Rheumatoid Arthritis: clinical, radiological and therapeutic considerations

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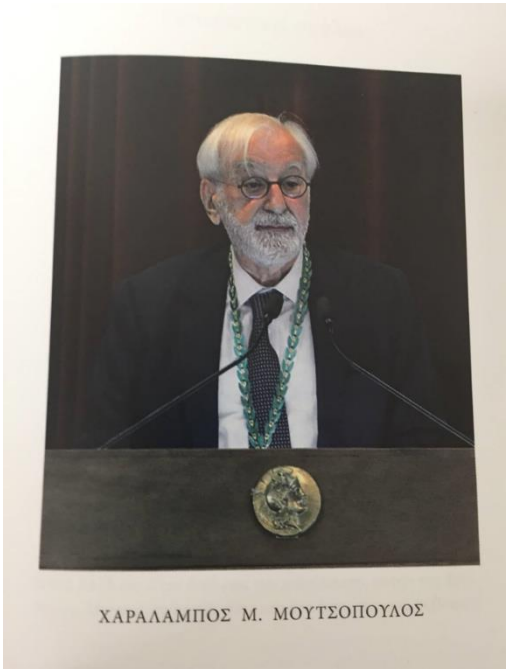
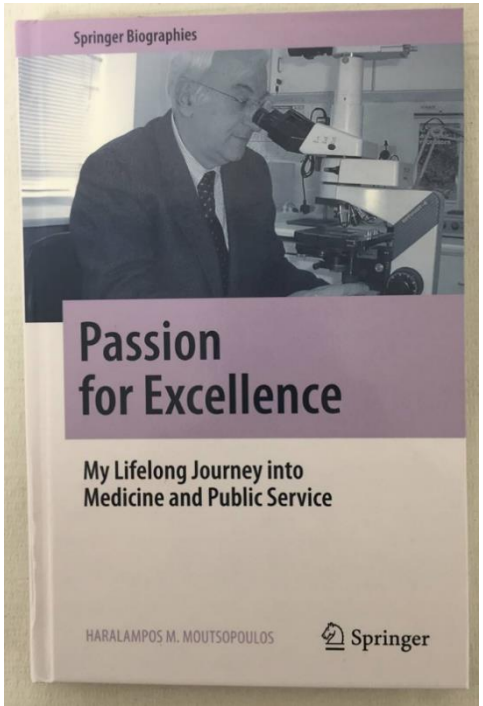
Declaration

I have no conflict of interest for this presentation.

Χαράλαμπος Μουτσόπουλος, Ιατρός - Ακαδημαϊκός





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› Ann Rheum Dis. 1984 Apr;43(2):285-7. doi: 10.1136/ard.43.2.285.

Antibodies to cellular antigens in Greek patients with autoimmune rheumatic diseases: anti-Ro(SSA) antibody a possible marker of penicillamine-D intolerance

H M Moutsopoulos, H Giotaki, P J Maddison, A C Mavridis, A A Drosos, F N Skopouli

PMID: 6608925 PMCID: PMC1001484 DOI: 10.1136/ard.43.2.285
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› Ann Rheum Dis. 1985 Apr;44(4):215-9. doi: 10.1136/ard.44.4.215.

Anti-Ro(SSA) positive rheumatoid arthritis (RA): a clinicoserological group of patients with high incidence of D-penicillamine side effects

H M Moutsopoulos, F N Skopouli, A K Sarras, C Tsampoulas, A K Mavridis, S H Constantopoulos, P J Maddison

PMID: 3872635 PMCID: PMC1001615 DOI: 10.1136/ard.44.4.215
Free PMC article

Comparative Study > J Autoimmun. 1988 Aug;1(4):381-8. doi: 10.1016/0896-8411(88)90008-x.

Clinical implications of the presence of anti-Ro (SSA) antibodies in patients with rheumatoid arthritis

F N Skopouli [1], A P Andonopoulos, H M Moutsopoulos

Affiliations + expand

PMID: 3266995 DOI: 10.1016/0896-8411(88)90008-x

CONCLUSIONS

Thus, anti-Ro(SSA) antibodies seem to characterize a distinct group of RA patients who are almost exclusively female, express more activated B-cell function, have a high prevalence of Sjögren's features.

RHEUMATOID ARTHRITIS IN GREEK AND BRITISH PATIENTS

A Comparative Clinical, Radiologic, and Serologic Study

A. A. DROSOS, J. S. LANCHBURY, G. S. PANAYI, and H. M. MOUTSOPOULOS

Objective. To compare the clinical, radiologic, and serologic expression of rheumatoid arthritis (RA) in 2 different populations.

Methods. Standard protocols and assessment criteria were used in this study of 108 Greek and 107 British patients with RA.

Results. British patients had more severe articular involvement than did Greeks, as judged by the duration of morning stiffness ($P < 0.005$), grip strength ($P < 0.0001$), and the numbers of swollen ($P < 0.001$) and tender ($P < 0.0001$) joints. The British RA patients also had more severe joint damage on radiologic examination, as evidenced by Steinbrocker stage III ($P < 0.005$) and IV ($P < 0.025$) disease and had more extraarticular manifestations ($P < 0.0001$), including rheumatoid nodules ($P < 0.0001$) and Raynaud's phenomenon ($P < 0.05$). Greek RA patients, however, more frequently presented with sicca manifestations ($P < 0.001$) and serum antibodies to Ro/SS-A ($P < 0.025$). Furthermore, Ro/SS-A antibodies were associated with a high incidence of side effects to D-penicillamine only in the Greeks.

Conclusion. Genetic and environmental factors may be responsible for these striking differences in disease expression between these 2 European populations with RA.

Differences in the clinical expression of disease between populations may reside in differences in environmental or genetic factors or both. An understanding of such factors will not only be useful in elucidating basic disease mechanisms, but could also lead to new

Arthritis and Rheumatism, Vol. 35, No. 7 (July 1992)

Table 1. Articular manifestations of rheumatoid arthritis in 108 Greek and 107 British patients*

Articular manifestation	Greek patients	British patients	*P*
Morning stiffness (minutes)	18.9 ± 41.4	41.5 ± 46.0	<0.005
Grip strength (mm Hg)			
Right hand	195.0 ± 76.5	113.9 ± 68.8	<0.0001
Left hand	189.5 ± 76.0	117.0 ± 67.1	<0.001
Total joint count			
Swollen	4.0 ± 5.4	8.9 ± 67.1	<0.001
Tender	6.8 ± 7.0	15.0 ± 7.7	<0.0001
Total joint score (0–3 scale)			
Swollen	4.7 ± 7.0	10.6 ± 6.2	<0.001
Tender	8.0 ± 21.0	19.4 ± 9.5	<0.001

* Values are the mean ± SD.

Drosos AA, et al. Arthritis Rheum 1992;35:745-8

Table 2. Extraarticular manifestations of rheumatoid arthritis in 108 Greek and 107 British patients*

Extraarticular manifestation	Greek patients	British patients	*P*
Total extraarticular manifestations	22 (20.4)	71 (66.4)	<0.0001
Rheumatoid nodules	6 (5.6)	55 (51.4)	<0.0001
Raynaud's phenomenon	3 (2.8)	15 (13.9)	<0.05
Sjögren's syndrome	43 (39.8)	17 (15.9)	<0.001

* Values are the number (%) of patients. The following were considered in calculating the total manifestations: rheumatoid nodules, Raynaud's phenomenon, serositis, skin vasculitis, lymphadenopathy, episcleritis, and livedo reticularis.

Drosos AA, et al. Arthritis Rheum 1992;35:745-8

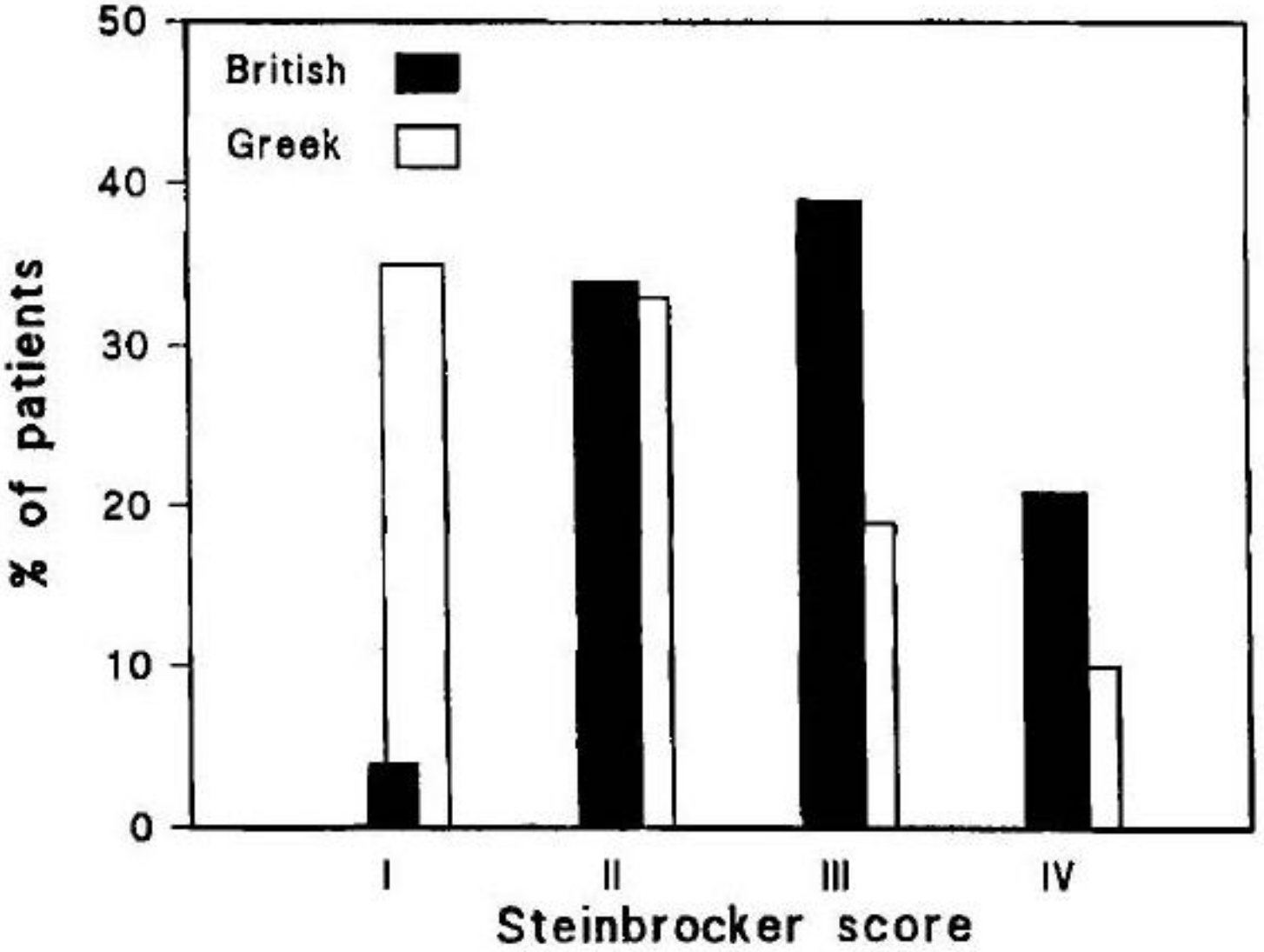


Figure 1. Staging of rheumatoid arthritis in radiographs of the hands of Greek and British patients. Radiographs were scored according to the method of Steinbrocker et al (see ref. 9).

