of previously undiagnosed RDs;
4. Determine the impact of RDs on quality of life and on functional and work capacity;
5. Investigate the access to healthcare of patients with RD;
6. Compare the burden of RDs in Portugal with the reality from other countries;
7. Define two cohorts, one with and another without RD, to be followed prospectively.

## Methodology

### Study design

A cross-sectional study will be performed.

### Study population

The study population will be composed by adults (≥ 18 years old) who are non-institutionalized and living in private households in Portugal, from the Mainland and Islands (Madeira and Açores). Exclusion criteria will be: residents in hospitals, nursing homes, military barracks, or prisons, and residents unable to speak Portuguese or with a complete inability to answer the questionnaire, either directly or through a person living with him/her. The sample will be representative of the Portuguese population. Locations will be selected as the primary unit of sampling and, according to the CENSUS 2001. Excluding the islands, there are 27,960 localities in Portugal), with a total population of 7,719,986 subjects aged 18 years or older[7]. The sample size will be stratified for region and dimension of the location (< 2,000; 2,000-9,999; 10,000-19,999; 20,000-99,999; and 100,000 inhabitants). The number of questionnaires in each stratum will be proportional to the real distribution of the population. Because there is no reliable list of households in Portugal, a random selection of points in the map of each location will be performed. Addresses will be selected, and afterwards the "random-walks" will start. Interviewers will register each selected address and, if someone is at home, they will collect information on age and gender of the different people living in that address, and will give information about the study. After validation of the selected address and inhabitants, the interviews will be scheduled. In order to assure the successful data collection, up to three visits to each address (one during the weekend) will be made. Interviewers will collect 20% additional addresses in each point to compensate for possible refusals to participate. At each address, the person whose birthday is closest to the day of the visit (aged 18 years or older) will be selected for the interview and, if available, will be immediately asked to answer the questionnaire.

### Primary objective and case definition

The primary objective will be the prevalence of the following rheumatic diseases: osteoarthritis (knee, hip and hand), low back pain (LBP), osteoporotic fractures (OPF), periarticular RD (PRD), fibromyalgia (FM), rheumatoid arthritis (RA), spondyloarthritis (SpA, as well as its major subtype, ankylosing spondylitis – AS), systemic lupus erythematosus (SLE), polymyalgia rheumatica (PMR), and gout (GO). A major risk of fragility fracture within 10 years will also be calculated.

**Case definition:** The diagnosis of RD, either active or in remission, will be based on the American College of Rheumatology (ACR, formerly the American Rheumatism Association) criteria (for RA, SLE, GO, OA, and FM)[8-17] or other internationally used criteria (for PMR, SpA and AS)[18,19].

*Knee osteoarthritis* will follow the ACR criteria[15]: the patient should have knee pain plus at least 3 of the following 6 clinical findings: a) age > 50 years; b) morning stiffness < 30 minutes of duration; c) crepitus on active motion; d) tenderness of the bony margins of the joint; e) bony enlargement noted on examination; e) a lack of palpable warmth of the synovium.

*Hip osteoarthritis* will be defined, according to the ACR criteria[13], as hip pain plus one of the following: a) hip internal rotation <15º and erythrocyte sedimentation rate (ESR) ≤45mm/hour (if ESR not available, substitute hip flexion ≤115º); b) hip internal rotation ≥15º and pain on hip internal rotation and morning stiffness of the hip ≤ 60 minutes and age > 50 years.

*Hand osteoarthritis* will be defined according to the ACR criteria[14]: the patient should fulfill the following 3 criteria: a) hand pain, aching, or stiffness; b) hard tissue enlargement of 2 or more of 10 selected joints; c) fewer than 3 swollen metacarpophalangeal joints; the fourth criteria corresponds to the presence of one of the following two: d) hard tissue enlargement of 2 or more DIP joints, or e) deformity of 2 or more of 10 selected joints.

*LBP* will be defined by self-report. The interviewers will be instructed to indicate what is understood by low back, more specifically the back area between the lower limits of the chest and the gluteal folds, and then to ask about pain in that area. In case of positive LBP, red flags will be searched, in order to detect a cause of specific LBP, namely infection, inflammatory disease and cancer[22]. The point prevalence of LBP will be estimated and, for this purpose, LBP on the day of the interview will be considered. Prevalence of LBP in the previous 6 months will also be estimated and further specified into acute LBP (less than 6 weeks), subacute LBP (between 6 weeks and 3 months) and chronic LBP (more than 3 months). Disabling acute LBP will be defined as a LBP preventing the patient from performing the activities of daily living, and with a score of at least eight, on a 0-10 pain visual analogue scale.

*Densitometric osteoporosis* will be underestimated due to the impossibility of screening all participants with dual energy x-ray absorptiometry (DXA). For the current study, a definition of OPF will be used and considered as positive in the case of history of a low impact bone fracture or of x-ray documenting vertebral fractures in post-menopausal women or men above 50 years old. The risk of a major fracture will be defined as a Fracture Risk Assessment Tool (FRAX – http://www.shef.ac.uk/FRAX/)[23] score of >10% (with or without DXA). Furthermore, some participants (the ones that will be evaluated by a rheumatologist, as explained below) will be submitted to a wrist DXA. The criteria to perform DXA will be in accordance with the guidelines from the Portuguese Society for Rheumatology (PSR)[24]. Osteoporosis will be defined according to the definition from the World Health Organization: bone density 2.5 standard deviations below the average of the healthy adult reference range (T score < -2.5)[25].

*PRDs* will be defined as a regional pain syndrome affecting muscles, tendons, bursas or periarticular soft tissues, with or without evidence of joint or bone involvement. The following PRDs will be specifically searched: tenosynovitis, adhesive capsulitis of the shoulder, enthesopathy, bursitis, palmar or plantar fasciitis, and carpal or tarsal tunnel syndrome present at the time of the interview. These will be diagnosed based on the main clinical manifestations and, in some instances, on exams (eg: radiographs, ultrasounds) findings.

For *fibromyalgia*, two classification criteria will be used, namely the 1990 ACR criteria[16], as well as the new ones, recently published[17]. According to the 1990 ACR criteria[16], fibromyalgia is defined as: a) history of widespread pain (present in both sides of the body, above and below the waist) for at least 3 months; b) pain in 11 of 18 tender point sites on digital palpation. According to the 2010 ACR criteria[17], fibromyalgia is defined as: a) widespread pain index (WPI) ≥ 7 and symptom severity (SS) scale score ≥ 5 or WPI 3-6 and SS scale score ≥ 9; WPI is the number of areas in which the patient has had pain over the last week and can vary between 0 and 19; SS scale score is the sum of severity of the 3 symptoms – fatigue, waking unrefreshed, and cognitive symptoms, plus the extent of somatic symptoms in general, and the final score is between 0 and 12; b) symptoms have been present at a similar level for at least 3 months; c) the patient does not have a disorder that would otherwise explain the pain.

Similarly, new classification criteria for *RA* have been recently developed[9]. Consequently, they will also be taken into account and the prevalence of RA will be reported according to both classification criteria, the 1987 ARA revised criteria for the classification of RA[8] and the new ones. RA will be diagnosed according to the 1987 ARA criteria[8] if 4 or more

of the following are present: a) morning stiffness longer than 1h present during at least 6 weeks; b) arthritis of 3 or more joint areas (≥ 6 weeks); c) arthritis of hand joints (≥ 6 weeks); d) symmetric arthritis (≥ 6 weeks); e) rheumatoid nodules; f) serum rheumatoid factor; g) typical radiographic changes of RA on hand radiographs. The new classification criteria consist of a scoring system, according to which an individual with a score ≥6 (out of 10) is considered to have RA[9]. Furthermore, with the adaptation for populational studies, the following situations will also be considered as RA: a confirmed diagnosis of RA, deformities clearly compatible with RA or RA criteria in the past[26].

*SpA* will be defined according to the Assessment of SpondyloArthritis International Society (ASAS) criteria for axial SpA[19] and also for peripheral SpA[20]. A diagnosis of axial SpA will be established if a patient with back pain ≥ 3 months and age at onset ≤45 years has sacroiliitis in imaging (magnetic resonance imaging or conventional radiograph) plus one or more SpA features or HLA-B27 positive plus 2 or more other SpA features. SpA features can be any of the following: inflammatory back pain, arthritis, enthesitis, uveitis, dactylitis, psoriasis, Crohn's disease/ulcerative colitis, good response to non-steroidal anti-inflammatory drugs, family history for SpA, HLA-B27, elevated C-reactive protein. Patients with SpA fulfilling the modified New York criteria will be further specified as having Ankylosing Spondylitis (AS)[21]. Peripheral SpA will be established in the presence of arthritis or enthesitis or dactylitis plus a) one of the following SpA features: psoriasis, inflammatory bowel disease, preceding infection, HLA-B27, uveitis, and sacroiliitis on imaging; or b) two of the remaining SpA features: arthritis, enthesistis, dactylitis, inflammatory back pain in the past, and positive family history for SpA[20].

*SLE* will be defined according to the 1997 revised ACR criteria[11] and at least 4 of the following must be present: a) malar rash; b) discoid rash; c) photosensitivity; d) oral ulcers; e) non-erosive arthritis; f) pleuritis or pericarditis; g) renal disorder; h) neurologic disorder; i) hematologic disorder; j) immunologic disorder; k) positive antinuclear antibody.

*PMR* will be diagnosed, according to the criteria published by Bird *et al.*[18], in the presence of 3 of the following: a) bilateral shoulder pain or stiffness; b) onset of illness of less than 2 weeks' duration; c) initial ESR greater than 40mm/h; d) duration of morning stiffness exceeding 1 hour; e) age 65 years or more; f) depression and/or weight loss; g) bilateral tenderness in the upper arms.

*Gout* will be defined according to the ACR criteria[12] and will be established in the presence of 6 of the following 11 criteria: a) more than one attack of acute arthritis; b) maximum inflammation developed within 1 day; c) oligoarthritis attack; d) redness observed over joints; e) first metatarsophalangeal joint painful or swollen; f) unilateral first metatarsophalangeal joint attack; g) unilateral tarsal joint attack; h) tophus (proven or suspected); i) hyperuricemia; j) asymmetric swelling within a joint on x-ray; k) complete termination of an attack.

### Secondary objectives

Secondary aims will be the evaluation of quality of life, functional and work capacity and access to health care, more specifically the comparison between participants with and without an RD.

Quality of life will be evaluated by the Short Form-36 (SF-36), which yields a continuous result in two scales, physical and mental, each ranging from 0 (worst state) to 100 (best state). This instrument has been validated for the Portuguese population[27, 28].

Functional capacity will be assessed by the Health Assessment Questionnaire (HAQ)[29], which measures difficulty in performing the activities of daily living, and ranges from 0 (no limitation) to 3 (highest limitation).

Work disability will be evaluated by absenteeism, presenteeism, early retirement, and unemployment due to work disability.

Access to health care will be evaluated by Rheumatology consultation (ever, frequent rheumatology consultations - >1 consultation/year, number of consultations in the last year) and exemption from user fees due to RD.

### Study Procedures

Trained interviewers will visit the target population at their homes door-to-door. This screening involves an interview for each participant and will be based on a standardized questionnaire. Its purpose is to obtain information on 1) socio-demographic characteristics, 2) medical history, 3) identification of subjects with a potential RD, and 4) assessment of physical function (HAQ), quality of life (SF-36), work ability and access to health care. Medical history will include questions about previous diagnosis of RD, intake of a list of antirheumatic

drugs, including non-steroidal anti-inflammatory drugs (NSAIDs) for more than one month in total, and the need for medical appointments due to musculoskeletal symptoms in the previous year. In the presence of a diagnosis of RD, questions will address the examinations performed to reach that diagnosis, as well as the name of the medical speciality that established the diagnosis.

The screening questionnaire will be developed in several steps:

1. Questionnaire development: preparation of the questionnaire by a team composed by rheumatologists and epidemiologists;
2. Validation study: to assess the properties of the screening questionnaire (mainly sensitivity and specificity) a validation study will be carried out prior to the start of the study, involving participants with and without an RD. The recruitment of these cases and controls will be hospital-based, from outpatient clinics;
3. Potential refinement of the questionnaire, if necessary after the validation study;
4. Preparation of the data collection forms to be applied through Computer Assisted Personal Interviewing methods;
5. Pilot study: a pilot study will be carried out to detect possible errors in the design of the data collection forms, to assess feasibility of the recruitment, to estimate the interviews' duration, and to estimate the percentage of non-responders and the causes of non-collaboration;
6. Application of the final questionnaire.