Drosos AA, et al. Arthritis Rheum 1992;35:745-8

RA in the Mediterranean area

Comment > Arthritis Rheum. 1994 Jan;37(1):147-8. doi: 10.1002/art.1780370125.

Differences between Spanish and British patients in the severity of rheumatoid arthritis: comment on the article by Drosos et al

E Ronda, M T Ruiz, E Pascual, T Gibson

PMID: 8129757 DOI: 10.1002/art.1780370125

> J Rheumatol. 1995 Apr;22(4):607-10.

HLA-DRB1 alleles associated with rheumatoid arthritis in southern France. Absence of extraarticular disease despite expression of the shared epitope

J F Benazet [1], D Reviron, P Mercier, H Roux, J Roudier

Affiliations + expand

PMID: 7540691

J Rheumatol. 1997 Nov;24(11):2129-33.

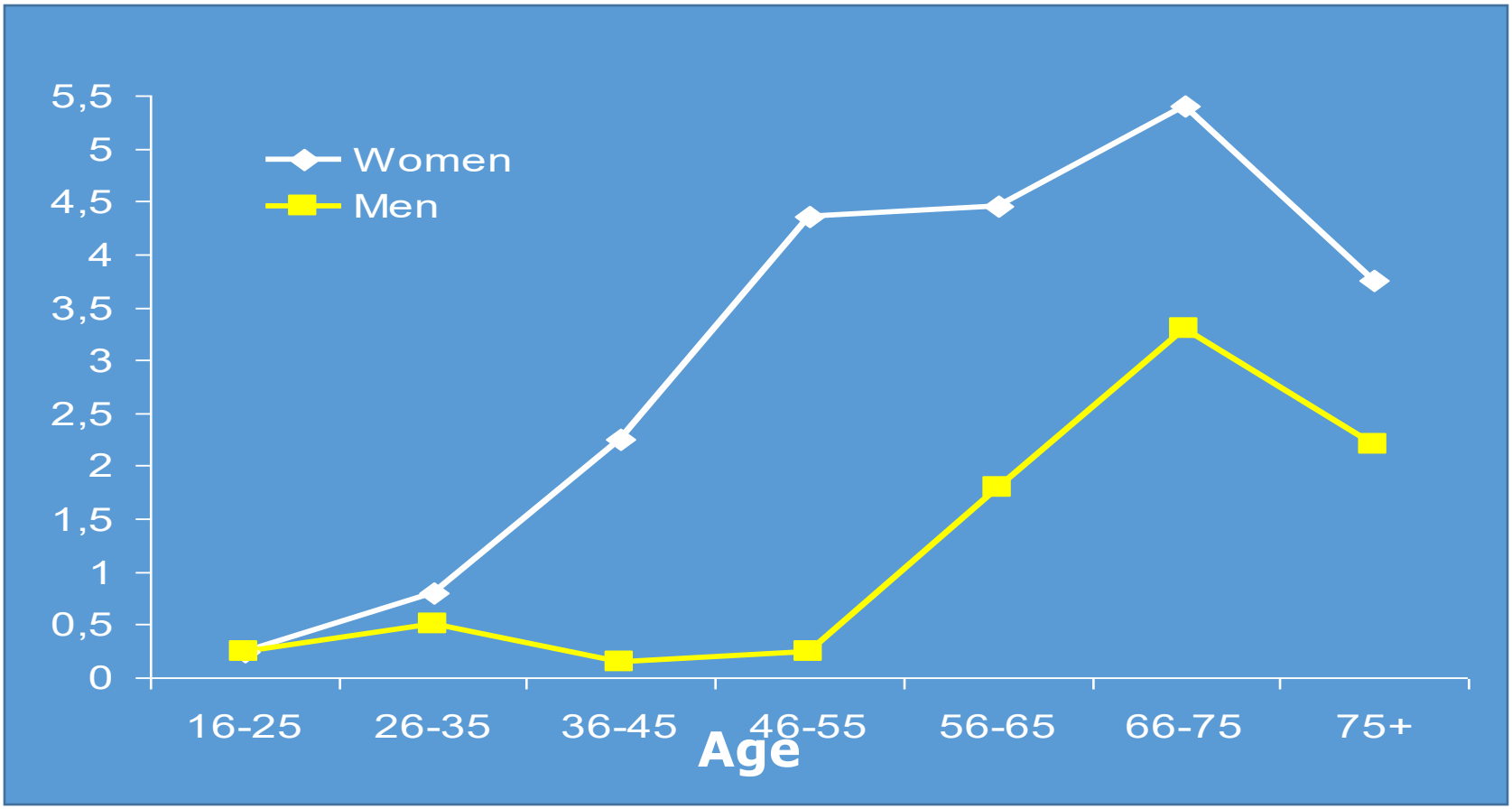
Epidemiology of adult rheumatoid arthritis in northwest Greece 1987–1995

A A Drosos [1], I Alamanos, P V Voulgari, D N Psychos, A Katsaraki, I Papadopoulos, G Dimou, C Siozos

Affiliations + expand

PMID: 9375871

Age and sex specific annual incidence rates of RA per 100,000 population during the period 1987-1995



These findings suggest a low prevalence and low incidence of RA in northwest Greece

› Scand J Rheumatol. 1994;23(5):264-8. doi: 10.3109/03009749409103727.

Low incidence of rheumatoid arthritis in France

F Guillemin [1], S Briançon, J M Klein, E Sauleau, J Pourel

Affiliations + expand

PMID: 7973481 DOI: 10.3109/03009749409103727

› Rheumatology (Oxford). 2002 Jan;41(1):88-95. doi: 10.1093/rheumatology/41.1.88.

The prevalence of rheumatoid arthritis in the general population of Spain

L Carmona [1], V Villaverde, C Hernández-García, J Ballina, R Gabriel, A Laffon; EPISER Study Group

Affiliations + expand

PMID: 11792885 DOI: 10.1093/rheumatology/41.1.88

Results

The prevalence of RA in Spain is comparable to that in other Mediterranean countries

Prevalence of Rheumatic Diseases in Greece: A Cross-Sectional Population Based Epidemiological Study. The ESORDIG Study

ALEXANDROS ANDRIANAKOS, PANAGIOTIS TRONTZAS, FOTIS CHRISTOYANNIS, PETROS DANTIS, COSTAS VOUDOURIS, ATHANASIOS GEORGOUNTZOS, GEORGE KAZIOLAS, ELIZABETH VAFIADOU, KYRIAKI PANTELIDOU, DIMITRIOS KARAMITSOS, LEONIDAS KONTELIS, PETROS KRACHTIS, ZOUBOULIO NIKOLIA, EVAGGELIA KASKANI, ELPINIKI TAVANIOTOU, CHRISTOS ANTONIADES, GEORGE KARANIKOLAS, and ANASTASIA KONTOYANNI

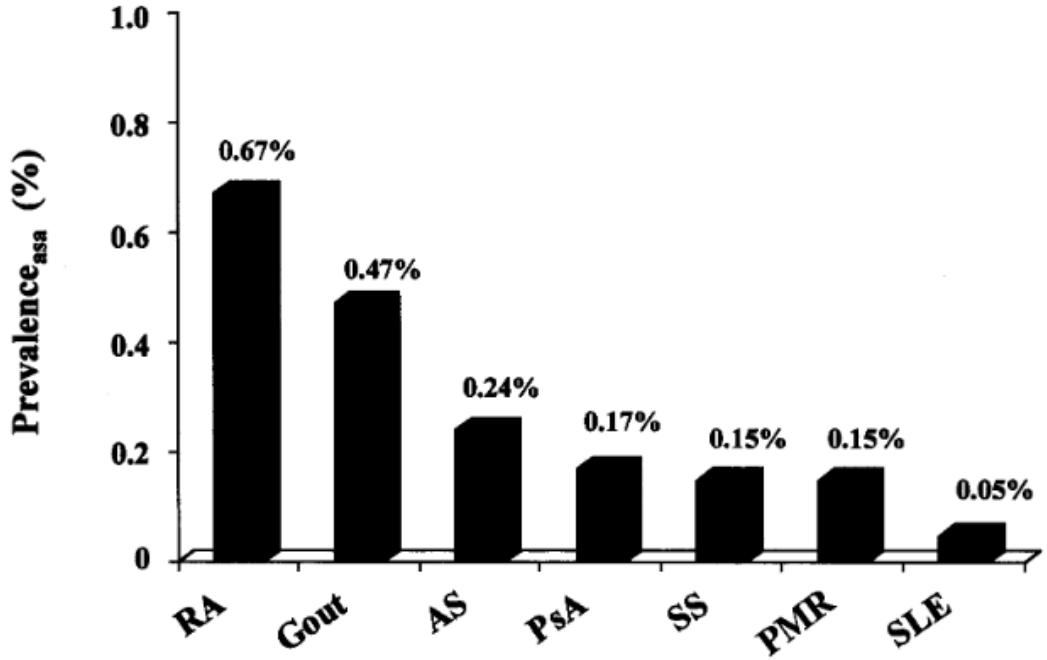


Figure 3. Age and sex adjusted prevalence (prevalence$_{asa}$) in the total target adult population of the most common inflammatory rheumatic diseases: rheumatoid arthritis (RA), gout, ankylosing spondylitis (AS), psoriatic arthritis (PsA), Sjögren's syndrome (SS), polymyalgia rheumatica (PMR), and systemic lupus erythematosus (SLE).

Review > Semin Arthritis Rheum. 2006 Dec;36(3):182-8. doi: 10.1016/j.semarthrit.2006.08.006. Epub 2006 Oct 11.

Incidence and prevalence of rheumatoid arthritis, based on the 1987 American College of Rheumatology criteria: a systematic review

Yannis Alamanos [1], Paraskevi V Voulgari, Alexandros A Drosos

Affiliations + expand

PMID: 17045630 DOI: 10.1016/j.semarthrit.2006.08.006

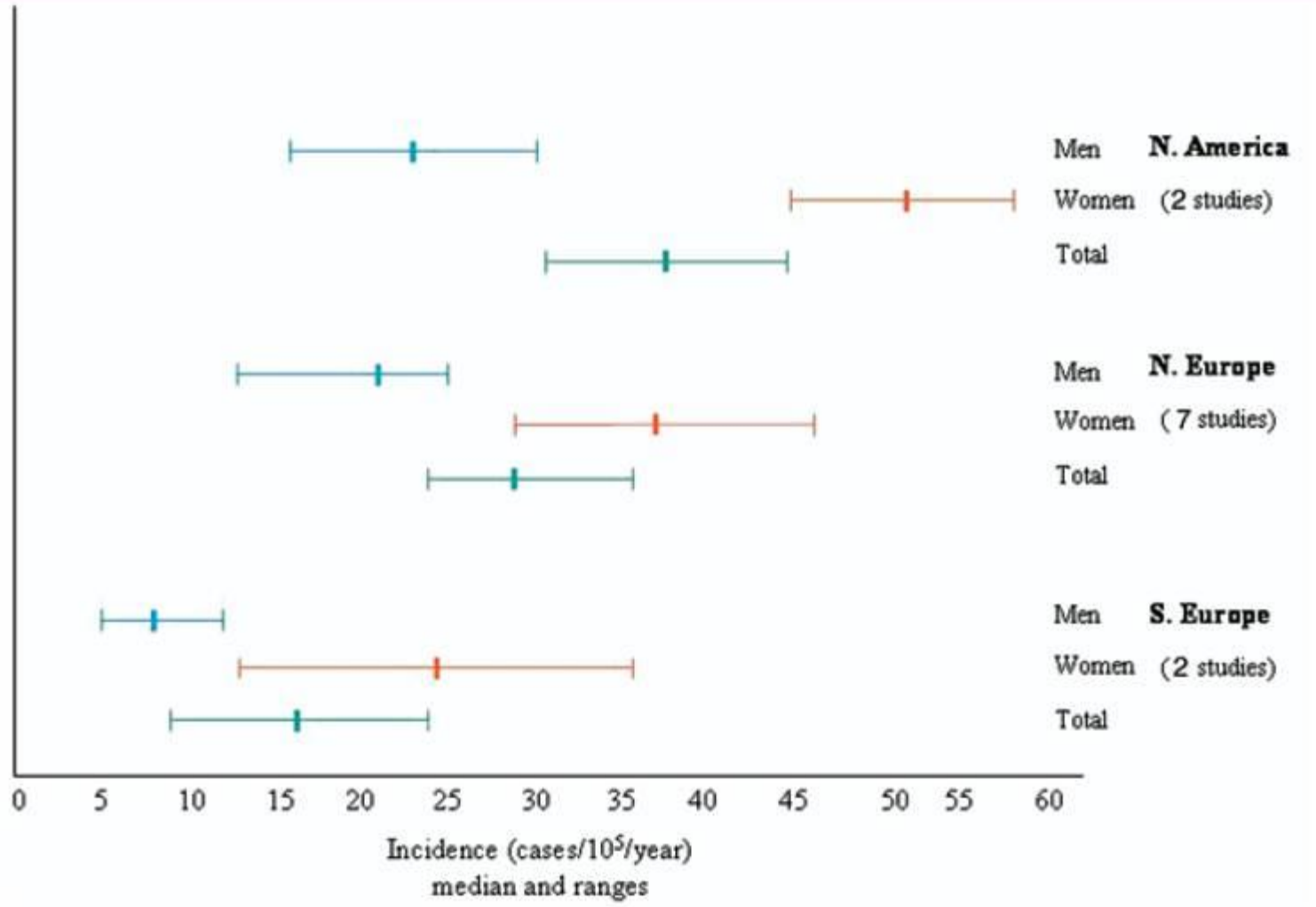


Figure 1 Incidence of RA in different areas of the world (medians and ranges of observed incidence rates in groups of countries). (Color version of figure is available online.)

Alamanos Y, et al. Semin Arthritis Rheum 2006;36:182-8

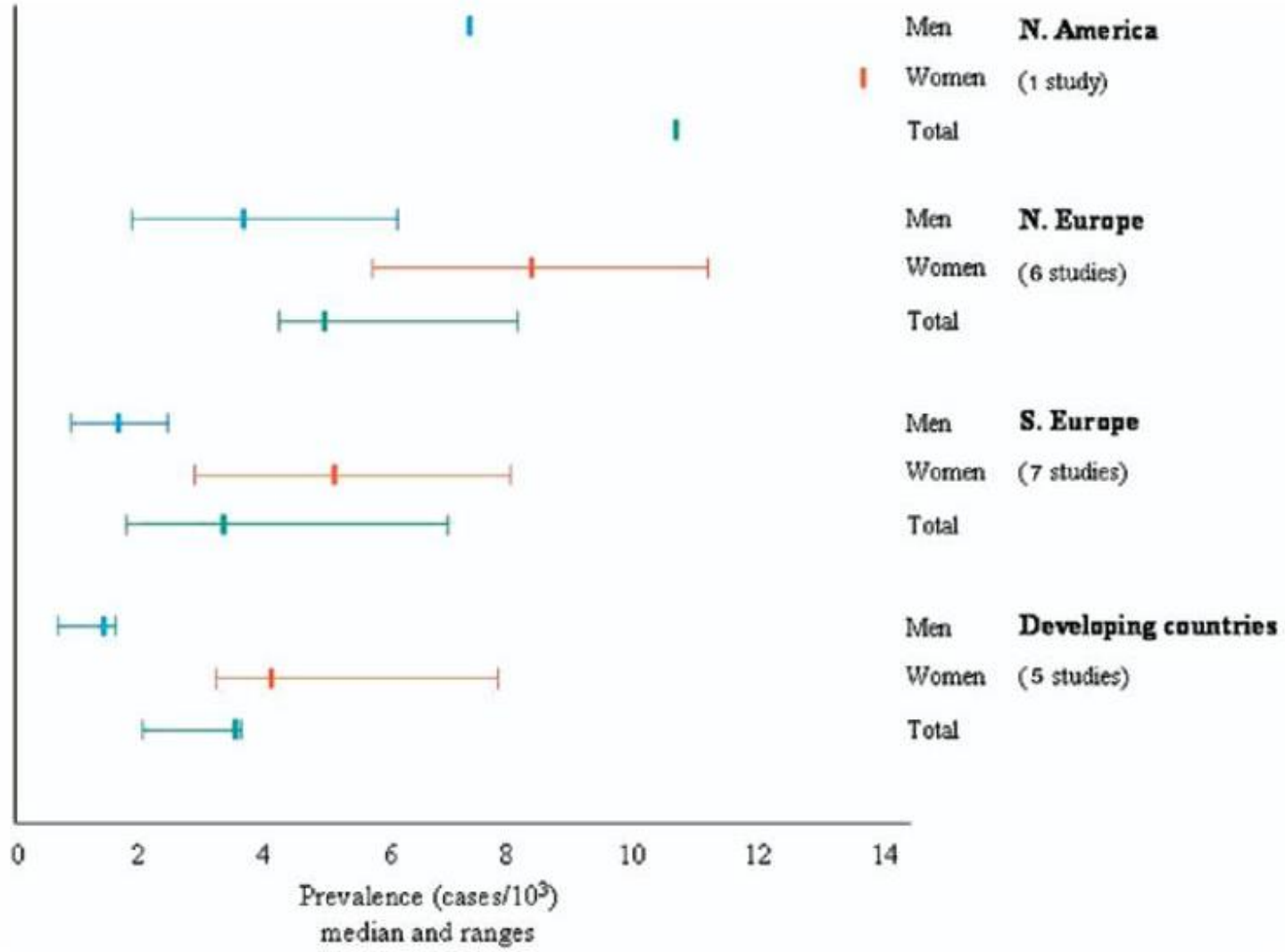


Figure 2 Prevalence of RA in different areas of the world (medians and ranges of prevalence estimates in groups of countries). (Color version of figure is available online.)

Alamanos Y, et al. Semin Arthritis Rheum 2006;36:182-8

The changing incidence of rheumatoid arthritis over time in north-west Greece: data from a referral centre

Al Venetsanopoulou[1], Y Alamanos[2], A Skalkou[1], PV Voulgari[1], Alexandros A Drosos[1]

[1]Rheumatology Clinic, Department of Internal Medicine, Medical School, University of Ioannina, Ioannina, Greece
[2]Institute of Epidemiology, Preventive Medicine and Public Health, Corfu, Greece

Table 1. Characteristics of rheumatoid arthritis (RA) patients diagnosed during the period 1980–2019 in north-west Greece (N = 1411).

Characteristic	Mean ± sd or n (%)
Age at diagnosis (years)	56.2 ± 15.5
Female sex	1025 (72.6)
ESR (mm/h)	47.6 ± 27.6
CRP (mg/L)	24.4 ± 31.5
RF positive	748/1378 (55.6)
ACPA positive	274/507 (54)
General symptoms	
Fever	199 (14.1)
Myalgias	31 (2.2)
Muscle weakness	29 (2.1)
Fatigue	5 (0.4)
Weight loss	5 (0.4)
Smoking status	
Ex-smoker	75/1194 (6.3)
Current smoker	252/1194 (21.1)
Never smoker	867/1194 (72.6)
Missing information	217
Alcohol consumption	
No	979/1158 (84.5)
Yes, occasionally	88/1158 (7.6)
Yes, regularly	78/1158 (6.7)
Missing information	253
Family history	
RA	47/1411 (3.3)

Table 2. Measurements of autoantibodies in patients with diagnosed rheumatoid arthritis according to the American College of Rheumatology 1987 criteria during the period 1980–2019.

Autoantibody		1980–1989	1990–1999	2000–2009	2010–2019	p
RF	Negative	111 (28.4)	152 (41.1)	175 (49.3)	159 (70.0)	
	Positive	280 (71.6)	218 (58.9)	181 (50.8)	69 (30.2)	< 0.001
	Not performed	8	15	30	12	
ACPA	Negative	9 (26.5)	29 (40.3)	74 (37.9)	121 (58.7)	
	Positive	25 (73.5)	43 (59.7)	121 (62.1)	85 (41.3)	< 0.001
	Not performed	365	313	190	33	

Data are shown as n (%).
ACPA, anti-citrullinated protein antibody; RF, rheumatoid factor.

Table 3. Mean annual incidence rate of rheumatoid arthritis according to American College of Rheumatology 1987 criteria per 100 000 inhabitants.

Values	Decade of diagnosis	Women	Men	Total
Overall	1980–1989	16.6 (14.8–18.7)	6.6 (5.4–7.9)	11.7 (10.7–13.0)
	1990–1999	14.8 (13.2–16.7)	5.6 (4.6–6.8)	10.4 (9.4–10.8)
	2000–2009	14.2 (12.7–16.0)	5.2 (4.2–6.3)	9.8 (8.9–10.8)
	2010–2019	7.9 (6.8–9.3)	4.1 (3.3–5.1)	6.1 (5.3–6.9)
RF positive	1980–1989	11.8 (10.3–13.5)	4.1 (3.5–5.6)	8.3 (7.4–9.3)
	1990–1999	8.5 (7.3–9.9)	3.1 (2.4–4.0)	5.8 (5.1–6.7)
	2000–2009	6.3 (5.3–7.5)	2.8 (2.3–3.9)	4.7 (4.0–5.3)
	2010–2019	1.8 (1.3–2.5)	1.6 (1.1–2.3)	1.7 (1.4–2.2)
RF negative	1980–1989	4.6 (3.8–5.8)	1.8 (1.2–2.6)	3.3 (3.5–4.8)
	1990–1999	6.1 (5.1–7.3)	1.9 (1.4–2.8)	4.1 (3.5–4.8)
	2000–2009	6.7 (5.6–7.9)	2.1 (1.6–2.9)	4.5 (3.8–5.2)
	2010–2019	5.7 (4.7–6.8)	2.3 (1.7–3.1)	4.0 (3.5–4.7)

Data are shown as incidence rate per 100 000 inhabitants (95% confidence interval).