Participants identified by this screening questionnaire as potentially having an RD, as well as some of the patients considered as not having an RD (20-30% depending on the accuracy of the questionnaires, as determined in interim analyses), will be evaluated by a rheumatologist according to a structured protocol. Participants will be evaluated in a diagnostic van, fully equipped for the purpose. The evaluation by a rheumatologist will include a medical history and physical examination and will be as closest as possible in time to the screening questionnaire. Available and appropriate laboratory test results or imaging findings will be evaluated during the diagnostic procedure. During the evaluation, blood will be drawn and kept frozen in a biobank for future research, with the patient consent. As explained before, wrist DXA will be performed to the participants evaluated by a rheumatologist and with a clinical indication for a DXA, as recommended by the PSR[24]. In cases where further laboratory investigation or radiographs are necessary, they will be performed as soon as possible (most of them can already take place inside the diagnostic van, such as conventional radiographs and blood draw for laboratory analysis). Afterwards, participants' data will be re-evaluated by a rheumatologist to reach a definite diagnosis. If necessary, the participant will be re-evaluated by a rheumatologist. Cases that pose diagnostic doubts will be discussed among a scientific committee composed by 3 rheumatologists and the principal investigator. Patients with an identified RD, not being followed by a rheumatologist but with clinical indication for will be referred to a rheumatology appointment in their referral hospital.

Non-responders will also be randomly analyzed, by means of comparison of socio-demographic characteristics, as well as clinical aspects, if available. Therefore, non-responders will be asked to answer a basic questionnaire designed specifically for this purpose. Reasons for non-participation will also be registered.

Prior to the start of the study, all participating interviewers and rheumatologists will be trained in order to standardize procedures. This training will cover the study protocol, how to conduct the interview, assessment of musculoskeletal symptoms, and standardizing the use of the RDs classification criteria. The field work will be only undertaken by interviewers with adequate skills to assure the quality of the data collection. Therefore, interviewers not achieving a reasonable level of knowledge after the training will be excluded from the process. Data collection forms will be further monitored centrally to check for missing data or inconsistencies, including potential participant telephone contact to confirm the answers.

At the end of the study, two cohorts will be defined for prospective follow-up, one composed by participants with an RD and another by participants without an RD. The aim of creating these cohorts is to investigate the evolution and outcomes of the RDs, as well as the potential appearance of an RD in the non-RD cohort.

### Statistical Considerations

The prevalence of the different RDs will be estimated with 95% confidence intervals adjusted for the design of the study and standardized for age and gender, according to the total adult population of the studied areas. Comparison of demographic

and clinical characteristics between groups (eg with and without RD) will be undertaken using *t* tests for continuous normally distributed variables or Wilcoxon for continuous non-normally distributed variables. Chi-squared tests will be used for categorical variables, and Fisher's Exact test will be used for categorical variables within smaller sample sizes. Comparison between more than two groups will be performed through one-way analysis of variance (ANOVA) for continuous variables and chi-squared test for categorical variables. Factors significantly associated with any disease group will be included in a logistic regression model for further analysis. The effect of specific conditions on quality of life and function will be assessed by linear regression, univariably and then multivariably, controlling for potential confounders and also analyzing potential effect modification. A probability of $p < 0.05$ will be considered significant. All data will be analyzed with SPSS v 17.0.

### Sample Size Calculation

Sample size calculation was based on the prevalence of RA, which is expected to be between 0.5 and 1%[30]. Assuming a 95% confidence interval, a 0.25% margin of error, a total population of 8,500,000 adults in Portugal, and increasing the sample size by 50% to account for the design effect and recruitment failures, a total of 9,000 participants will be required.

### Ethical considerations

Confidentiality will be safeguarded by the non-existence of identifiers on the database. Contacts will only be kept for logistical reasons, in order to reach participants for posterior observation by a rheumatologist. All participants will sign an informed consent. Blood from the participants evaluated by rheumatologists will be drawn and kept frozen in a biobank for future research, as long as the patient gives his/her consent.

This project will be submitted to the National Ethics Committee from the Portuguese College of Physicians (Ordem dos Médicos), and also to the Comissão Nacional de Protecção de Dados (CNPD), the Portuguese data protection authority (in accordance with the Portuguese law number 67/98, October 26th regarding protection of personal data). The study will be conducted in accordance with the applicable laws and regulations including, but not limited to, the Guideline for Good Clinical Practice (GCP) and the ethical principles stated in the Declaration of Helsinki (amended in Edinburgh).

### Acknowledgements

The authors acknowledge Prof. Loreto Carmona (Sociedad Española de Reumatología, Madrid, Spain) and Prof. Henrique de Barros (Faculdade de Medicina da Universidade do Porto, Porto, Portugal) for their critical and detailed review of the first version of the manuscript, as well as Dr Viviana Tavares (Hospital Garcia de Orta, Almada, Portugal), Prof. João Eurico Fonseca (Faculdade de Medicina da Universidade de Lisboa, Lisboa, Portugal) and Prof. José António Pereira da Silva (Faculdade de Medicina da Universidade de Coimbra, Coimbra, Portugal) for their suggestions that truly contributed to the improvement of this protocol.

### Scientific patronage

This project has received the recognition and scientific patronage of the Direcção Geral de Saúde (General Directorate for Health).

This protocol was prepared as the basis of this epidemiologic study. Nevertheless, it can be complemented by additional amendments in the future, if considered to be convenient and beneficial for the project.

### Correspondência para

Jaime C. Branco
Serviço de Reumatologia
Centro Hospitalar de Lisboa Ocidental, EPE
Hospital Egas Moniz
Rua da Junqueira, 126
1349-019 Lisboa
E-mail: jaime.branco@fcm.unl.pt

### References

1. Badley EM, Rasooly I, Webster GK. Relative importance of musculoskeletal disorders as a cause of chronic health problems, disability, and health care utilization: findings from the 1990 Ontario Health Survey. J Rheumatol 1994;21:505-514.
2. Yelin E, Callahan LF. The economic cost and social and psychological impact of musculoskeletal conditions. National Arthritis Data Work Groups. Arthritis Rheum 1995;38:1351-1362.
3. Makela M, Heliovaara M, Sievers K, Knekt P, Maatela J, Aromaa A. Musculoskeletal disorders as determinants of disability in Finns aged 30 years or more. J Clin Epidemiol 1993;46:549-559.
4. Carmona L, Ballina J, Gabriel R, Laffon A. The burden of musculoskeletal diseases in the general population of Spain: results from a national survey. Ann Rheum Dis 2001;60:1040-1045.
5. Andrianakos A, Trontzas P, Christoyannis F, et al. Prevalence of rheumatic diseases in Greece: a cross-sectional population based epidemiological study. The ESORDIG Study. J Rheumatol 2003;30:1589-1601.
6. Hill CL, Parsons J, Taylor A, Leach G. Health related quality of life in a population sample with arthritis. J

Rheumatol 1999;26:2029-2035.
7. INE (Instituto Nacional de Estatística). 2008.
8. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315-324.
9. Aletaha D, Neogi T, Silman A, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis 2010;69:1580-1588.
10. Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982;25:1271-1277.
11. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1997;40:1725.
12. Wallace SL, Robinson H, Masi AT, Decker JL, McCarty DJ, Yu TF. Preliminary criteria for the classification of the acute arthritis of primary gout. Arthritis Rheum 1977;20:895-900.
13. Altman R, Alarcon G, Appelrouth D, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hip. Arthritis Rheum 1991;34:505-514.
14. Altman R, Alarcon G, Appelrouth D, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hand. Arthritis Rheum 1990;33:1601-1610.
15. Altman R, Asch E, Bloch D, et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. Arthritis Rheum 1986;29:1039-1049.
16. Wolfe F, Smythe HA, Yunus MB, et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. Arthritis Rheum 1990;33:160--172.
17. Wolfe F, Clauw DJ, Fitzcharles MA, et al. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. Arthritis Care Res (Hoboken) 2010;62: 600-610.
18. Bird HA, Esselinckx W, Dixon AS, Mowat AG, Wood PH. An evaluation of criteria for polymyalgia rheumatica. Ann Rheum Dis 1979;38:434-439.
19. Rudwaleit M, van der Heijde D, Landewe R, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. Ann Rheum Dis 2009;68:777-783.
20. Rudwaleit M, van der Heijde D, Landewé R, et al. New ASAS classification criteria for peripheral spondyloarthritis Ann Rheum Dis 2009;68:127.
21. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum 1984;27:361-368.
22. Henschke N, Maher CG, Refshauge KM, et al. Prevalence of and screening for serious spinal pathology in patients presenting to primary care settings with acute low back pain. Arthritis Rheum 2009;60:3072-3080.
23. Kanis JA, Borgstrom F, De Laet C, et al. Assessment of fracture risk. Osteoporos Int 2005;16:581-589.
24. Tavares V, Canhao H, Gomes JA, et al. [Recommendations for the diagnosis and management of osteoporosis]. Acta Reumatol Port 2007;32:49-59.
25. Kanis JA, Melton LJ, 3rd, Christiansen C, Johnston CC, Khaltaev N. The diagnosis of osteoporosis. J Bone Miner Res 1994;9:1137-1141.
26. MacGregor AJ, Ollier WPR, Silman AJ. Modification of ACR classification criteria for rheumatoid arthritis for use in population studies. Br J Rheumatol 1992:21.
27. Ferreira P. A Medição do Estado de Saúde: Criação da Versão Portuguesa do MOS SF-36. 1998.
28. Severo M, Santos AS, Lopes C, Barros H. Reliability and validity in measuring physical and mental health construct of the Portuguese version of MOS SF-36 Acta Med Port 2006;19: 281-288.
29. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum 1980;23:137-145.
30. Gabriel SE. The epidemiology of rheumatoid arthritis. Rheum Dis Clin North Am 2001;27:269-281.

# BEHÇET'S DISEASE ASSOCIATED WITH SUBARACHNOID HEMORRHAGE DUE TO INTRACRANIAL ANEURYSM

Senel K*, Pasa O*, Baykal T*, Ugur M*, Levent A**, Melikoglu M***, Melikoglu MA****

Behçet's disease (BD) is a multisystemic, recurrent inflammatory disorder affecting the eyes, skin and mucosa, locomotor, respiratory, gastrointestinal, nervous and vascular systems[1]. Although the venous system is affected in 95% of cases with vascular involvement, arterial involvement is rare with an incidence of 2,2-7,7%[2,3]. Besides stenosis and thrombosis, aneurysm can also be occur as an arterial involvement in BD. Aneurysm formation in vasculo-Behcet's disease usually presents in the systemic major arteries whereas intracranial aneurysm is extremely rare[4]. The intracranial aneurisms have been reported to be mainly located in the anterior circulation in most of the previously published cases. The literature reveals few cases with aneursym presented in the posterior circulation[2,3,5].

We report a 45 year-old Turkish man with BD, who had subarachnoid haemorrhage due to the rupture of a posterior cerebral artery aneursym. A digital subtraction angiography of left vertebral artery showed an aneursym of the posterior cerebral artery (Figure 1). Although endovascular embolization was planned for the treatment, it was not performed because aneurysm seemed to be spontaneously partial thrombosed in the control cerebral angiography after 4 week (Figure 2). He was discharged from hospital after ten days. In the control visit after six months, he was neurologically stable.

To our knowledge, there have been approximately 30 previously documented reports in 16 BD patients[3-8]. The ages of these cases were ranged between 12- 65 years and the male: female ratio was 13: 3. The clinical picture was subarachnoid haemorrhage in 11 patients, infarction in 3, and intracranial haemorrhage in one. The preceding duration of the disease ranged from 1 month to 25

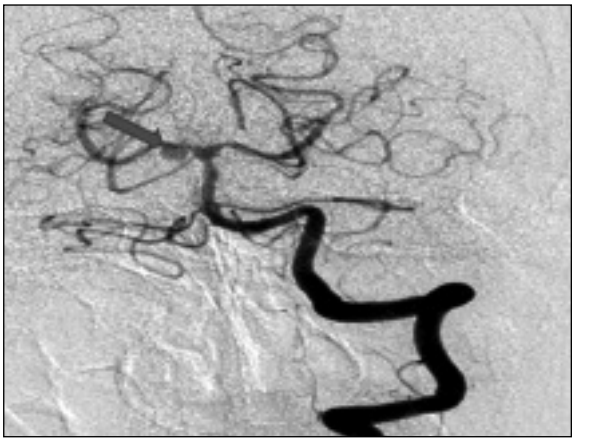


**Figure 1.** Digital subtraction angiography. A left vertebral artery angiography shows an aneurysm on the posterior cerebral artery

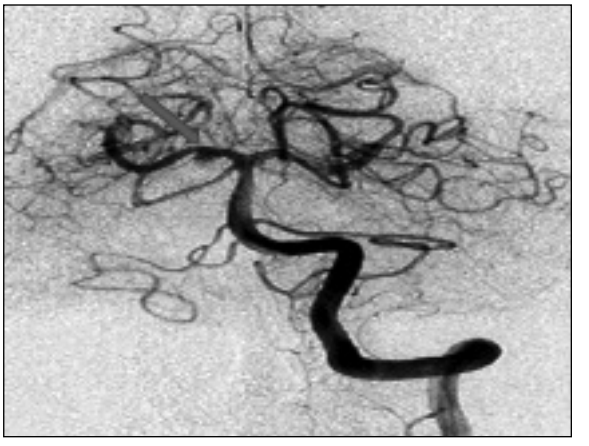


**Figure 2.** The control cerebral angiography after 4 weeks shows spontaneously a partial thrombosed aneurysm of the posterior cerebral artery

*Department of Rheumatology, Ataturk University Medical Faculty, Erzurum, Turkey
**Department of Radiology, Ataturk University Medical Faculty, Erzurum, Turkey
***Department of Dermatology, Erzurum Regional Education and Research Hospital, Erzurum, Turkey
****Department of Rheumatology, Erzurum Regional Education and Research Hospital, Erzurum, Turkey

years. The aneurysms most frequently affected the middle cerebral artery. In 16 patients with 30 aneurysm, 9 had a total of 13 middle cerebral aneurysms; 8 had multiple aneurysm[7]. The role of vasculitis in the aetiology of this cerebral aneurysms has not been clarified[4]. However, the pathophysiology of the aneurysm formation is based on two factors, one of which is ruptured of internal and external elastic lamina due to thinning of tunica media and the other vasculitis developing due to lymphocytic infiltration of vasa vasorum[8]. Vascular complications in BD develop 3-16 years after the disease onset and the inflammatory changes may increase the rebleeding tendency of the aneurysm[8,9]. Our review of the literature showed that the cerebral aneurysm were mostly located in the anterior cerebral circulation similar to those in the aneurysm cases without BD. As in our case, only in few BD cases, aneurysm formation located in the posterior circulation[2,3,5].

In conclusion, we demonstrated that aneurysms of posterior circulation might be observed during the course of BD. However, it is necessary to investigate the anterior and also posterior circulation by non-invasive techniques.

**Correspondence to**
Professor Kazim Senel
Department of Rheumatology
Ataturk University Medical Faculty
Erzurum, Turkey
E-mail: kazimsenel@gmail.com

**References**

1. Akman-Demir G, Serdaroglu P, Tasci B. Clinical patterns of neurological involvement in Behçet's disease: Evaluation of 200 patients. Brain 1999;122:2171--2182.
2. Aktas EG, Kaplan M, Ozveren MF. Basilar artery aneurysm associated with Behcet's disease; a case report. Turkish Neurosurgery 2008;18:35-38.
3. Itoh K, Umehara F, Utatsu Y, Maruyama Y, Osame M. Medullary infarction due to vertebral dissecting aneurysm in a patient with Behcet's disease. Rinsho Shinkeigaku 1996;36:986-989.
4. Nakasu S, Kaneko M, Matsuda M. Cerebral aneurysms associated with Behcet's disease: a case report. J Neurol Neurosurg Psychiatry 2001;70:682-684.
5. Kizilkilic O, Albayram S, Adaletli I, Ak H, Islak C, Kocer N. Endovascular treatment of Behçet's disease-associated intracranial aneurysms: report of two cases and review of the literature. Neuroradiology 2003;45:328-334.
6. Katoh K, Matsunaga K, IshigatsuboY, Chiba J, Tani K, Kitamura H, Tani S, Handwerger BS. Pathologically defined neuro-,vasculo-, entero-Behcet's disease. J Rheumatol 1985;12:1186-1190.
7. Kaku Y, Hamada JI, Kuroda JI, Kai Y, Morioka M, Kuratsu JI . Multiple peripheral middle cerebral artery aneurysms associated with Behçet's disease. Acta Neurochir 2007;149:823-827.
8. Matsumoto T, Uekusa T, Fukuda Y. Vasculo-Behcet's disease. A pathologic study of eight cases. Hum Pathol 1991;22:45-51.
9. Tüzün H, Besirli K, Sayin A, Vural FS, Hizli N, Yazici H. Management of aneurysms in Behcet's syndrome: an analysis of 24 patients. Surgery 1997;121:150-156.

# NO PULSE: A MEDICAL CONUNDRUM

Inês Pires Silva*, Carla Noronha**, António Panarra**, Nuno Riso**, Manuel Vaz Riscado**

Takayasu's arteritis (TA) is a chronic inflammatory disease that affects large vessels, predominantly the aorta and main branches, leading to vessel wall thickening, fibrosis, stenosis, aneurysms and thrombus formation[1].

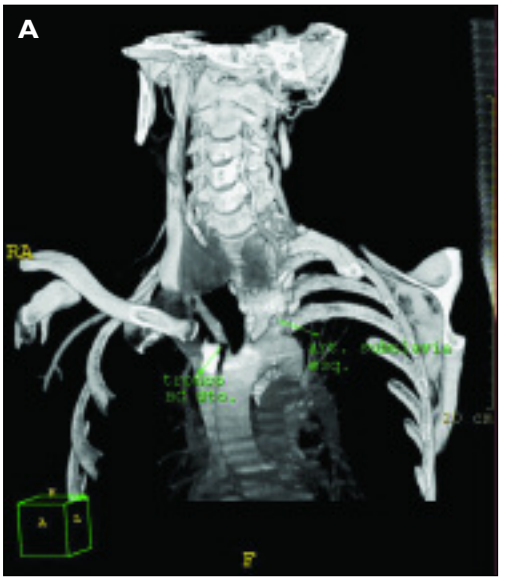
TA presents a biphasic course: firstly, an inflammatory phase; and a later one, where vascular occlusion mainly occurs[2].

Diagnosis of TA is always challenging as the clinical presentation varies, biopsy of large-vessel lesions (gold standard) is rarely performed and because there are no serological or imaging specific diagnostic tests.

The treatment differs according to the phase of the disease. In the inflammatory phase the treatment is mainly immunosuppressive; however, in the latter, vaso-occlusive phase, surgical treatment is needed.

The authors describe the case of a 40 year-old caucasian woman referred to our Autoimmune Clinics due to a nine months duration of dizziness with episodic syncope, occipital headache, right cervicodinia and recurrent amaurosis fugax. Bilateral calf and right upper limb claudication, Raynaud's phenomenon, polyarthralgia, diffuse alopecia, oral ulcers, anorexia and weight loss of fifteen kilograms in two years were also reported. Her past history included: heavy smoking habits (28 pack-year); lumbar vertebral fracture surgery; G5P5A2 (2 first trimester spontaneous abortions) and intake of oral contraceptives. Physical examination was remarkable for a good general health status, but with anisosphygmia (BP RA: 60/30 mmHg; BP LA: 100/60 mmHg), asymmetry in arterial pulses (especially on the right) and bilateral carotid bruit (stronger on the left side).

Some diagnostic tests were performed: a) Lab workup (CBC, ESR, CRP, coagulation times, biochemistry profile, immunological profile, urinalysis), EKG, chest X-ray, head CT and ophtalmological exam were normal. b) nailfold capillaroscopy re-



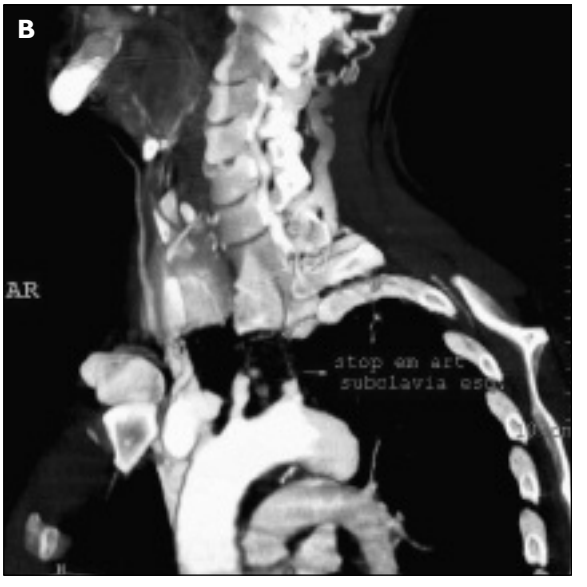




**Figure 1a and 1b.** Cervico-Thoracic revealing a complete occlusion of the left subclavian artery and a marked stenosis of the right brachiocephalic trunk

*Serviço de Oncologia Médica, Instituto Português de Oncologia de Lisboa Francisco Gentil (IPOLFG), Portugal, Programme for Advanced Medical Education
**Unidade de Doenças Auto-imunes, Serviço de Medicina 2, Hospital Curry Cabral, Lisboa, Portugal

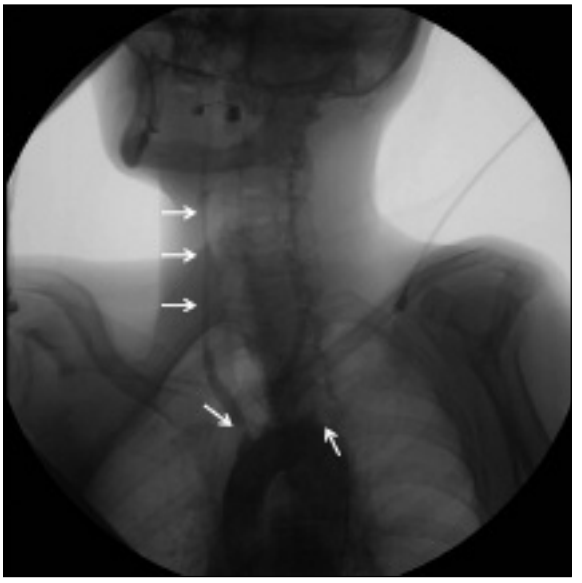


**Figure 2.** Supra-aortic Angiography confirming a complete occlusion of the left subclavian artery and a marked stenosis of the right brachiocephalic trunk

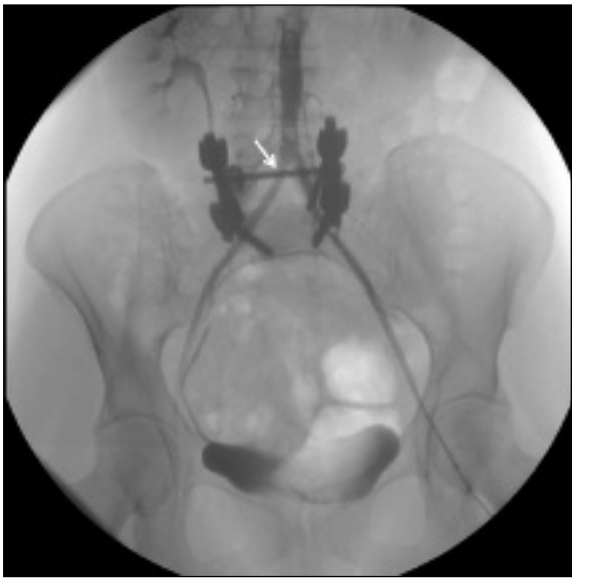


**Figure 3.** Lower limb Angiography revealing a stenosis of the right primitive iliac artery

vealed a secondary Raynaud's phenomenon; c) echocardiogram showed mitral regurgitation; c) 24h-Ambulatory Blood Pressure measurement documented a hypotensive profile; d) Arterial cervical doppler ultrasound revealed low peak systolic velocity and pulsability, marked high diastolic velocity in the brachiocephalic trunk, in bilateral carotideal axes and the left subclavian artery; e) Cervico-thoracic angio-CT (Figures 1a and 1b) complemented by cervico-thoracic-abdominal angiography (Figures 2 and 3) revealed occlusion of the left subclavian artery, concentric stenosis of brachiocephalic trunk and mild stenosis of carotid axis and primitive right iliac artery.