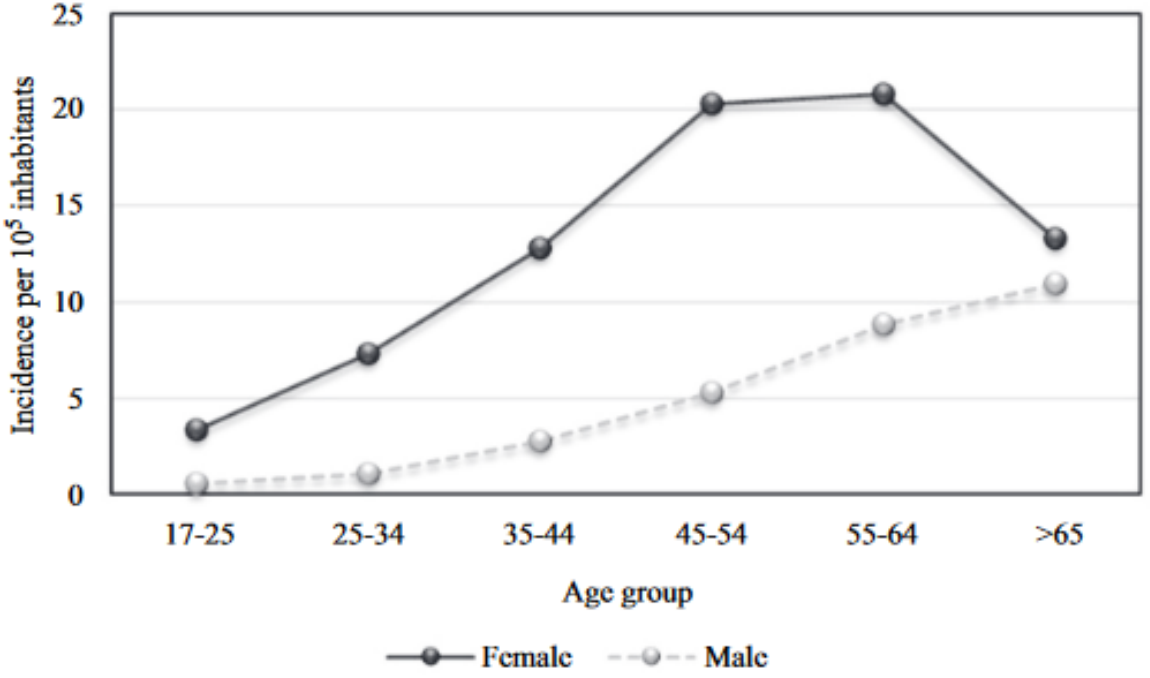


Figure 2. Line chart of age- and sex-specific mean annual incidence rates of rheumatoid arthritis per 100 000 inhabitants in north-west Greece during the period 1980–2019.

Table 4. Mean annual incidence rate of rheumatoid arthritis according to American College of Rheumatology 1987 criteria per 100 000 inhabitants for each of the six districts in north-west Greece.

Region	Decade of diagnosis	Women	Men	Total
Ioannina	1980–1989	29.1 (25.1–33.8)	11.8 (9.3–15.1)	20.8 (18.3–23.6)
	1990–1999	21.6 (18.4–25.5)	8.4 (6.4–11.0)	15.2 (13.2–17.5)
	2000–2009	20.0 (17.0–23.5)	7.3 (5.5–9.6)	13.8 (8.0–11.2)
	2010–2019	12.3 (10.0–15.1)	6.4 (4.8–8.6)	9.4 (8.0–11.2)
Arta	1980–1989	10.9 (7.8–15.3)	3.9 (2.2–7.0)	7.6 (5.6–10.1)
	1990–1999	14.0 (9.7–18.2)	3.1 (2.1–7.0)	9.1 (7.0–11.8)
	2000–2009	11.6 (8.3–16.0)	3.7 (2.1–6.7)	7.7 (5.8–10.3)
	2010–2019	7.7 (5.2–11.7)	5.3 (3.2–8.7)	6.6 (4.8–9.0)
Thesprotia	1980–1989	14.7 (9.8–22.2)	7.3 (4.1–13.1)	11.8 (7.9–15.5)
	1990–1999	14.8 (10.0–21.8)	9.5 (5.9–15.4)	12.2 (9.0–16.5)
	2000–2009	15.9 (11.1–23.0)	7.2 (4.2–12.3)	11.6 (8.6–15.7)
	2010–2019	5.9 (3.3–10.7)	4.9 (2.6–9.3)	5.5 (3.5–8.4)
Preveza	1980–1989	17.9 (13.1–24.6)	6.0 (3.5–10.5)	12.8 (9.2–16.0)
	1990–1999	13.9 (9.8–19.6)	5.4 (3.1–9.3)	9.7 (7.2–13.3)
	2000–2009	18.6 (13.9–24.8)	5.9 (3.5–9.9)	12.4 (9.6–15.9)
	2010–2019	5.7 (3.4–9.6)	1.79 (0.0–3.2)	3.7 (2.4–5.9)
Corfu	1980–1989	3.2 (1.8–5.4)	1.4 (0.0–3.2)	2.3 (1.5–3.6)
	1990–1999	6.2 (4.3–9.0)	2.1 (1.1–4.1)	4.3 (3.5–6.0)
	2000–2009	5.4 (3.6–7.9)	1.6 (0.8–3.3)	3.5 (2.5–5.4)
	2010–2019	3.7 (2.3–5.9)	0.7 (0.2–2.1)	2.8 (1.5–3.5)
Lefkada	1980–1989	12.9 (6.2–22.3)	2.5 (0.7–9.1)	7.9 (4.6–13.5)
	1990–1999	13.7 (7.8–23.9)	2.3 (0.6–8.4)	8.0 (4.8–13.5)
	2000–2009	9.5 (4.5–18.0)	5.2 (2.2–12.2)	7.3 (4.4–12.3)
	2010–2019	4.0 (0.6–10.3)	3.0 (1.4–8.8)	3.5 (1.7–7.2)

Data are shown as incidence rate per 100 000 inhabitants (95% confidence interval).

Rheumatology International
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Rheumatology
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CORRESPONDENCE

Decline in the incidence of rheumatoid arthritis in north-western Greece in 1980–2019

Aliki I. Venetsanopoulou[1] · Yannis Alamanos[2] · Paraskevi V. Voulgari[1] · Alexandros A. Drosos[1,3]

Received: 17 March 2023 / Accepted: 1 April 2023

WHAT IS THE CAUSE OF THIS DIFFERENCE BETWEEN THE NORTHERN AND SOUTHERN EUROPE ?

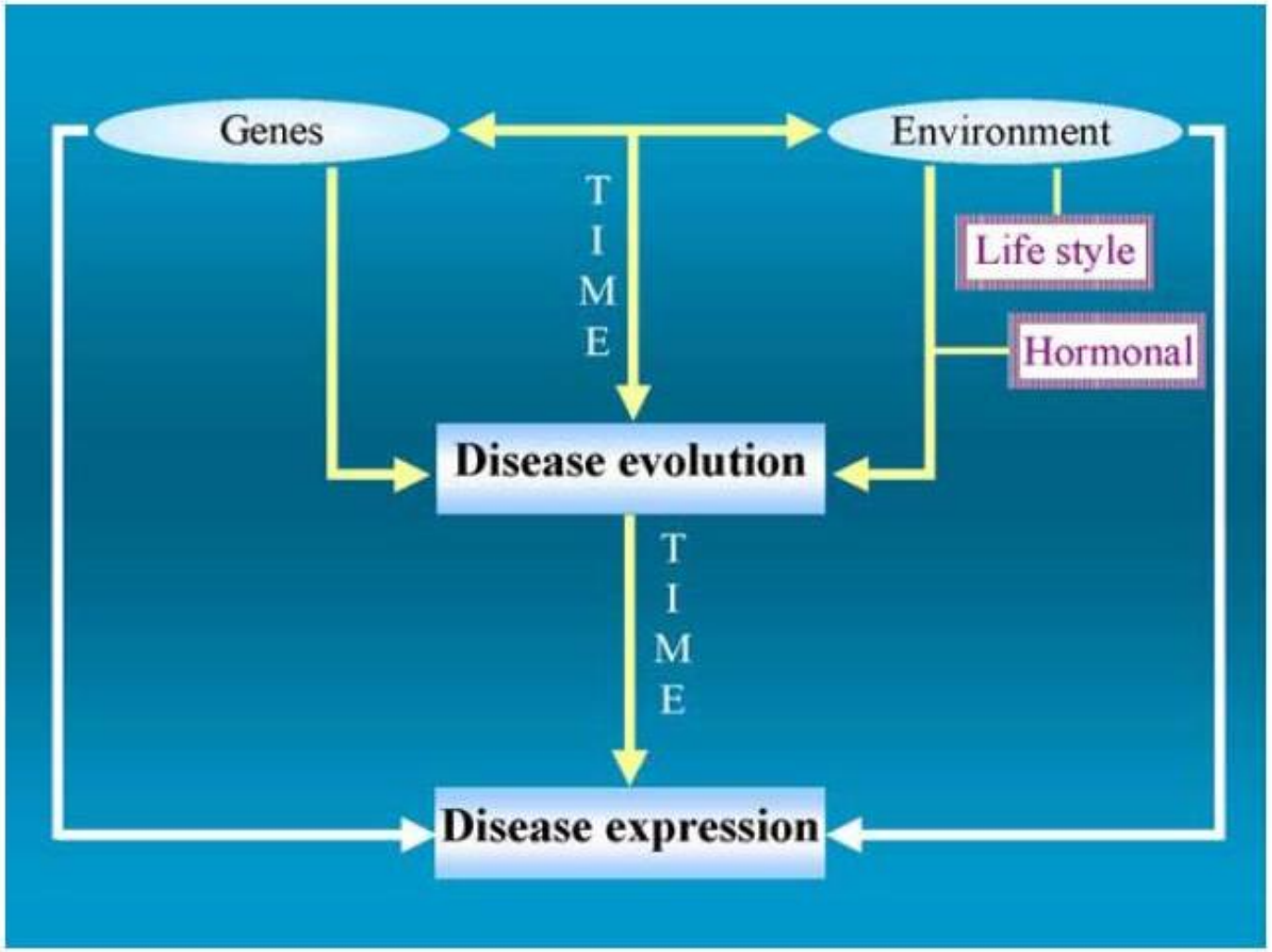

Fig. 1. Hypothetical model of rheumatoid arthritis causation: interaction of genes with environmental factors, as well as with hormonal and lifestyle factors over time in an individual, may give rise to disease evolution and its expression.

Alamanos Y, Drosos AA. Autoimmun Rev 2005;4:130-6

EXPERT REVIEW OF CLINICAL IMMUNOLOGY
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REVIEW

Epidemiology of rheumatoid arthritis: genetic and environmental influences

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ABSTRACT

Introduction: Rheumatoid arthritis (RA) is a chronic systemic disease characterized by articular involvement and extra-articular manifestations. The incidence and prevalence of the disease vary across populations, and there is an ongoing debate on whether a change of RA occurrence over time exists or is due to methodological issues and other biases. Moreover, the disease's onset is related to an interaction of genetic and environmental factors that influence its expression.

Areas covered: This review explores the latest knowledge on RA epidemiology and the possible risk factors associated with its presentation to identify potential warning signs that may in the future help disease management.

Expert opinion: Current epidemiological evidence suggests a significant impact of smoking, sex hormones, and lifestyle status in RA occurrence. However, the association between these variables has not yet been thoroughly studied. Still, their effect must be interpreted as they may present subsequently integral indicators for a more rational approach of the disease.

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REVIEW

Epidemiology and Risk Factors for Rheumatoid Arthritis Development

Aliki I. Venetsanopoulou[1], Yannis Alamanos[2], Paraskevi V. Voulgari[1], Alexandros A. Drosos[1]

[1]Department of Rheumatology, School of Health Sciences, Faculty of Medicine, University of Ioannina, Ioannina, Greece, [2]Institute of Epidemiology, Preventive Medicine and Public Health, Corfu, Greece

ABSTRACT

Rheumatoid arthritis (RA) is a prevalent chronic inflammatory arthritis worldwide, significantly impacting patients and population health. The disease affects women primarily, with a female-to-male ratio of three to one. Its pathogenesis is multifactorial, including genetic and environmental risk factors. Epidemiological studies highlight the link between the environment and genetic susceptibility to RA. The so-called shared epitope is the most significant risk factor that seems to act synergetic with other environmental factors in the disease occurrence. In addition, recent findings suggest a potential role of new substantial environmental factors, such as the observed pollution of the planet's natural resources, on the susceptibility and progression of the disease. This review summarises the most decisive evidence on epidemiology and genetic, environmental, and lifestyle risk factors for RA. It shows that studying genetic and environmental factors in correlation could lead to prevention strategies that may impact the natural history of the disease.