A strong suspicion diagnosis of TA[3] in the occlusive stage was established. A multidisciplinary treatment was adopted: smoking cessation, double antiplatelet therapy, statins, trimetazidine and endovascular surgery (stenting and brachiocephalic trunk and right primitive iliac angioplasty); immunosuppressive treatment was deferred due to surgical approach.

However, three months later, she complained of dysphonia, cough, upper dyspnea and bilateral cervical enlargement consistent with firm, painful polyadenopathy. An infiltrative and vegetant supraglotic mass was identified and consistent with a moderately differentiated squamous cell carcinoma of the larynx (T3N3M0). She was submitted to total laringectomy, followed by radiotherapy. Presently, she is in oncological remission.

This case is particularly challenging because of the two concomitant diagnoses: TA and larynx neoplasia. TA was presumed due to clinico-radiological presentation, as vascular biopsy was not possible. The association to malignancy (Meig's Syndrome, Leukemias and oropharynx carcinoma)[4-7] has been reported in literature, though still unclear.

**Acknowledgments**

The Programme for Advanced Medical Education is sponsored by Fundação Calouste Gulbenkian, Fundação Champalimaud, Ministério da Saúde e Fundação para a Ciência e Tecnologia, Portugal.

**Correspondence to**

Inês Pires da Silva
Rua Manuel Marques, nº 10, 9º B.
1750-171 Lisboa, Portugal
E-mail: inespiresilva@gmail.com

**References**

1. Nishimoto N, Nakahara H, Yoshio-Hoshino N, Mima T. Successful treatment of a patient with Takayasu arteritis using a humanized anti-interleukin-6 receptor antibody. Arthritis Rheum 2008; 58: 1197-200.
2. Rodriguez-Osorio X, Blanco M, Arias S, Castillo J. Biomarcadores y tomografía de emisión de positrones en la valoración de la actividad de la arteritis de takayasu. Neurologia 2008; 23: 329-332.
3. Arend WP, Michel BA, Bloch DA, et al: The American

College of Rheumatology 1990 criteria for the classification of Takayasu's arthritis. Arthritis Rheum 1990; 33: 1129-1134.
4. Salman MC, Basaran A, Guler T, et al. Meigs' syndrome with highly elevated CA125 levels in a patient with Takayasu arteritis: a case report. Arch Gynecol Obstet 2005; 272:90-92.
5. B'Chir Hamzaoui S, Abdallah M, Baili L, et al. Takayasu's arteritis associated with acute myeloblastic leukaemia. J Mal Vasc 2006; 31: 280-283.
6. Amberger C, Denzlinger C, Janzen J, Müller-Schimpfle M, Mohren M, Kötter I. Takayasu's arteritis secondary to myelodysplasia as a predictor of poor outcome: two case reports. Clin Exp Rheumatol 2004; 22: 346-348.
7. Kavanagh BD, Brizel DM, Leopold KA, Acker JC. Radiation Therapy for Head and Neck Cancer in a Patient with Takayasu's Arteritis. Acta Oncologica 1994; 33: 73-74.

# XVII Jornadas Internacionais do Instituto Português de Reumatologia

## Lisboa, Portugal
## 9 a 10 de Dezembro 2010

# PSYCHOGENIC EXCORIATION IN A SYSTEMIC LUPUS ERYTHEMATOSUS PATIENT

Bárbara Santos Pires da Silva*, Camila Cristina Bonin*, Jozélio Freire de Carvalho**

A 37-year-old woman, with systemic lupus erythematosus since 1996, characterized by malar rash, mouth ulcers, photosensitivity, polyarthritis, Raynaud's phenomenon, alopecia, and positive antinuclear antibody. She has also severe antiphospholipid syndrome manifested by six episodes of deep venous thrombosis, three pulmonary thromboembolism episodes and persistent positive lupus anticoagulant. She has been medicated with warfarin and also with diphosphate of chloroquine (250 mg/day), dapsone (100 mg/day), methotrexate (12.5 mg/week) and prednisone (20 mg/day) due to persistent skin lesions on her face.

A Dermatology appointment was scheduled due to the persistence of the lesions refractory to therapy. The consultant dermatologist diagnosed a Psychogenic Excoriation. She had no other clinical sign or symptom of lupus activity, normal cell blood count, C-reactive protein 0.43 mg/L, erythrocyte sedimentation rate of 2 mm/1st hour, and CH100= 280 IU/mL (normal range: 150-350 IU/mL).

The psychogenic excoriation diagnosis was based on linear lesions that are not typical of lupus (Figure 1) and also on the absence of lupus clinical and laboratory abnormalities.

She was treated with anti-histaminic and then referred to the psychiatric department. Sertraline was started and prednisone was tapered until completely stopped. She evolved with complete healing of her dermatological disease. The other immunosuppressive drugs were also stopped during the follow-up. Currently, she is doing well, without lupus activity, under diphosphate of chloroquine, warfarin and fluoxetine.

Psychogenic or neurotic excoriation, also called dermatotilomania, is a psychodermatologic condition that attempt about 2% of dermatologic cases, being women more affected[1-3]. It occurs due to excessive scratching by tooth, tweezers, nails and others instruments. The pruritus sensation can or can not be present. The lesions are usually found on face and also on superior and inferior members, areas where patients can easily reach. They may occur in absence or in response to skin pathology or sensation of itching[1-3]. It is a condition which usually responds adequately to selective serotonin reuptake inhibitors[4] and behavior therapy as observed in our patient.

**Correspondence to**
Jozélio Freire de Carvalho
Disciplina de Reumatologia da Faculdade de Medicina da USP
Av. Dr. Arnaldo, 455, 3º andar, sala 3190,
Cerqueira César, São Paulo-SP, Brasil. 01246-903
Tel./Fax.: 5511-30617490
E-mail: jotafc@gmail.com

**References**

1. Arnold LM, McElroy SL, Mutasim DF, Dwight MM, Lamerson CL, Morris EM. Characteristics of 34 adults with psychogenic excoriation. J Clin Psychiatry 1998; 59: 509-514.
2. Fried RG. Evaluation and treatment of "psychogenic" pruritus and self-excoriation. J Am Acad Dermatol 1994; 30: 993-999.
3. Mutasim DF, Adams BB. The psychiatric profile of patients with psychogenic excoriation. J Am Acad Dermatol 2009; 61: 611-613.
4. Sharma H. Psychogenic excoriation responding to fluoxetine: a case report. J Indian Med Assoc 2008; 106: 245-262.

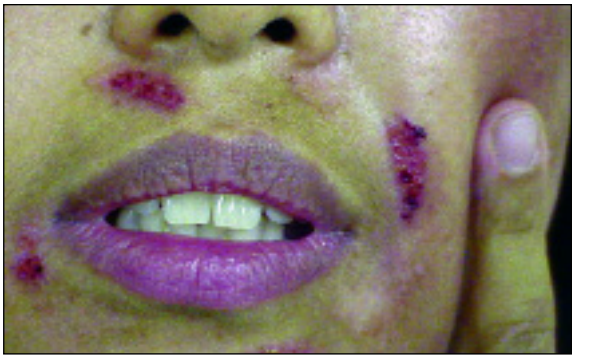


**Figure 1.** Linear erythematosus lesions suggestive of psychogenic excoriations on the lupus patient face

*Biomedicine, University City of São Paulo, São Paulo, Brazil
**Rheumatology Division, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo-SP, Brazil
JF Carvalho received grants from *Federico Foundation and CNPq (300665/2009-1)*

# GIANT GOUTY TOPHI IN THE HAND: A SURGICAL CHALLENGE

Diogo Casal*, Paula Moniz*, Pedro Martins**

The prevalence and annual incidence of gout has been on the rise in Western countries for several reasons (e.g., diet, lifestyle, alcohol use, use of diuretics)[1-3]. Nowadays, the prevalence of gout is 9% in men and 6% in women older than 80 years[2,4]. In Western countries, up to 2% of the entire male population is affected by this disease[5]. Involvement of the hand and wrist is frequent, especially in women[6-8].

Management of tophaceous gout is generally medical[9-10]. However, there are patients who may require surgical intervention. The literature on the surgical management of hand gouty tophi in the past 30 years is largely composed of isolated case reports and relatively small series[6]. Nevertheless, evidence from these reports indicates that if functional disability persists despite aggressive medical management, surgical intervention can be beneficial[6,11]. Surgical indications generally include restoration of joint and tendon mobility, nerve decompression, prevention of skin breakdown, debridement of septic joints, and debulking of painful or disfiguring tophi[6,11]. Pain relief is a secondary, important indication[6,11].

Regarding surgical treatment, it is usually considered unwise to attempt excision of all tophaceous material when doing so would compromise structures important to hand integrity or function[6,11]. Tophi that are firmly adherent to skin, tendon, and bone are gently curetted or excised sharply, without compromising the integrity of the surrounding structures[6,11,12]. The emphasis is on debulking the tophus rather than excise it completely. Interestingly, recurrence of tophi after surgical excision is uncommon[6,11].

We describe the clinical case of a 77-year-old man with a 30-year history of gout that was referred to the hand clinic due to massive tophi in most of the finger joints of his two hands (Figures 1 and 2). Some of the tophi exuded a white, chalky material (Figure 1). He had received colchicine and urate-lowering drugs intermittently over the previous several years. Surgery was undertaken to excise the largest tophi in his left hand (Figure 3). However, complete excision was not possible, in order not to compromise important vascular, nervous and tendon structures (Figure 4).

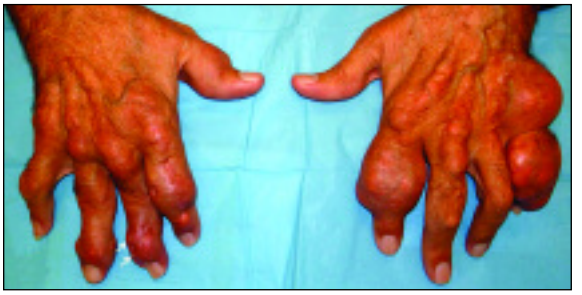


**Figure 1.** Pre-operative appearance of the dorsum of the hands of a patient with long-standing gout and large gouty tophi, especially in the second and fifth fingers of this left hand. Sinus tracts from the tophi occasionally drained spontaneously a pasty white material mixed with blood (white arrows)

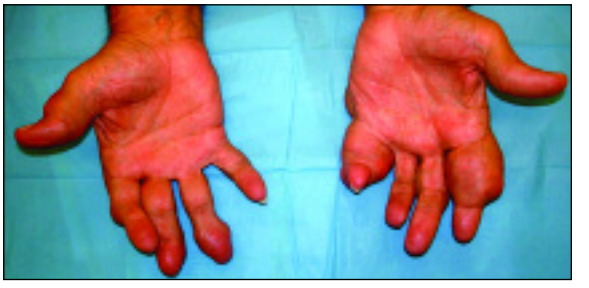


**Figure 2.** Pre-operative appearance of the palmar aspect of the hands of the patient, showing the large tophi present in the dorsum extended to the medial and lateral borders of the fingers. At the level of the second and fifth fingers of the left hand, the tophi reached the palmar aspect of the fingers

*Resident; Plastic and Reconstructive Surgery Department, São José Hospital
**Consultant; Plastic and Reconstructive Surgery Department, São José Hospital

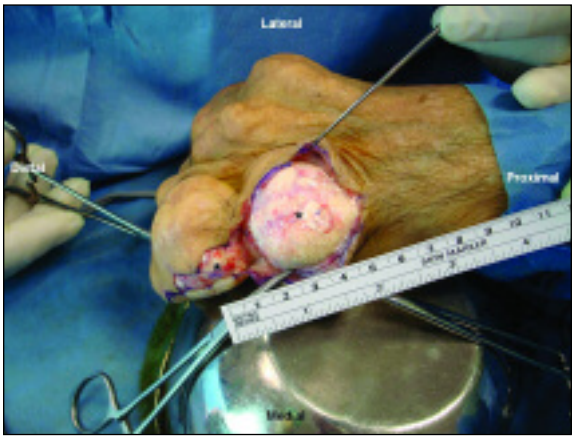



**Figure 3.** Intra-operative view of the left hand of the patient. Two large tophi (*) embedded in the extensor tendons of the fifth finger are visible. The tophi were tightly adherent to the surrounding tendons, joint capsules, bones, vessels and nerves. The complete extirpation of these two masses was not possible because the tophi completely surrounded the two main neurovascular bundles of the fifth finger (the palmar radial and ulnar neurovascular bundles)

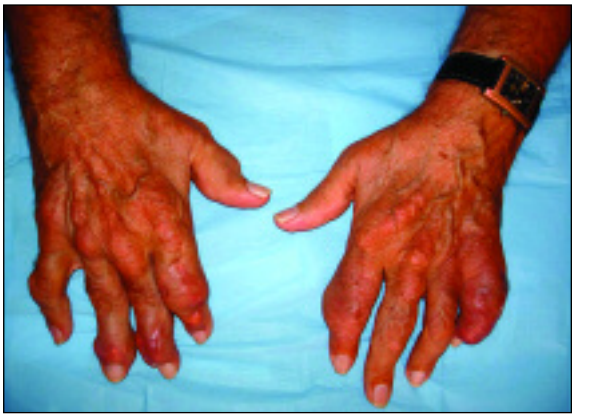


**Figure 4.** Dorsal view of the dorsum of the hands of the patient two months after surgery, showing the reduction in size of the tophi over the second and fifth fingers of the left hand. However, these masses are still present in the borders of these fingers, that is to say, where the two main neurovascular bundles of the fingers are located

We believe this case eloquently demonstrates that surgery of large gouty tophi in the hand is frequently difficult, hazardous, and often leads to suboptimal results[6,11]. Hence, patients and doctors should strive to obtain a good control of uric acid levels, in order to reduce the risk of tophi formation and the need for surgery[6,11].

**Correspondence to**
Diogo Casal
Rua Luís Pastor de Macedo, N 32, 5D,
1750-159,
Lisbon, Portugal
E-mail: diogo_bogalhao@yahoo.co.uk

**References**

1. Weaver AL. Epidemiology of gout. Cleve Clin J Med 2008; 75: 9-12.
2. Arromdee E, Michet CJ, Crowson CS, O'Fallon WM, Gabriel SE. Epidemiology of gout: is the incidence rising? J Rheumatol 2002; 29: 2403-2406.
3. Richette P, Bardin T. Gout. Lancet 2010; 375:318-28.
4. De Leonardis F, Govoni M, Colina M, Bruschi M, Trotta F. Elderly-onset gout: a review. Rheumatol Int 2007; 28: 1-6.
5. Mikuls TR, Farrar JT, Bilker WB, Fernandes S, Schumacher HR Jr., Saag KG. Gout epidemiology: results from the UK General Practice Research Database, 1990-1999. Ann Rheum Dis 2005; 64: 267-272.
6. Fitzgerald BT, Setty A, Mudgal CS. Gout affecting the hand and wrist. J Am Acad Orthop Surg 2007; 15: 625--635.
7. ter Borg EJ, Rasker JJ. Gout in the elderly, a separate entity? Ann Rheum Dis 1987; 46: 72-76.
8. Simkin PA, Campbell PM, Larson EB. Gout in Heberden's nodes. Arthritis Rheum 1983; 26: 94-7.
9. Gomes TS, Sequeira G, Simões P. Artropatia Gotosa. Acta Reumatol Port 2010; 35:102-104.
10. Ribeiro A, Bogas M, Costa J, Costa L, Araújo D. Rasburicase no tratamento da gota tofácea. Acta Reumatol Port 2009; 34: 551-554.
11. Kumar S, Gow P. A survey of indications, results and complications of surgery for tophaceous gout. N Z Med J 2002; 115: U109.
12. Straub L, Smith J, Carpenter G, Dietz G. The surgery of gout in the upper extremity. J Bone Joint Surg Am 1961;43: 731-752.

# FINDINGS OF RENAL BIOPSY IN LUPUS PATIENTS WITH LOW LEVELS OF PROTEINURIA

Shönrock AC*, Rosa RG*, Weigert S*, Skare TL*

To the Editor

Lupus nephritis is a feared complication of systemic lupus erythematosus (SLE) that occurs in approximately 60% of patients[1]. There are multiple histologic subtypes and the optimal treatment varies accordingly to them[2]. In order to identify the nephritis type, a renal biopsy is necessary, as clinical parameters have poor reliability. Besides establishing the exact diagnosis, renal biopsy will help decide when treatment is futile[1,2]. The degree of active or chronic changes helps determine the likelihood of response to treatment.

Although the ACR classification criteria for SLE defines nephritis as the presence of proteinuria over 500mg/day or cellular casts of any type, some clinicians only recommend biopsy when levels over 1.000mg/day of proteinuria are found[3]. This approach is based on the assumption that those with mild proteinuria and hematuria and normal creatinine have WHO class II disease[3]. Others advocate that biopsy should be done in patients with lower levels of proteinuria. Christopher-Stine et al[4] studying 21 patients with low level proteinuria found that 77% of their patients had a major form of nephritis.

We reviewed the charts of 353 lupus patients that attended our clinic from January 2004 to January 2010 and found 10 cases of renal biopsy done in patients with proteinuria under 1.0 g/day. These cases were analyzed to see if renal biopsy had any role in changing treatment. Clinical characteristics and histological individual findings of these 10 patients are shown in Table I.

We notice that at least 60% of patients had a diagnosis of class 3, 4 and 5 and needed therapeutic adjustments. The others had findings that did not require immunossupressive therapy (two with class 2 and two with renal disease not related to lupus).

Even though the present sample is small and do not allow drawing major conclusions, it clearly shows that patients with low levels of proteinuria may have significant renal disease. In this context an early indication for biopsy may provide early immunosupression and better prognosis.

**Table I. Clinical and biopsy characteristics of lupus patients with low level of proteinuria**

| | Age | Anti DNA | Creatinine mg/dl | Complement C3 | Complement C4 | Hematuria (*) | Proteinuria /24h | HAS (**) | Renal biopsy |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 20 | + | 0.87 | ↓ | ↓ | No | 0.96 | Yes | Class 4 (AI=7/24;CI=2/12) |
| 2 | 37 | - | 0.83 | N | N | No | 0.71 | No | Class 5 |
| 3 | 27 | + | 0.7 | ↓ | ↓ | Yes | 0.32 | No | Class 4 (AI=5/24;CI=2/12) |
| 4 | 43 | + | 0.88 | ↓ | ↓ | Yes | 0.45 | Yes | Class 2B |
| 5 | 46 | - | 1.58 | ↓ | ↓ | Yes | 0.17 | Yes | Hypertensive glomerulosclerosis |
| 6 | 58 | - | 1.04 | N | N | Yes | 0.43 | No | IgA nephropaty |
| 7 | 40 | + | 0.79 | ↓ | ↓ | Yes | 0.72 | Yes | Class 4 (AI=14/24;CI=4/12) |
| 8 | 32 | - | 0.58 | ↓ | ↓ | Yes | 0.81 | No | Class 5 |
| 9 | 41 | - | 1.37 | ↓ | ↓ | No | 0.52 | No | Class 2A |
| 10 | 38 | + | 0.97 | ↓ | ↓ | Yes | 0.44 | Yes | Class 3 (AI=3/24;CI=1/12) |

(*)–hematuria = more than 5 red blood cells/high power field; (**)–HAS = levels equal or over 140 mm systolic and 90 diastolic blood pressure; AI= activity index; CI= chronicity index

*Rheumatology Unit, Evangelic University Hospital Curitiba, PR Brazil

**Correspondence to**
Thelma L Skare
Rua João Alencar Guimarães, 796
80310420 Curitiba PR Brazil
E-mail: tskare@onda.com.br

**References**

1. Beck LH Jr, Salant DJ. Treatment of membranous lupus nephritis: where are we now? J Am Soc Nephrol 2009; 20:690-691.
2. Waldman M, Appel GB. Update on the treatment of lupus nephritis. Kidney Int 2006; 70:1403-1412.
3. Salach RH, Cash JM. Managing lupus nephritis: algorithms for conservative use of renal biopsy. Cleve Clin J Med 1996;63;106-115.
4. Christopher-Stine L, Siedner M, Lin J, et al. Renal biopsy in lupus patients with low levels of proteinuria. J Rheumatol 2007; 34: 332-333.

# 8th European Lupus Meeting

## Porto, Portugal
## 6 a 9 de Abril de 2011

# OSTEONECROSE: UM PROBLEMA EMERGENTE NOS DOENTES COM VIH

Tânia Santiago*, João Rovisco*, Jorge Silva**, José António Pereira da Silva***

Ao Exmo. Editor

A osteonecrose (ON), também denominada necrose asséptica ou necrose avascular, caracteriza-se por uma alteração da vascularização que origina necrose do osso subcondral. A incidência da ON na população geral é aproximadamente 0,13%[1]. Predomina no sexo masculino, diagnosticando-se em média aos 40 anos de idade. Em 1990, foi descrito o primeiro caso de ON num doente com VIH por Goorney et al[2]. Desde então, várias publicações confirmam um aumento da incidência desta patologia nos doentes com VIH, superior à observada na população geral. A localização e as manifestações clínicas da ON em doentes com VIH são similares às da população geral. Em 85% dos casos ocorre envolvimento da cabeça femoral e em quase metade é bilateral[3].

Os autores descrevem o caso clínico de um doente do sexo masculino, de 43 anos de idade, VIH positivo e sob terapêutica antiretroviral altamente activa (HAART). Foi internado no Serviço de Reumatologia para estudo de uma coxalgia bilateral, com 4 meses de evolução, de início insidioso de características mecânicas e incapacitante para a marcha. Objectivamente, a mobilização activa e passiva da articulação coxofemoral desencadeava dor intensa, havendo limitação franca nos movimentos de rotação interna e externa. Na marcha era visível uma claudicação antálgica. Perante este quadro clínico, foi realizado um estudo analítico (que não revelou alterações) e radiografia das articulações coxofemorais com incidência póstero-anterior e oblíqua externa. Radiologicamente apresentava perda bilateral da esfericidade da cabeça femoral, com colapso de ambas cabeças sob a cavidade acetabular (Figuras 1 e 2). Reunindo os dados da clínica e da imagiologia, considerámos como principal hipótese de diagnóstico uma osteonecrose bilateral da cabeça do fémur. Deste modo, foi instituída terapêutica médica (com analgésicos e anti-inflamatórios não esteróides), obtendo-se uma resposta favorável, e pedida a colaboração da Ortopedia.

Perante a existência de sinais radiológicos inequívocos de ON da cabeça femoral foram equacionadas as várias causas possíveis, incluindo as traumáticas e não-traumáticas. A corticoterapia e o consumo excessivo de álcool são responsáveis por mais de 90% dos casos. No caso do nosso doente não havia antecedentes de eventos traumáticos, uso de corticoterapia ou história de alcoolismo. No entanto, era um doente VIH positivo e sob HAART desde há vários anos.

Actualmente reconhece-se que a ON é uma complicação emergente nestes doentes, com uma incidência de 0,45%, cerca de 45 vezes a da população geral[4]. Este facto pode ter as seguintes explicações: i) a elevada suspeita de diagnóstico; ii) o aumento da sobrevivência destes doentes; iii) a alta prevalência de factores de risco para ON nesta população. A etiologia da ON nos doentes com VIH é multifactorial, e provavelmente relaciona-se com a elevada prevalência dos factores etiológicos clássicos para a ON[6]. De referir, que muitos dos factores de risco estão associados à própria infecção VIH, à terapia anti-retroviral ou às co-morbilidades, como pancreatite, hiperlipidémia, hipercoaguabilidade, osteopenia/osteoporose e corticoterapia. Até à data não foi conclusivo que os inibidores da protease ou a HAART constituam factores de risco independentes para desenvolver ON[7].