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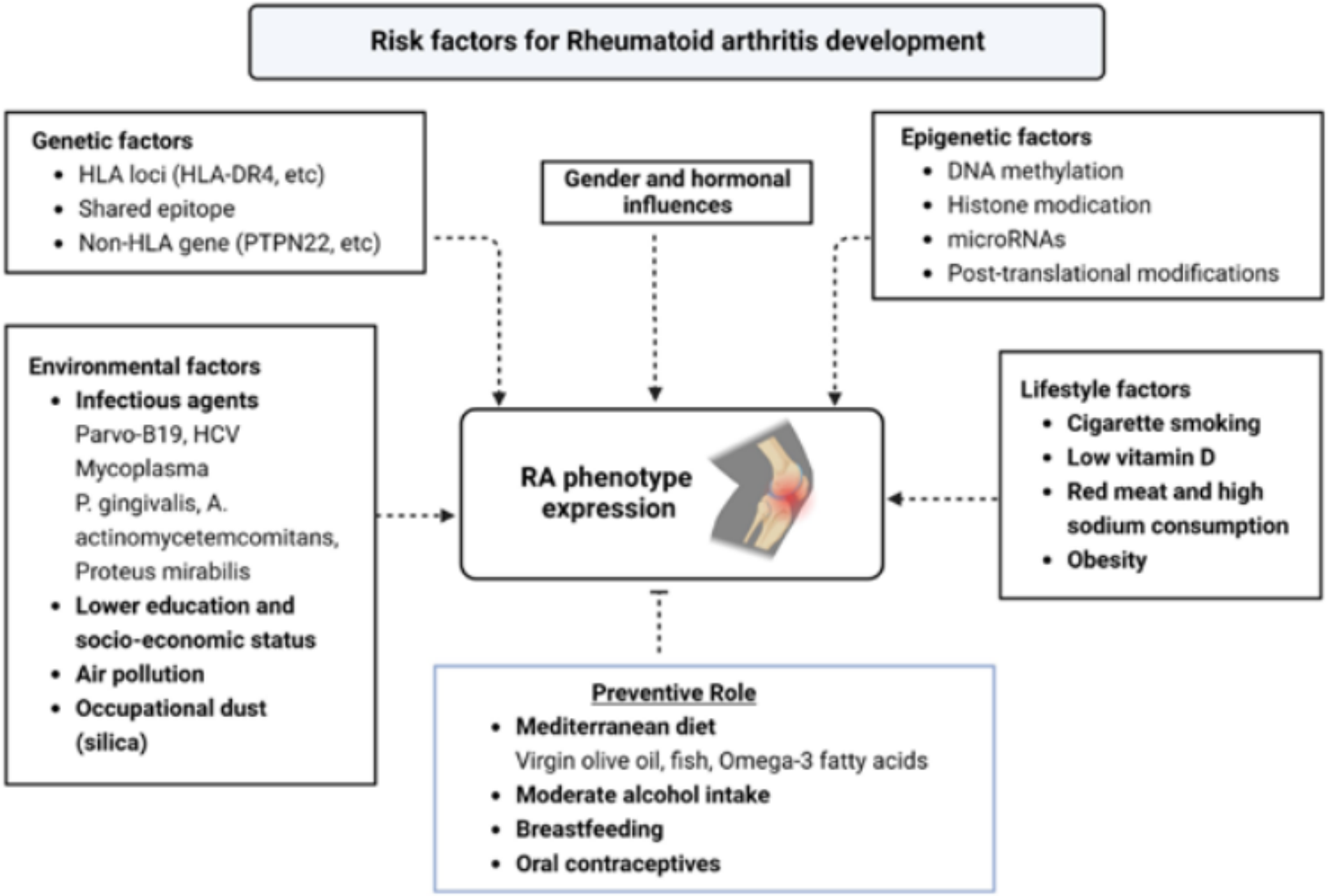

Figure 1. Risk factors associated with RA development and phenotype expression.

Genetic susceptibility: HLA genes

- SE motif may be directly involved in **pathogenesis** by the presentation of a **peptide to arthritogenic T cells**
- **SE influences:**
- The **susceptibility toward** disease
- Its **severity**, including the presence of **extra-articular** manifestations such as nodulosis and vasculitis
- The **degree of radiographic joint destruction**, and
- The production of **rheumatoid factor,and ACPA**

› Arthritis Rheum. 1992 Jul;35(7):749-55. doi: 10.1002/art.1780350706.

HLA class II sequence polymorphisms and susceptibility to rheumatoid arthritis in Greeks. The HLA-DR beta shared-epitope hypothesis accounts for the disease in only a minority of Greek patients

K A Boki [1], G S Panayi, R W Vaughan, A A Drosos, H M Moutsopoulos, J S Lanchbury

Affiliations + expand

PMID: 1352449 DOI: 10.1002/art.1780350706

Results

We found that 57% of the Greek patients lack the putative HLA-DRβ motif, which suggests that considerable immunogenetic heterogeneity underlies disease susceptibility in this population.

Comparative Study > Rheumatology (Oxford). 2000 Aug;39(8):844-9.
doi: 10.1093/rheumatology/39.8.844.

Class II MHC antigens in early rheumatoid arthritis in Bath (UK) and Madrid (Spain)

A Balsa [1], N J Minaur, D Pascual-Salcedo, C McCabe, A Balas, B Fiddament, J L Vicario, N L Cox, E Martín-Mola, N D Hall

Affiliations + expand

PMID: 10952737 DOI: 10.1093/rheumatology/39.8.844

Results

Rheumatoid patients in Bath differ from their Spanish counterparts in class II antigen expression and allele frequency.

› Arthritis Rheum. 2001 Feb;44(2):307-14.
doi: 10.1002/1529-0131(200102)44:2<307::AID-ANR47>3.0.CO;2-K.

Rheumatoid arthritis in southern Spain: toward elucidation of a unifying role of the HLA class II region in disease predisposition

M Pascual [1], A Nieto, M A López-Nevot, L Ramal, L Matarán, A Caballero, A Alonso, J Martín, E Zanelli

Affiliations + expand

PMID: 11229460 DOI: 10.1002/1529-0131(200102)44:2<307::AID-ANR47>3.0.CO;2-K

Free article

Conclusion

The low prevalences of RA and of mild disease observed in Spain, and in southern Europe in general, can be explained in great part by the low frequency of DQ3–DR4 haplotypes, especially those carrying DRB1*0401.

Meta-Analysis > Semin Arthritis Rheum. 2002 Jun;31(6):361-70. doi: 10.1053/sarh.2002.31725.

Shared epitopes and rheumatoid arthritis: disease associations in Greece and meta-analysis of Mediterranean European populations

John P A Ioannidis [1], Katerina Tarassi, Ioannis A Papadopoulos, Paraskevi V Voulgari, Kyriaki A Boki, Chryssa A Papasteriades, Alexandros A Drosos

Affiliations + expand

PMID: 12077708 DOI: 10.1053/sarh.2002.31725

We examined the strength of the association between shared epitopes (SE) and RA susceptibility, articular disease severity and EAM in Mediterranean populations.

Meta-Analysis > Arthritis Rheum. 2004 Feb;50(2):400-12. doi: 10.1002/art.20006.

Impact of shared epitope genotype and ethnicity on erosive disease: a meta-analysis of 3,240 rheumatoid arthritis patients

Jennifer D Gorman [1], Raymond F Lum, John J Chen, Maria E Suarez-Almazor, Glenys Thomson, Lindsey A Criswell

Affiliations + expand

PMID: 14872482 DOI: 10.1002/art.20006

Free article

Results

The SE is associated with the development of erosive disease in many ethnic groups; however, striking exceptions exist.

Seminars in Arthritis and Rheumatism 43 (2013) 29–38

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Seminars in Arthritis and Rheumatism

journal homepage: www.elsevier.com/locate/semarthrit

Rheumatoid Arthritis

Genetics in rheumatoid arthritis beyond HLA genes: What meta-analyses have shown?

Anthoula Chatzikyriakidou [a,b], Paraskevi V. Voulgari, MD[b], Alexandros Lambropoulos [a], Alexandros A. Drosos, MD, FACR[b,*]

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ARTICLE INFO

Keywords:
Rheumatoid arthritis
Meta-analysis
Gene
Polymorphism

ABSTRACT

Objective: Rheumatoid arthritis (RA) is a complex disorder with many genetic and environmental factors to account for disease susceptibility. Individual genetic association studies usually suffer from small sample size leading to biased results of polymorphisms association with RA liability. Therefore, meta-analyses seem to resolve this limitation, up to a point, increasing the power of statistical analyses. In this review, we summarize the current knowledge of non-HLA genetic factors contributing to RA predisposition based on meta-analyses.

Methods: Using the key words: rheumatoid arthritis, meta-analysis, and polymorphism, we searched the PubMed database for the associated articles. Up to the middle of November 2012, seventy-nine articles fulfilled the criteria and highlighted the current findings on the genetic factors contributing to RA susceptibility.

Results: The association with RA was confirmed for 32 gene polymorphisms, being population specific in some cases. However, meta-analyses did not confirm an association in case of 16 gene variants, previously studied in individual studies for their association with RA.

Conclusions: The use of bioinformatics tools and functional studies of the summarized implicated genes in RA pathogenesis could shed light on the molecular pathways related to the disorder, helping to the development of new drug targets for a better treatment of RA.

Glucocorticoid receptor variants may predispose to rheumatoid arthritis susceptibility

A Chatzikyriakidou[1], I Georgiou[1], PV Voulgari[2], AN Georgiadis[2], ES Argyriou[2], AA Drosos[2]

[1]Genetics Unit, Department of Obstetrics and Gynaecology and [2]Rheumatology Clinic, Department of Internal Medicine, Medical School, University of Ioannina, Ioannina, Greece

Objectives: Deregulation of glucocorticoid (GC) secretion could be associated with rheumatoid arthritis (RA). The GC receptor (GR) has two isoforms. In the present study, we explored the role of GR-α polymorphisms rs33388, rs33389, and Bcl I, and the GR-β variant rs6198 in RA susceptibility.

Methods: One hundred and thirty-six RA patients and 148 ethnic matching controls were studied. Polymorphisms rs33388 and Bcl I were genotyped by polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP), and variants rs33389 and rs6198 by polymerase chain reaction single-strand conformation polymorphism (PCR-SSCP) coupled with sequencing. Arlequin and SPSS softwares were used in the statistical analysis.

Results: The polymorphisms studied were in Hardy–Weinberg equilibrium in both groups. A marginally statistical significant difference was observed in the distribution of rs33388 genotypes between RA patients and controls ($p=0.053$). When the A and T alleles were compared, the statistical significance was $p=0.025$. Specific complex genotypes were also differentially distributed: the GR-α complex genotypes (a) [homozygote (homo) wild-type (wt) rs33388–homo wt rs33389] (11% RA vs. 21% controls; $p=0.023$), (b) [homo wt rs33388–homo wt rs33389–homo non-wt Bcl I] (0.7% RA vs. 4.7% controls; $p=0.042$), and (c) the GR-β complex genotype [homo wt rs33388–homo wt rs33389–homo non-wt Bcl I–homo wt rs6198] (0.7% RA vs. 4.7% controls; $p=0.042$).

Conclusions: GR-α and GR-β polymorphisms are potentially associated with RA susceptibility. However, additional studies in larger and other ethnic groups of patients are needed to confirm the results of the present study.

Autoimmunity Reviews 11 (2012) 636–641

Contents lists available at SciVerse ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

miRNAs and related polymorphisms in rheumatoid arthritis susceptibility

Anthoula Chatzikyriakidou [a], Paraskevi V. Voulgari [b], Ioannis Georgiou [a], Alexandros A. Drosos [b,*]

[a] Genetics Unit, Department of Obstetrics and Gynecology, Medical School, University of Ioannina, Ioannina, Greece
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ARTICLE INFO

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Rheumatoid arthritis
microRNA
Single nucleotide polymorphism

ABSTRACT

The epigenetic mechanisms in regulation of genes' expression seem to be another field of research that gains land in genetic association studies of rheumatoid arthritis (RA) susceptibility factors. Recently, a new class of molecules has been discovered, the microRNAs (miRNAs). miRNAs are related to post-transcriptional regulation of genes' expression. Different expression patterns of mir-146a, miRNA-155, miRNA-124a, mir-203, mir-223, mir-346, mir-132, mir-363, mir-498, mir-15a, and mir-16 were documented in several tissue sample types of RA patients. The polymorphisms of these miRNAs and their gene targets, which previously have been associated with RA or other autoimmune diseases, are also reviewed. Finally, using web-based tools we propose polymorphisms of the discussed miRNAs and their gene-targets that worth to be studied for their role in RA predisposition.

Joint Bone Spine 77 (2010) 411–413

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www.em-consulte.com

Original article

A polymorphism in the 3'-UTR of interleukin-1 receptor-associated kinase (IRAK1), a target gene of miR-146a, is associated with rheumatoid arthritis susceptibility

Anthoula Chatzikyriakidou[a], Paraskevi V. Voulgari[b], Ioannis Georgiou[a], Alexandros A. Drosos[b,*]

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ARTICLE INFO

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Keywords:
Rheumatoid arthritis
MicroRNA
MiR-146a
IL-1R-associated kinase
Polymorphism

ABSTRACT

Objectives: Rheumatoid arthritis (RA) is a chronic inflammatory disorder with many genetic factors predisposing to disease susceptibility. MicroRNAs are a new discovered class of molecules that participate in post-transcriptional regulation of genes' expression. MicroRNA-146a was found to be increased in synovial fibroblasts, synovial tissue and PBMC from patients with RA. The aim of the present study was to reveal if there is any association of miRNA-146a variant rs2910164 and the two interleukin (IL) 1 receptor associated kinase (IRAK1, a target gene of mir-146a) polymorphisms rs3027898 and rs1059703 with RA predisposition.
Methods: One hundred and thirty-six RA patients and 147 controls were enrolled in the study.
Results: Strong statistically significant difference was observed in IRAK1 rs3027898 A>C polymorphism distribution between RA patients and controls ($p = 0.044$), which was higher comparing the distribution of allele A vs. allele C between the studied groups ($p = 0.017$).
Conclusion: This is the first study that addresses association of a variant in a target of miR-146a, IRAK1 gene, with RA susceptibility. Further studies in other ethnic groups of patients could help to understand the extent of the proposed association.

International Journal of
Rheumatic Diseases

International Journal of Rheumatic Diseases 2016; **19**: 146–149

ORIGINAL ARTICLE

Evidence of *ERBB3* gene association with rheumatoid arthritis predisposition

Anthoula CHATZIKYRIAKIDOU,[1] Paraskevi V. VOULGARI[2] and Alexandros A. DROSOS[2]

[1]*Laboratory of General Biology and Genetics, Medical School, Aristotle University of Thessaloniki, Thessaloniki, and* [2]*Rheumatology Clinic, Department of Internal Medicine, Medical School, University of Ioannina, Ioannina, Greece*

Abstract

Aim: *ERBB3* (v-erb-b2 erythroblastic leukemia viral oncogene homolog 3) gene was reported to be related with susceptibility to several autoimmune diseases. Taking this into account, we searched, for the first time, the *ERBB3* gene association with rheumatoid arthritis liability.

Methods: One hundred and eighty-six RA patients and 147 controls were enrolled in the study. Polymerase chain reaction – restriction fragment length polymorphism assay was conducted in rs2271189 and rs2292239 genotyping.

Results: A statistically significant difference was observed in rs2271189 allele distribution between RA patients and controls ($P = 0.029$, odds ratio: 1.460, 95% confidence interval: 1.040–2.050).

Conclusion: As far as we know, this is the first study which correlates *ERBB3* gene with RA susceptibility, adding to a previous report of chromosome 12q13 association with RA liability. Furthermore, we confirmed that polymorphism rs2271189 can predict better *ERBB3* gene association with disorders than the previously reported *ERBB3* variants. More studies in other ethnic groups of patients are needed so as to reveal the extent of the herein observed genetic association.

Key words: *ERBB3*, polymorphism, rheumatoid arthritis.

Life style factors

- Smoking
- Obesity
- Physical activity
- Diet
- Others

RA and Environment: smoking

› Clin Exp Rheumatol. 2005 Nov-Dec;23(6):861-6.

Does cigarette smoking influence disease expression, activity and severity in early rheumatoid arthritis patients?

N G Papadopoulos [1], Y Alamanos, P V Voulgari, E K Epagelis, N Tsifetaki, A A Drosos

Affiliations + expand

PMID: 16396705

Aim of the study

- To investigate the association **of smoking** with disease expression, activity and severity in a cohort of patients with early RA
- We examined 293 patients
- Disease duration: < 1 year
- Without prior treatment with DMARDs or steroids

Papadopoulos NG, et al. Clin Exp Rheumatol 2005;23:861-6

Conclusions

- **Cigarette smoking** was associated with **increased disease activity**, **severity and worse prognosis**, independently from several other possible confounders.

- The **high prevalence of rheumatoid factor** in tobacco-exposure patients shows an association of smoking with B-cell hyperactivity.

- Especially, the **presence of IgA** RF in smoking patients suggests that smoking may cause a chronic antigenic stimulation of respiratory tract.

Papadopoulos NG, et al. Clin Exp Rheumatol 2005;23:861-6

QUEST-RA From January 2005 to April 2008: 6004 patients from 70 clinics in 25 countries

Obesity and Rheumatoid arthritis

Editorial > Ann Rheum Dis. 2014 Nov;73(11):1911-3. doi: 10.1136/annrheumdis-2014-205741.

The impact of obesity on the development and progression of rheumatoid arthritis

Axel Finckh [1], Carl Turesson [2]

Affiliations + expand

PMID: 25288687 DOI: 10.1136/annrheumdis-2014-205741

Review > Clin Exp Rheumatol. 2011 Jul-Aug;29(4):712-27. Epub 2011 Sep 1.

Obesity, adipose tissue and rheumatoid arthritis: coincidence or more complex relationship?

C S Derdemezis [1], P V Voulgari, A A Drosos, D N Kiortsis

Affiliations + expand

PMID: 21640051

Gender, body mass index and rheumatoid arthritis disease activity: results from the QUEST-RA study

D. Jawaheer[1*], J. Olsen[1], M. Lahiff[2], S. Forsberg[3], J. Lähteenmäki[3], I.G. da Silveira[4], F.A. Rocha[5], I.M. Magalhães Laurindo[6], L.M. Henrique da Mota[7], A.A. Drosos[8], E. Murphy[9], C. Sheehy[10], E. Quirke[10], M. Cutolo[11], S. Rexhepi[12], J. Dadoniene[13], S.M.M. Verstappen[14], T. Sokka[15,16], for QUEST-RA

*[1]University of California Los Angeles, Los Angeles, California, USA; [2]University of California Berkeley, Berkeley, California, USA; [3]North Karelia Central Hospital, Joensuu, Finland; [4]Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS), Porto Alegre, Brazil; [5]Universidade Federal do Ceará, Fortaleza, Brazil; [6]Universidade Estadual de São Paulo, São Paulo, Brazil; [7]Hospital Universitário de Brasília, Brasilia, Brazil; [8]University of Ioannina, Ioannina, Greece; [9]Waterford Regional Hospital, Waterford, Ireland; [10]Connolly Hospital, Dublin, Ireland; [11]University of Genova, Genova, Italy; [12]Rheumatology Department, Pristine, Serbia; [13]Institute of Experimental and Clinical Medicine at Vilnius University, Vilnius, Lithuania; [14]University Medical Centre Utrecht, Utrecht, The Netherlands; [15]Jyväskylä Central Hospital, Jyväskylä, Finland; [16]Medcare Oy, Äänekoski, Finland; *currently at Children's Hospital Oakland Research Institute, Oakland, California, USA.*

Clinical and Experimental Rheumatology 2010; **28**: 454-461.

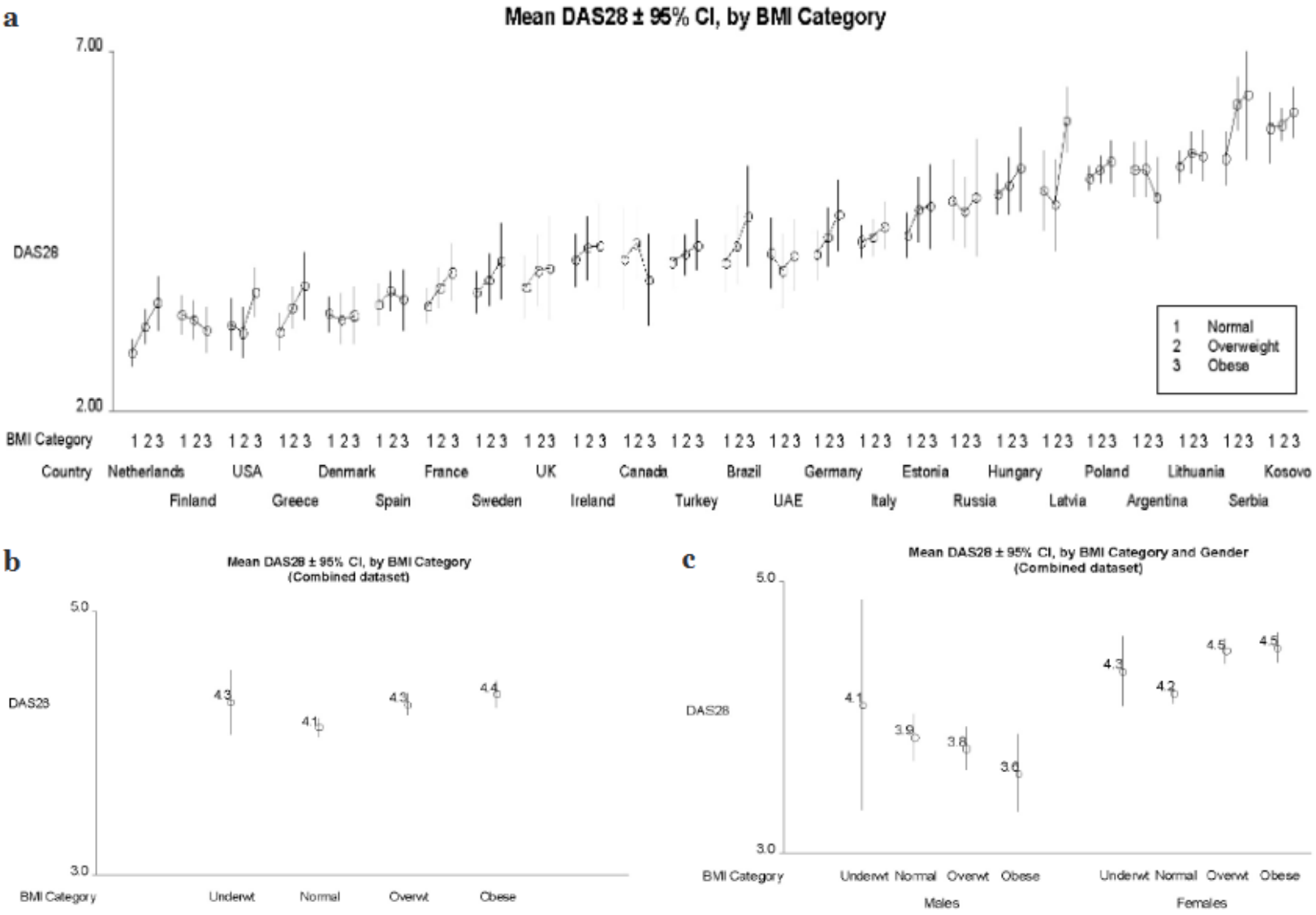


Fig. 1. Plots showing the mean DAS28 scores and the 95% confidence intervals (y-axis) by BMI category (x-axis), *i.e.* normal, overweight and obese, (**a**) for each country participating in the QUEST-RA study, (**b**) for the combined dataset and (**c**) for female and male patients separately