Do ponto vista prático, num doente VIH e com artralgia persistente sem resposta aos analgésicos, a suspeita de ON deve estar presente. Por outro lado, realçamos que a serologia do VIH deve estar incluída no estudo analítico do doente com ON, especialmente se os factores de risco classicamente associados a esta patologia não estiverem presentes.

*Interno do Internato Complementar de Reumatologia, Serviço de Reumatologia, Hospitais da Universidade de Coimbra
**Assistente Hospitalar Graduado de Reumatologia, Serviço de Reumatologia, Hospitais da Universidade de Coimbra
***Director de Serviço, Serviço de Reumatologia, Hospitais da Universidade de Coimbra

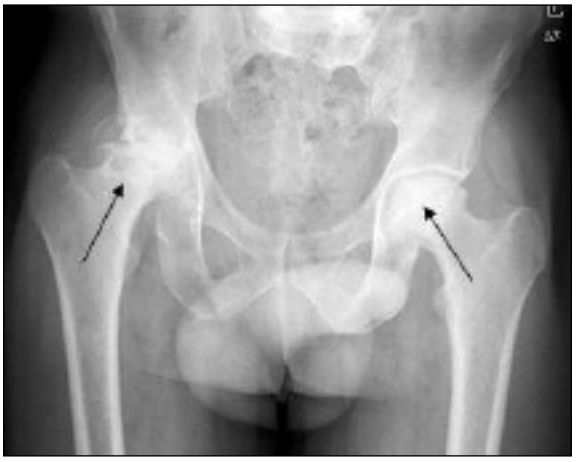


**Figura 1.** Osteonecrose bilateral da cabeça femoral: perda completa do espaço articular, esclerose subcondral e perda esfericidade e da continuidade da cortical

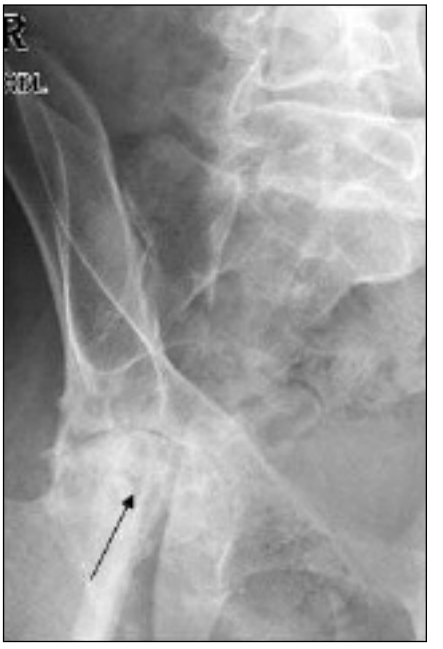


**Figura 2.** Osteonecrose da cabeça femoral direita

**Correspondência para**
Tânia Santiago
Hospitais da Universidade de Coimbra
Serviço de Reumatologia
Praceta Mota Pinto
3000 Coimbra
E-mail: tlousasantiago@hotmail.com

**Referências**

1. Gutierrez F, Padilla S, Ortega E, et al. Avascular necrosis of the bone in HIV-infected patients: Incidence and associated factors. AIDS 2002; 16: 481-483.
2. Scribner AN, Troia-Cancio PV, Cox BA, et al. osteonecrosis in HIV: A case-study. J Acq Imm Defic Synd 2000; 25:19-25.
3. Allison GT, Bostrom MP, Glesby MJ. Osteonecrosis in HIV disease: epidemiology, etiologies, and clinical management. AIDS 2003; 17: 1-9.
4. Brown P, Crane L. avascular necrosis of bone in patients with human immunodeficiency virus infection: report of 6 cases and review of the literature. Clin Infect Dis 2001; 32:1221-1226.
5. Morse CG, Mican JM, Jones EC, et al. The incidence and natural history of osteonecrosis in HIV-infected adults. Clin Infect Dis. 2007; 44:739-748.
6. Allison GT, Bostrom MP, Glesby MJ. Osteonecrosis in HIV disease: epidemiology, etiologies and clinical management. AIDS 2003; 17:1-9.
7. Martin K, Lawson-Ayayi S, Miremont-Salame G, et al. Symtomatic bone disorders in HIV-infected patients: incidence in the Aquitaine cohort (1999-2002). HIV Med 2004; 5:421.

# CARPAL TUNNEL SYNDROME IN TWO CASES OF ALL ULNAR HAND: A WORD FOR NERVE'S ULTRASOUND

Murat Kara*, Gülten Erkin*, Fevziye Ünsal Malas**, Bayram Kaymak**, Hilmi Uysal*, Levent Özçakar**

To the editor,

Anatomic communications between the ulnar and median nerves have been described in the hand, known as a Riche-Cannieu anastomosis. A particular and rare form of such an anastomosis is the "all ulnar hand", when all the intrinsic muscles are innervated only by the ulnar nerve without any proximal connections between the ulnar and median nerves at the forearm[1]. All ulnar hand concomitant with the presence of carpal tunnel syndrome (CTS) may pose challenges in daily practice leading to misdiagnosis and inappropriate medical or surgical procedures. Herein, we present two cases of all ulnar hand with coexisting CTS and discuss the pertinent difficulties and the role of ultrasonography (US) in the diagnosis algorithm.

## Case 1

A 53-year-old woman was referred for electrophysiological examination with a pre-diagnosis of CTS. She had been suffering pain, weakness and tingling sensations in her hands for several years. In the physical examination, there was evident atrophy (Figure 1) and weakness only on the right side. She had bilateral hypoesthesia in the first three fingers. Special tests for CTS (Tinel's sign and Phalen's maneuver) were positive on both sides. Nerve conduction studies revealed bilateral severe CTS and all ulnar hand anomaly on the left side (Table I). Intramuscular recordings using needle electrodes from the thenar and lumbrical muscles could not be achieved with stimulation of the median nerve at the wrist level; however stimulation of the ulnar nerve yielded normal compound muscle action potentials (CMAP), indicating all ulnar hand. There was no evidence of denervation. Thereafter, in order to visualize the median nerves, we have performed US evaluations. Median nerves cross sectional areas at the entrance of the carpal tunnel were 22.5 $mm^2$ on the right side and 26.1 $mm^2$ on the left side. Accordingly, the diagnosis of bilateral CTS was confirmed[2]. Since conservative treatment applied in another center had failed to improve her complaints, the patient was appointed for surgery.

## Case 2

A 48-year-old man was referred with a likely diagnosis of CTS. He declared that he suffered pain and paresthesias in the left hand. On physical examination, there was no weakness, atrophy or hypoesthesia. Tinel's sign and Phalen's maneuver were negative on both sides. Nerve conduction studies revealed mild CTS and all ulnar hand anomaly on the left side (Table I). The patient was followed conservatively with nonsteroidal antiinflammatory drugs and a static wrist splint in the neutral position.

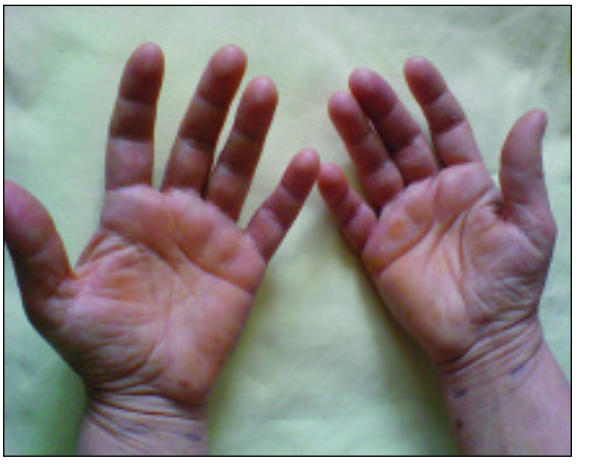


**Figure 1.** Palmar view of the patient's hands demonstrating significant thenar atrophy on the right side

*Ankara Physical Medicine and Rehabilitation Education and Research Hospital, Department of Physical Medicine and Rehabilitation, Ankara, Turkey
**Hacettepe University Medical School, Department of Physical Medicine and Rehabilitation, Ankara, Turkey

**Table I. Nerve conduction study findings of the patients' left hands**

| | Recording site | Stimulation | Amplitude | Latency (msec) | Velocity (m/sec) |
|---|---|---|---|---|---|
| **Case 1** | | | | | |
| *Motor* | | | | | |
| Median | APB | Wrist | – | | |
| | | Elbow | – | | |
| | 1. Lumbrical | Wrist | – | | |
| | | Elbow | – | | |
| Ulnar | ADM | Wrist | 7.4 mV | 2.8 | |
| | | Elbow | 7.2 mV | 6.05 | 63.1 |
| Ulnar | APB | Wrist | 13.7 mV | | 3.2 |
| | | Elbow | 11.9 mV | 6.55 | 62.7 |
| | 1.Lumbrical | Wrist | 7.9 mV | | 3.0 |
| *Sensory* | | | | | |
| Median | D2 | Wrist | 6.9 µV | 6.2 | 26.7 |
| Ulnar | D5 | Wrist | | | |
| **Case 2** | | | | | |
| *Motor* | | | | | |
| Median | APB | Wrist | | – | |
| | | Elbow | | – | |
| | 1.Lumbrical | Wrist | | – | |
| | | Elbow | | – | |
| Ulnar | ADM | Wrist | 12.8 mV | 2.4 | |
| | | Elbow | 12.0 mV | 7.5 | 54.9 |
| Ulnar | APB | Wrist | 12.0 mV | 4.2 | |
| | | Elbow | 11.3 mV | 9.2 | 55.7 |
| *Sensory* | | | | | |
| Median | D2 | Wrist | 10.0 µV | 2.3 | 54.3 |
| Ulnar | D5 | Wrist | 15.0 µV | 2.2 | 54.5 |

APB, abductor pollicis brevis; ADM, abductor digiti minimi; D2, second digit; D5, fifth digit

Riche-Cannieu anastomosis is an anatomic, only motor connection between the deep branch of the ulnar nerve and the recurrent branch of the median nerve in the palm[3]. In this anatomic variation, the typically median nerve innervated muscles can receive either partially or, rarely, totally motor innervation from the ulnar nerve so called as "all ulnar hand"[4]. Interestingly, the scenario may further be challenged in clinical practice if CTS is also present. To our best knowledge, there are only a few reports where CTS and all ulnar hand variation coexist[5]. In such patients, technical difficulties may be encountered during median nerve conduction studies at first; and second, the findings of physical examination and electrophysiological tests may be disproportionate due to the preservation of the thenar muscles innervated by the deep branches of the ulnar nerve. Similarly, in our first patient there was no weakness or atrophy in the thenar muscles despite overt CTS.

During clinical and electrodiagnostic evaluations of patients with CTS, clinicians should be aware of these types of anomalous innervations. Moreover, like its use in idiopathic CTS for demonstrating the possible underlying etiologies, US -a convenient as well as inexpensive, noninvasive, repeatable technique- may be a useful adjunct in such cases[6].

**Correspondence to**
Murat Kara
Türkocağı sok. No: 3 Opera
Sıhhıye, Ankara, Turkey
Tel: 90 312 3103230
Fax: 90 312 3104242
E-mail: mkaraftr@yahoo.com

**References**

1. Kim BJ, Date ES, Lee SH, Lau EW, Park MK. Unilateral all ulnar hand including sensory without forearm communication. Am J Phys Med Rehabil 2004; 83: 569-573.
2. Kaymak B, Ozçakar L, Çetin A, Candan Cetin M, Akinci A, Hasçelik Z. A comparison of the benefits of sonography and electrophysiologic measurements as predictors of symptom severity and functional status in patients with carpal tunnel syndrome. Arch Phys Med Rehabil 2008; 89: 743-748.
3. Dumitru D, Walsh NE, Weber CF. Electrophysiologic study of the Riche-Cannieu anomaly. Electromyogr Clin Neurophysiol 1988; 28: 27-31.
4. Ganes T. Complete ulnar innervation of the thenar muscles combined with normal sensory fibres in a subject with no peripheral nerve lesion. Electromyogr Clin Neurophysiol 1992; 32: 559-563.
5. Refaeian M, King JC, Dumitru D, Cuetter AC. Carpal tunnel syndrome and the Riche-Cannieu anastomosis: electrophysiologic findings. Electromyogr Clin Neurophysiol 2001; 41: 377-382.
6. Ozçakar L, Çakar E, Kıralp MZ, Dinçer U. Static and dynamic sonography: a salutary adjunct to electroneuromyography for cubital tunnel syndrome. Surg Neurol 2009; 72: 311-312.

# MÉZIÈRES' METHOD AND MUSCULAR CHAINS' THEORY: FROM POSTURAL RE-EDUCATION'S PHYSIOTHERAPY TO ANTI-FITNESS CONCEPT

Luís Coelho*

Dear Editor,

I will try to resume, using a few words, the theoretical data of a complete method, with so many importance, from those icon of "medical gymnastique", called Françoise Mézières (1909-1991). I consider the "Letter to the Editor" as a mean of exposing the basis of a method that is not scientifically granted (and that means that it has to be considered as a theoretical paradigm, like was formulated by the Thomas Kuhn and Michel Foucault epistemological models).

The comprehension of the Mézières' method in its truly theoretical and methodological amplitude, implies the comprehension of some rheumatological pathologies as a result of postural deformities. Specially, degenerative pathologies, like osteoarthritis, are related with postural structure.

This same "postural structure" has been "worked out" using antiques gymnastique methods that are based in a "strengthening" model. Françoise Mézières resumed that kind of gymnastique, like Yoga or Pilates, in her book called "La gymnastique statique"[1]. In the same year (1947), Mézières has realized the "observation" that caused a revolution in the manner of dealing with some rheumatological diseases. That "observation" resulted in this conclusion: the body, in a miofascial sense, compounds a global behaviour – called "muscular compensations" – mediated by the existence of global muscular groups of tonic nature, the "muscular chains". These "chains", that were reinvented by a lot of others authors (like Godelieve Denys-Struyf[2], Leopold Busquet[3] or Souchard[4] from the Global Postural Re-education), would explain the body design, in a "statical posture" conception[5], based in the scientifical division of the muscular system between dynamic and static/tonic muscles, and it would create a morphoanalysis' model of treatment – the Mézières' method – concentrated in the "global stretching postures of the contracted muscular chains", using a treatment tripe: deslordosis, desrotation and diaphragmatic liberation.

So, the Mézières' concept defines postural deformities as "muscular excess" of tonic musculature – principally posterior musculature – describing lordosis as the primary cause of all deformities[6]. Mézières defined an amount of laws in her book "Originalité de la méthode Mézières"[7] (1st: "Les nombreux muscles postérieurs se comportent comme un seul et même muscle"; 2nd: "Les muscles des chaînes sont trop toniques et trop courts"; 3rd: "Toute action localisée, aussi bien élongation que raccourcissement, provoque instantanément le raccourcissement de l'ensemble du système"; 4th: "Toute opposition à ce raccourcissement provoque instantanément des latéroflexions et des rotations du rachis et des membres"; 5th: "La rotation des membres due à l'hypertonie des chaînes s'effectue toujours en dedans"; 6th: "Toute élongation, détorsion, douleur, tout effort implique instantanément le blocage respiratoire en inspiration") that were important to define revolutionary methodologies of treatment and a novel concept with implications to the physical therapy's world and sports' world, which was understood by Bertherat[8] and remembered by «Postural Reconstruction»'s Nisand[9].

In a physical therapy's and sports' world that is so obsessively stuck to treatment's methodologies based in the "strengthening model" of the "weak muscles", the Mézières' concept implies a radical modification in the therapies' methods. These should give value to the relaxation, the tonic inhibition and the global and progressive stretching of the muscular regions with imbalance. Moreover, such methodological implications oblige to a serious revision of the System's operation. A new model of Fitness and "Workout" is needed. In this concept, it is considered the creation of the *anti-fitness* concept[10].

*Licenciado em Fisioterapia, Consultório e Clínica de Reabilitação, Lda. – Lisboa

**Correspondence to**
Luís Coelho
Rua Actor Vale 10, r/c Esq.
1900-025 Lisboa
E-mail: coelholewis@hotmail.com

**References**

1. Mézières F. La gymnastique statique. Paris: Vuibert, 1947.
2. Denys-Struyf G. Les chaînes musculaires et articulaires. SBO & RTM, 1978.
3. Busquet L. Les chaînes musculaires. Kine Plus 1996;57:19-25.
4. Souchard Ph-E. Le champs clos. Paris: Maloine, 1981.
5. Bienfait M. Os desequilíbrios estáticos: fisiologia, patologia e tratamento fisioterápico. São Paulo: Summus editora, 1995.
6. Mézières F. La révolution en gymnastique orthopédique. Paris: Vuibert, 1949.
7. Mézières F. Originalité de la méthode Mézières. Paris: Maloine, 1984.
8. Bertherat T. Le corps a ses raisons. Paris: Éditions du Seuil, 1976.
9. Nisand M. La méthode Mézières: un concept révolutionnaire. Paris: Éditions Josette Lyon, 2006.
10. Coelho L. O anti-fitness ou o manifesto anti-desportivo. Introdução ao conceito de reeducação postural. Quinta do Conde: Editora Contra Margem, 2008.

- **1st Porto's Autoimmune Meeting**
  **Local e Data:** Porto, Portugal, 8 a 9 de Outubro 2010

- **XII Fórum de Apoio ao Doente Reumático**
  **Local e Data:** Portugal, 8 a 9 de Outubro 2010

- **3e Initiative 2010**
  **Local e Data:** Cascais, Portugal, 8 a 9 de Outubro 2010

- **32nd American Society for Bone and Mineral Research Annual Meeting**
  **Local e Data:** Toronto, Canada, 15 a 19 de Outubro 2010

- **VI Jornadas de Reumatologia e Medicina Familiar do Algarve**
  **Local e Data:** Vilamoura, Portugal, 22 a 23 de Outubro 2010

- **XXXI Curso de Reumatologia dos Hospitais da Universidade de Coimbra**
  **Local e Data:** Coimbra, Portugal, 22 a 23 de Outubro 2010

- **74th American College of Rheumatology Annual Meeting**
  **Local e Data:** Atlanta, EUA, 7 a 11 de Novembro 2010

- **5th European Workshop on Immune-mediated Inflammatory Diseases**
  **Local e Data:** Sitges, Espanha, 1 a 3 de Dezembro 2010

- **XVII Jornadas Internacionais do Instituto Português de Reumatologia**
  **Local e Data:** Lisboa, Portugal, 9 a 10 de Dezembro 2010

- **8th European Lupus Meeting**
  **Local e Data:** Porto, Portugal, 6 a 9 de Abril de 2011

A Acta Reumatológica Portuguesa publica artigos originais sobre todos os temas da Reumatologia ou com ela relacionados. São também publicados artigos de revisão, casos clínicos, imagens, cartas ao editor e outros que se incluam na estrutura editorial da revista (recomendações, artigos sobre prática clínica reumatológica, notícias de reuniões de sociedades científicas, por ex.).

A Acta Reumatológica Portuguesa subscreve os requisitos para apresentação de artigos a revistas biomédicas elaboradas pela Comissão Internacional de Editores de Revistas Médicas (*International Commitee of Medical Journal Editors*), publicada na íntegra inicialmente em N Engl J Med 1991; 324: 424-28 e actualizada em Outubro de 2008 e disponível em www.ICMJE.org. A potítica editorial da Acta Reumatológica Portuguesa segue as Recomendações de Política Editorial (*Editorial Policy Statements*) emitidas pelo Conselho de Editores Científicos (*Council of Science Editors*), disponíveis em www.councilscienceeditors.org/services/draft_approved.cfm.

A Revista está indexada no PubMed/Medline e os artigos estão disponíveis *online* na íntegra, com acesso aberto e gratuito.

Os artigos devem preferencialmente ser redigidos em inglês. Os artigos em língua portuguesa também podem ser submetidos para apreciação.

O rigor e a exactidão dos conteúdos, assim como as opiniões expressas são da exclusiva responsabilidade dos autores.

Os autores devem declarar potenciais conflitos de interesse.

Os artigos não podem ter sido anteriormente publicados noutra revista. Quando o artigo é aceite para publicação é mandatório o envio via e-mail de documento digitalizado, assinado por todos os autores, com a transferência dos direitos de autor para a Acta Reumatológica Portuguesa.

Os artigos publicados ficarão propriedade da revista, não podendo ser reproduzidos, no todo ou em parte, sem autorização dos editores.

A aceitação dos originais enviados para publicação é sempre condicionada a avaliação pelos consultores editoriais. Nesta avaliação os artigos poderão ser:

a) aceites sem alterações;

b) aceites após modificações propostas pelos revisores;

c) recusados.

Em todos os casos os pareceres dos consultores serão integralmente comunicados aos autores.

Quando são propostas alterações, o autor deverá enviar via e-mail no prazo de 1 mês, uma carta ao editor e a cada um dos revisores respondendo a todas as questões colocadas e uma versão revista do artigo com as alterações inseridas destacadas com cor diferente.

**Instruções aos Autores**

Todos os manuscritos que não estejam em conformidade com as instruções que se seguem podem ser enviados para modificações antes de serem revistos pelos consultores.

Todos os trabalhos devem ser enviados por e-mail para: **dias.costa.ml@gmail.com.**

Os manuscritos devem ser acompanhados de declaração de originalidade e de cedência dos direitos de propriedade do artigo, assinada por todos os autores, conforme minuta publicada em anexo.

O texto deve ser enviado em formato digital (e-mail), a dois espaços, com letra tamanho12 e com margens não inferiores a 2,5 cm, em Word para Windows. Todas as páginas devem ser numeradas.

As imagens devem ser fornecidas independentemente do texto em formato JPEG ou TIFF.

Os textos devem ser organizados da seguinte forma:

***Página 1***

a) Título em português e inglês

b) Nome dos autores e respectiva afiliação

c) Serviço(s) ou organismo(s) onde o trabalho foi executado

d) Subsídio(s) ou bolsa(s) que contribuíram para a realização do trabalho

e) Morada e e-mail do autor responsável pela correspondência relativa ao manuscrito

f) Título breve para rodapé

***Página 2***

a) Título (sem autores)

b) Resumo em português e inglês, que para os artigos originais deve ser estruturado da seguinte forma: Objectivos, Material e Métodos, Resultados, Conclusões. O resumo dos artigos originais não deve exceder as 350 palavras e o dos casos clínicos as 180 palavras.

c) Palavras-chave em português e em inglês (Keywords)

Um máximo de 5 palavras-chave, utilizando a terminologia que consta na lista do Index Medicus: «Medical Subject Headings» (MeSH), deve seguir-se ao resumo.

***Página 3 e seguintes***

**Artigos originais:** O texto deve ser apresentado com os seguintes subtítulos: Introdução (incluindo Objectivos), Material e Métodos, Resultados, Discussão, Conclusões, Agradecimentos (se aplicável), Referências.

**Os artigos originais não deverão exceder as 4.000 palavras, com um total de 6 figuras/tabelas e 60 referências.**

**Caso clínico:** os subtítulos serão, Introdução, Caso clínico, Discussão, Referências.

**O caso clínico não deve exceder as 2.000 palavras e 25 referências. Deve ser acompanhado de figuras ilustrativas. O número de tabelas/figuras não deve ser superior a 6.**

A partir da segunda página, inclusive, todas as páginas devem ter em rodapé o título breve indicado na página 1.

**Referências:** As referências bibliográficas devem ser classificadas e numeradas por ordem de entrada no texto, em *superscript* e não entre parêntesis. As abreviaturas usadas na nomeação das revistas devem ser as utilizadas pelo *Index Medicus*.

**Nas referências com 6 ou menos autores todos devem ser nomeados. Nas referências com 7 ou mais autores devem ser nomeados os 3 primeiros seguidos de et al.**

Notas: Os números da página inicial e final devem ser totalmente apresentados (565-569 e não 565-9)

Não indicar o número da revista nem o mês da publicação.