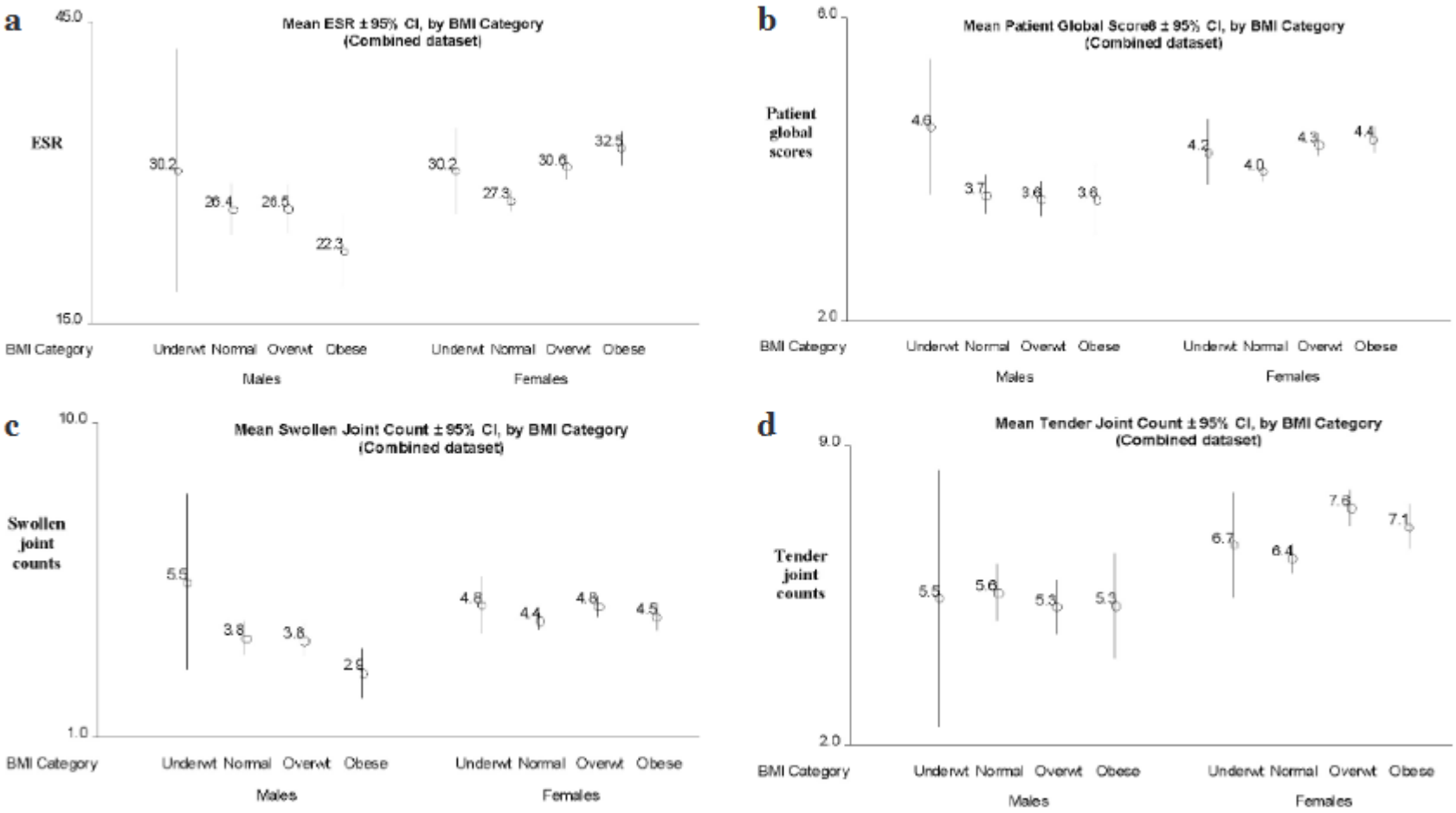


Fig. 2. Plots showing the mean (**a**) Erythrocyte Sedimentation Rate (ESR), (**b**) Patient Global Scores, (**c**) Swollen Joint Counts, and (**d**) Tender Joint Counts, with 95% confidence intervals (y-axis) by BMI category (**x**-axis) in the combined dataset, for female and male patients separately.

Comparative Study > Clin Exp Rheumatol. 2010 Jul-Aug;28(4):454-61. Epub 2010 Aug 30.

Gender, body mass index and rheumatoid arthritis disease activity: results from the QUEST-RA Study

D Jawaheer [1], J Olsen, M Lahiff, S Forsberg, J Lähteenmäki, I G da Silveira, F A Rocha, I M Magalhães Laurindo, L M Henrique da Mota, A A Drosos, E Murphy, C Sheehy, E Quirke, M Cutolo, S Rexhepi, J Dadoniene, S M M Verstappen, T Sokka; QUEST-RA

Collaborators, Affiliations + expand

PMID: 20810033 PMCID: PMC3012645

Free PMC article

Conclusion

BMI appears to be associated with RA disease activity in women, but not in men.

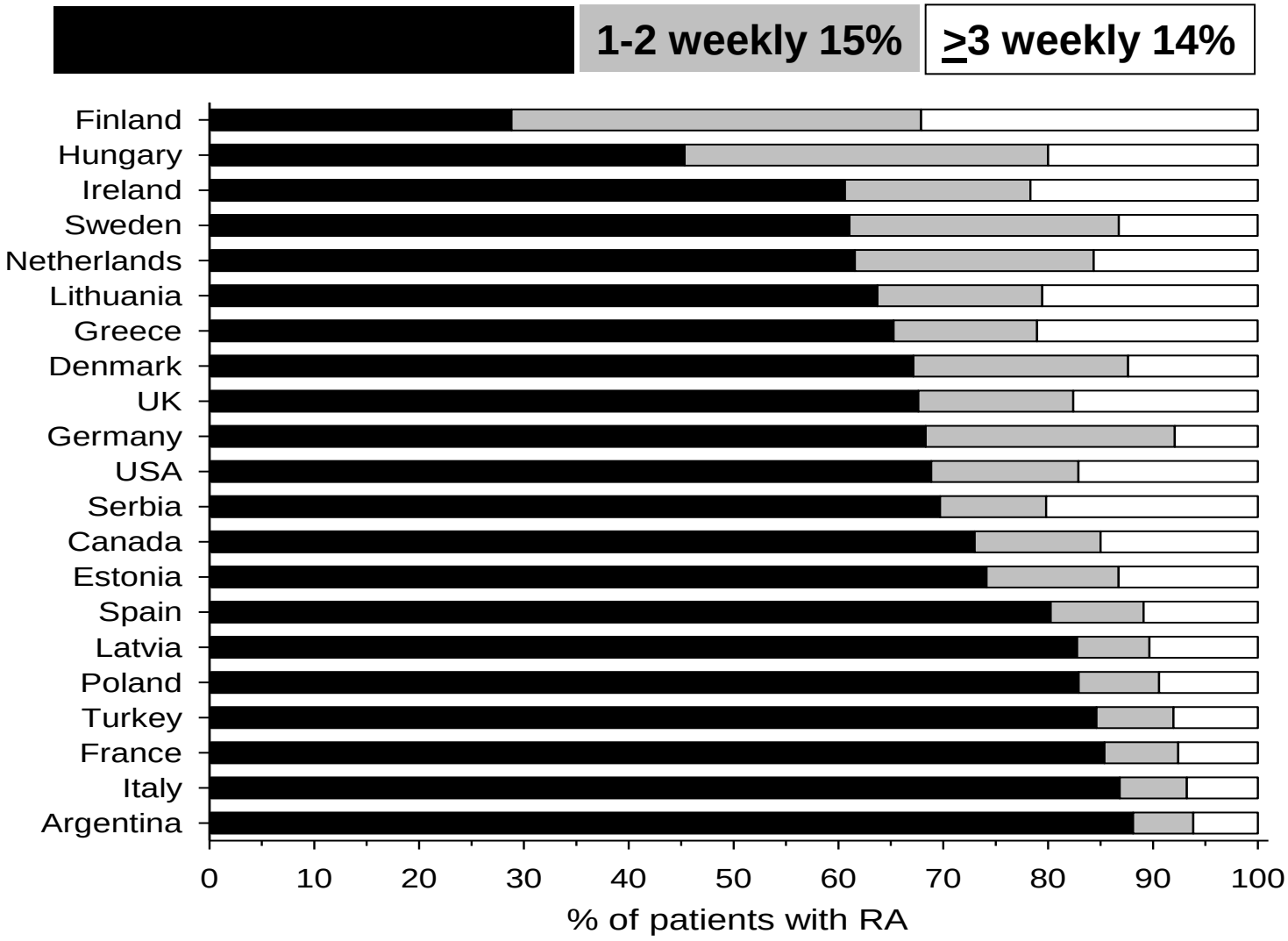
Arthritis & Rheumatism (Arthritis Care & Research)
Vol. 59, No. 1, January 15, 2008, pp 42–50
DOI 10.1002/art.23255

ORIGINAL ARTICLE

Physical Inactivity in Patients With Rheumatoid Arthritis: Data From Twenty-One Countries in a Cross-Sectional, International Study

TUULIKKI SOKKA,[1] ARJA HÄKKINEN,[2] HANNU KAUTIAINEN,[3] JEAN FRANCIS MAILLEFERT,[4] SERGIO TOLOZA,[5] TROELS MØRK HANSEN,[6] JAIME CALVO-ALEN,[7] ROLF ODING,[8] MARGARETH LIVEBORN,[8] MARGRIET HUISMAN,[9] RIEKE ALTEN,[10] CHRISTOF POHL,[10] MAURIZIO CUTOLO,[11] KAI IMMONEN,[12] ANTHONY WOOLF,[13] EITHNE MURPHY,[14] CLAIRE SHEEHY,[14] EDEL QUIRKE,[14] SELDA CELIK,[15] YUSUF YAZICI,[16] WITOLD TLUSTOCHOWICZ,[17] DANUTA KAPOLKA,[18] VLADO SKAKIC,[19] BERNADETTE ROJKOVICH,[20] RAILI MÜLLER,[21] SIGITA STROPUVIENE,[22] DAINA ANDERSONE,[23] ALEXANDROS A. DROSOS,[24] JURIS LAZOVSKIS,[25] AND THEODORE PINCUS,[16] ON BEHALF OF THE QUEST-RA GROUP

QUEST-RA: Self-reported level of physical exercise



Sokka et al. Arthritis Rheum 2008;59:42-50

Multicenter Study > Ann Rheum Dis. 2009 Nov;68(11):1666-72. doi: 10.1136/ard.2009.109983.
Epub 2009 Jul 30.