Seguem-se alguns exemplos de como devem constar os vários tipos de referências:

– *Revista*

Apelido e iniciais do(s) autor(es). Título do artigo. Nome da revista Ano; Volume: Páginas.

Ex.: Hill J, Bird HA, Hopkins R, Lawton C, Wright V. Survey of satisfaction with care in a rheumatology outpatient clinic. Ann Rheum Dis 1992; 51:195-197.

– *Artigo publicado online (inserir DOI )*

Ex.: Peter A Merkel, David Curthbertson, Bernhard Hellmich et al. Comparison of disease activity measures for ANCA-associated vasculitis. Ann Rheum Dis Published Online First: 29 July 2008. doi:10.1136/ard.2008. 097758

– *Capítulo de livro*

Nome(s) e iniciais do(s) autor(es) do capítulo. Título do capítulo. In: Nome(s) e iniciais do(s) editor(es) médico(s). Título do livro. Cidade: Nome da casa editora, ano de publicação: primeira a última página do capítulo.

Ex.: Stewart AF. Hypercalcemia resulting from medications. In: Favus MJ, ed. Primer on the Metabolic Bone Diseases and Disorder of Mineral Metabolism. New York: Raven Press, 1993: 177-178.

– *Livro*

Nome(s) e iniciais do(s) autor(es). Título do livro. Cidade: Nome da casa editora, ano de publicação: página(s).

Ex.: Lorig K. Patient Education. A practical approach. St. Louis: Mosby-Year Book;1992: 51.

– *Documento electrónico*

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. Acedido em 25 Janeiro de 2008

As referências a trabalhos ainda não publicados, comunicações em reuniões, não publicadas em livros de resumos, ou comunicações pessoais devem ser citadas no texto e não como referências formais.

A exactidão e o rigor das referências são da responsabilidade do autor.

**Tabelas:** As tabelas a inserir devem ser assinaladas no texto em numeração romana e cumprir o limite descrito acima. Cada tabela deverá ser apresentada em folha separada, dactilografada a 2 espaços. Na parte superior devem apresentar um título sucinto mas informativo, de modo a poder ser compreendido sem recurso ao texto. Na parte inferior da tabela deve constar a explicação das abreviaturas utilizadas. Nas tabelas devem ser evitados os traços verticais e os traços horizontais, estes devem servir apenas como separadores de títulos e subtítulos.

**Figuras:** As figuras a inserir devem ser assinaladas no texto em numeração árabe e cumprir o limite definido acima. As legendas das figuras devem ser dactilografadas a dois espaços numa folha separada, depois da bibliografia. As figuras devem ser enviadas em suporte informático com ficheiros separados para cada figura, em formato JPEG ou TIFF.

**Editoriais:** Os editoriais serão solicitados por convite do Editor. Os editoriais serão comentários sobre tópicos actuais ou sobre artigos publicados na revista. O texto dos editoriais não deve exceder as 1.200 palavras, um máximo de 15 referências e não deve conter quadros ou figuras.

**Artigos de revisão:** Estes artigos serão preferencialmente solicitados pelo Editor. No entanto, os autores interessados em apresentar um artigo de revisão podem contactar o Editor para discussão dos tópicos a apresentar.

O artigo de revisão não deve exceder as 4.000 palavras, 6 tabelas/figuras e 100 referências.

**Cartas ao Editor:** As cartas ao editor devem constituir um comentário crítico a um artigo da revista ou uma pequena nota sobre um tema ou caso clínico. Não devem exceder as 600 palavras, uma figura ou um quadro, e um máximo de 10 referências bibliográficas.

**Imagens em reumatologia:** Podem ser submetidas imagens de particular interesse. As figuras, no máximo de 4, devem ser enviadas em formato JPEG ou TIFF de boa resolução. O texto acompanhante não deve ultrapassar as 500 palavras.

**Modificações e revisões:** No caso da aceitação do artigo ser condicionada a modificações, estas deverão ser feitas pelos autores no prazo de 1 mês.

**Quando são propostas alterações, o autor deverá endereçar uma carta ao editor e a cada um dos revisores respondendo a todos as questões colocadas. Deverá ainda submeter uma versão revista do artigo com as alterações inseridas destacadas com cor diferente.**

As provas tipográficas serão, sempre que possível, enviadas aos autores contendo a indicação do prazo para revisão consoante as necessidades editoriais da revista.

**Minuta da carta de submissão a enviar ao Editor, digitalizada, por e-mail:**

Enviar este documento com o manuscrito para:
**dias.costa.ml@gmail.com**

Editor
Acta Reumatológica Portuguesa

O(s) autor(es) certifica(m) que o manuscrito intitulado: _____
(ref. ARP_____) é original, que todas as afirmações apresentadas como factos são baseados na investigação do(s) autor(es), que o manuscrito, quer em parte quer no todo, não infringe nenhum *copyright* e não viola nenhum direito da privacidade, que não foi publicado em parte ou no todo e que não foi submetido para publicação, no todo ou em parte, noutra revista, e que os autores têm o direito ao *copyright*.

Todos os autores declaram ainda que participaram no trabalho, se responsabilizam por ele e que não existe, da parte de qualquer dos autores conflito de interesses nas afirmações proferidas no trabalho.

Os autores, ao submeterem o trabalho para publicação, transferem para a Acta Reumatológica Portuguesa todos os direitos a interesses do *copyright* do artigo.

**Todos os autores devem assinar**

Data: _____
Nome (maiúsculas): _____
Assinatura: _____

Acta Reumatologica Portuguesa publishes original articles, reviews, case reports, images and letters to the editor on all subjects related to Rheumatology.

Acta Reumatologica Portuguesa subscribes the requirements for the acceptance of manuscripts in biomedical journals proposed by the International Committee of Medical Journal Editors, published initially in N Engl J Med 1991; 324: 424-28, updated in October 2008 and available in www.ICMJE.org. The editorial policy of Acta Reumatológica Portuguesa follows the Editorial Policy Statements published by the Council of Science Editors, available in www.councilscienceeditors.org/services/draft_approved.cfm.

The Journal is indexed on PubMed/Medline. The articles are available online with open and free access.

The articles should be written in English. Portuguese written manuscripts can also be submitted.

The accuracy of the manuscript contents as well as written opinions are of the exclusive responsibility of the author(s).

Published articles will remain property of the journal and cannot be reproduced, as a whole or as a part, without the authorization of the editor.

For accepted articles a statement signed by all authors transferring the copyright to Acta Reumatologica is mandatory and should be send by e-mail.

Authors have to disclose potential conflicts of interest.

The acceptance of articles is subjected to the evaluation of the editorial board. Articles may be:

a) accepted without changes;

b) accepted after modifications suggested by the board;

c) refused.

All the comments made by the reviewers will be sent to the author.

When changes are proposed, the author should send reply letters to the editor and to each of the reviewers answering to all the raised questions. The author should also send a reviewed version of the manuscript with the changes highlighted in a different colour within 1 month.

**Instructions to authors**

Manuscripts not in accordance with the instructions may be sent for modification before review by the editorial board.

All manuscripts must be sent by e-mail to:
**dias.costa.ml@gmail.com**

Manuscripts must be accompanied by a cover letter, signed by all authors, stating the name of the article, that it is an original work, that the authors held the copyright of the manuscript, that it does not represent any conflict of interest, and that they transfer the copyright to the journal (se form below).

Text should be sent in digital support by e-mail, typed double-spaced, type 12, with 1-inch margins, in Word for Windows. All pages must be sequentially numbered.

Images should be sent independently from the text in JPEG or TIFF file.

Manuscripts should be organized as explained below:

***Page 1***

a) Title in Portuguese and in English;

b) Authors' names and affiliations;

c) Institution(s) to which the work should be attributed;

d) Source(s) of grants support;

e) Name, address and e-mail of the corresponding author

f) Short running title.

***Page 2***

a) Title (without authors)

b) Abstract

Abstract in English structured as follows for the original articles: Objectives; Patients and Methods; Results; Conclusions. The abstract should not exceed 350 words for original articles and 180 words for case reports.

c) Keywords

A maximum of 5 keywords – must be MeSH terms – should be presented after the abstract.

***Page 3 and following pages***

**Original papers:** The text of original papers should be presented with the following subtitles: Introduction, Objectives, Patients and Methods, Results, Discussion, Conclusions, Acknowledgements, References.

**Original papers should not exceed 4,000 words, 6 Tables/Figures and 60 references.**

**Case report:** Subtitles for case reports should be: Introduction, Case report, Discussion, References.

**A case report should not exceed 2,000 words and 25 references. It should present illustrative figures. The number of Tables/Figures should not exceed 6.**

From the second page on, all pages should have a short title on footnote.

**References:** References should be cited by the numerical system, superscript and listed, in the order cited in the text. Journal titles are abbreviated in accordance with the style of Index Medicus.

**List all authors when 6 or less; when 7 or more list only first 3 and add "et al".**

Do not abbreviate the page number (i.e. correct: 565--569 and not: 565-9).

The Journal number and the month of publication should not be presented.

References of unpublished work, presentations or personal observations should be inserted in the text (in parenthesis) and not as a "classical" or true reference.

Authors are responsible for the accuracy of the references.

**Examples:**

*– Journal article*

Name(s) and initials of author(s). Article title. Journal name Year; Volume or number: Page(s).

Ex: Hill J, Bird HA, Hopkins R, Lawton C, Wright V. Survey of satisfaction with care in a rheumatology outpatient clinic: Ann Rheum Dis 1992; 51: 195-197.

*– Article published Online (insert DOI )*

Ex.: Peter A Merkel, David Curthbertson, Bernhard Hellmich et al. Comparison of disease activity measures for ANCA-associated vasculitis. Ann Rheum Dis Published Online First: 29 July 2008. doi:10.1136/ard.2008.097758

*– Chapter in Book*

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

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.

*– Book*

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

Ex: Lorig K. Patient Education. A practical approach. St Louis: Mosby-Year Book, 1992: 51.

*– Online document*

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 em 25 Janeiro de 2008

**Tables:** Tables should be cited in the text with Roman numerals. Each table should be double typed on a separate sheet, have a title and contain no vertical rulers. Horizontal lines should be used only as separators between titles and subtitles. Explain all abbreviations at the bottom.

The number of tables should be limited as described above.

**Figures:** Cite each figure in the text in consecutive order using Arabic numerals. Legends should be listed at the end of the manuscript, after the references, double typed. Send the figures in separate files to each figure in the format JPEG or TIFF.

The number of figures should be limited as described above.

**Editorials:** Editorials will be requested by the editor and will be comments on important issues or on articles published in the journal. Editorials should not exceed 1200 words, with a maximum of 15 references and no tables or figures.

**Review articles:** Review articles will be commissioned by the editor. However, authors interested in presenting a review article are welcomed to contact the editor.

Review articles should not exceed 4000 words, 6 tables/figures and 100 references.

**Letters:** Letters to the editor must be a comment on a journal article or a short clinical study or case report. They cannot exceed 600 words, a maximum of 10 references and one table or one figure.

**Images in Rheumatology:** Images of particularly interest can be submitted. They should contain a maximum of 4 figures, in JPEG or TIFF format. The accompanying text must have a maximum of 500 words.

**Modifications and proofreading:** Articles accepted subject to modifications, will be sent to the authors that will have 1 month to modify them according to suggestions. A letter should be written for each reviewer and the changes should be highlighted in the main manuscript with a different font color. Contributors will receive page proofs of the accepted papers for approval.

**Cover Letter draft:**

Send with manuscript to The Editor: **dias.costa.ml@gmail.com**

The authors certify that the manuscript entitled _____ (ref ARP_____) is original, all data are based on their own research and that the manuscript does not violate copyright or privacy regulations. They further state that the manuscript hasn't been partly or totally published or submitted to publication elsewhere.
The authors declare that they hold total copyright for this paper and that they assume collective responsibility for its contents and also that any conflict of interest is acknowledged.
And submitting this paper, the authors transfer copyrights interests to Acta Reumatológica Portuguesa.

***All authors must sign.***
Name (capitals): _____
Date:_____
Signature: _____