Disparities in rheumatoid arthritis disease activity according to gross domestic product in 25 countries in the QUEST-RA database

T Sokka [1], H Kautiainen, T Pincus, S Toloza, G da Rocha Castelar Pinheiro, J Lazovskis, M L Hetland, T Peets, K Immonen, J F Maillefert, A A Drosos, R Alten, C Pohl, B Rojkovich, B Bresnihan, P Minnock, M Cazzato, S Bombardieri, S Rexhepi, M Rexhepi, D Andersone, S Stropuviene, M Huisman, S Sierakowski, D Karateev, V Skakic, A Naranjo, E Baecklund, D Henrohn, F Gogus, H Badsha, A Mofti, P Taylor, C McClinton, Y Yazici

Affiliations + expand

PMID: 19643759 PMCID: PMC2756954 DOI: 10.1136/ard.2009.109983

Free PMC article

Conclusions

- The clinical status of patients with RA was correlated significantly with GDP among 25 mostly European countries according to all disease measures.
- The burden of arthritis appears substantially greater in "low GDP" than in "high GDP" countries

Epidemiology of RA

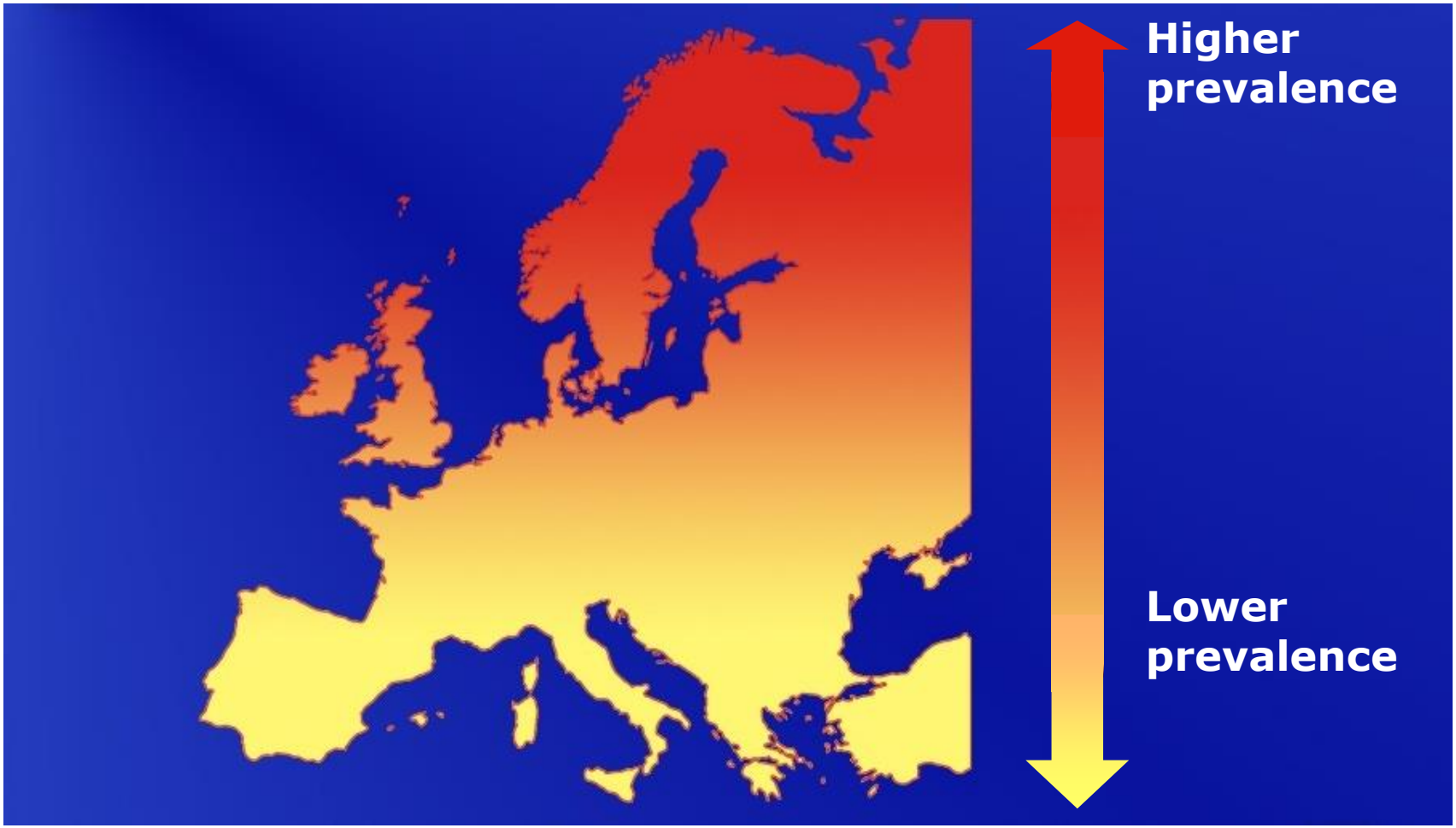
The overall prevalence of RA is about **1% in adult Caucasian**, but the range of rates varies from a low **of 0.2% to a high of 5.3%** worldwide. There is a geographical trend, with higher **prevalence in the Northern hemisphere than in the Southern hemisphere.**

Table 1
Incidence and prevalence of rheumatoid arthritis in various populations.

Populations	Incidence (cases per 100,000 population)	Prevalence (cases per 100 population)
Northern Europe	29 (24–36)	0.5 (0.44–0.8)
Southern Europe	16.5 (9–24)	0.33 (0.31–0.5)
North America	38 (31–45)	0.5
Developing countries	No data	0.35 (0.24–0.36)

Symmons DP, et al. Br J Rheumatol 1994;33:735-9
Guillemin F, et al. Scand J Rheumatol 1994;23:264-8
Symmons D, et al. Rheumatology (Oxford) 2002;41:793-800
Carmona L, et al. Rheumatology (Oxford) 2002;41:88-95.

Epidemiology of RA: prevalence in Europe



Conclusions (I)

- The results of the above studies reinforce the notion that the **incidence and prevalence of RA differ among countries and geographical areas**

- **In South Europe** the prevalence of **RA seems to be lower** as **compared to Northern European and American countries**

- **In Mediterranean** countries **RA seems to be milder**, with **fewer extraarticular and radiological features**

Conclusions (II)

- These differences may be attributed to:
- **Different methods of cases** ascertainment among studies
- **Immunogenetics**
- **Environmental** (climate – infections)
- **Lifestyle** (smoking, diet, obesity, physical activity)

WHAT IS THE IMPACT OF THESE DIFFERENCES IN CLINICAL PRACTICE?

Morbidity and mortality

- **Patients from Northern Europe suffer of severe ExRA, which has been associated with an increased mortality** compared with patients with RA from the Southern Europe.

- Moreover, **patients with severe ExRA** manifestations **are at an increased risk** of **developing cardiovascular disease or severe infections**.

- **RA severity** in general may also **affect survival** in patients with RA.

Turesson C, et al. Rheumatology (Oxford) 1999; 38:668–674
Turesson C, et al. J Rheumatol 2002; 29:62–67

ARTHRITIS & RHEUMATISM
Vol. 48, No. 1, January 2003, pp 54–58
DOI 10.1002/art.10705

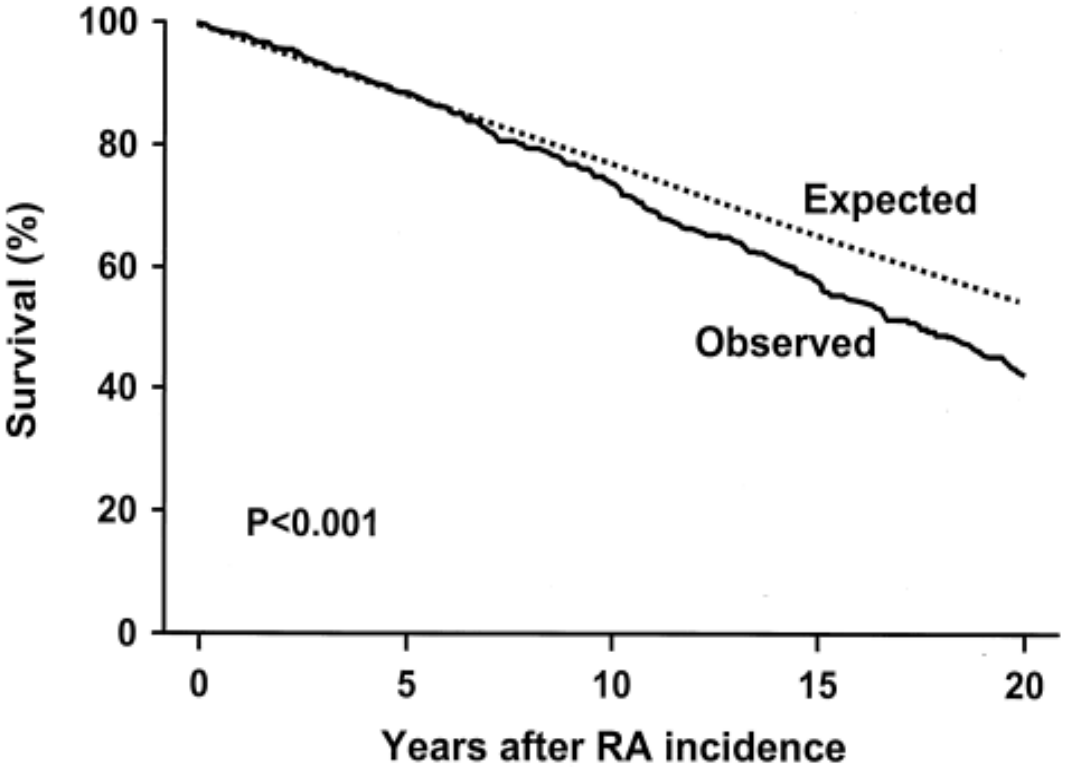
Survival in Rheumatoid Arthritis

A Population-Based Analysis of Trends Over 40 Years

Sherine E. Gabriel,[1] Cynthia S. Crowson,[1] Hilal Maradit Kremers,[1] Michele F. Doran,[2]
Carl Turesson,[3] W. Michael O'Fallon,[1] and Eric L. Matteson[1]

CONCLUSION

- Survival in RA patients is significantly lower than expected.



Cardiovascular risk in RA patients

Comparative Study > Arthritis Res Ther. 2006;8(3):R82. doi: 10.1186/ar1952. Epub 2006 Apr 28.

Atherogenic lipid profile is a feature characteristic of patients with early rheumatoid arthritis: effect of early treatment--a prospective, controlled study

Athanasios N Georgiadis [1], Eleni C Papavasiliou, Evangelia S Lourida, Yannis Alamanos, Christina Kostara, Alexandros D Tselepis, Alexandros A Drosos

Affiliations + expand

PMID: 16646989 PMCID: PMC1526648 DOI: 10.1186/ar1952

> Semin Arthritis Rheum. 2008 Aug;38(1):13-9. doi: 10.1016/j.semarthrit.2007.09.008. Epub 2008 Jan 14.

Early treatment reduces the cardiovascular risk factors in newly diagnosed rheumatoid arthritis patients

Athanasios N Georgiadis [1], Paraskevi V Voulgari, Maria I Argyropoulou, Yannis Alamanos, Moses Elisaf, Alexandros D Tselepis, Alexandros A Drosos

Affiliations + expand

PMID: 18191989 DOI: 10.1016/j.semarthrit.2007.09.008

Conclusions

- Early RA patients have dyslipidemia with low HDL and high LDL/HDL atherogenic risk factor.
- In addition these patients presented high intima media thickness of the carotid arteries.
- All the above features improved after treatment with MTX and steroids.

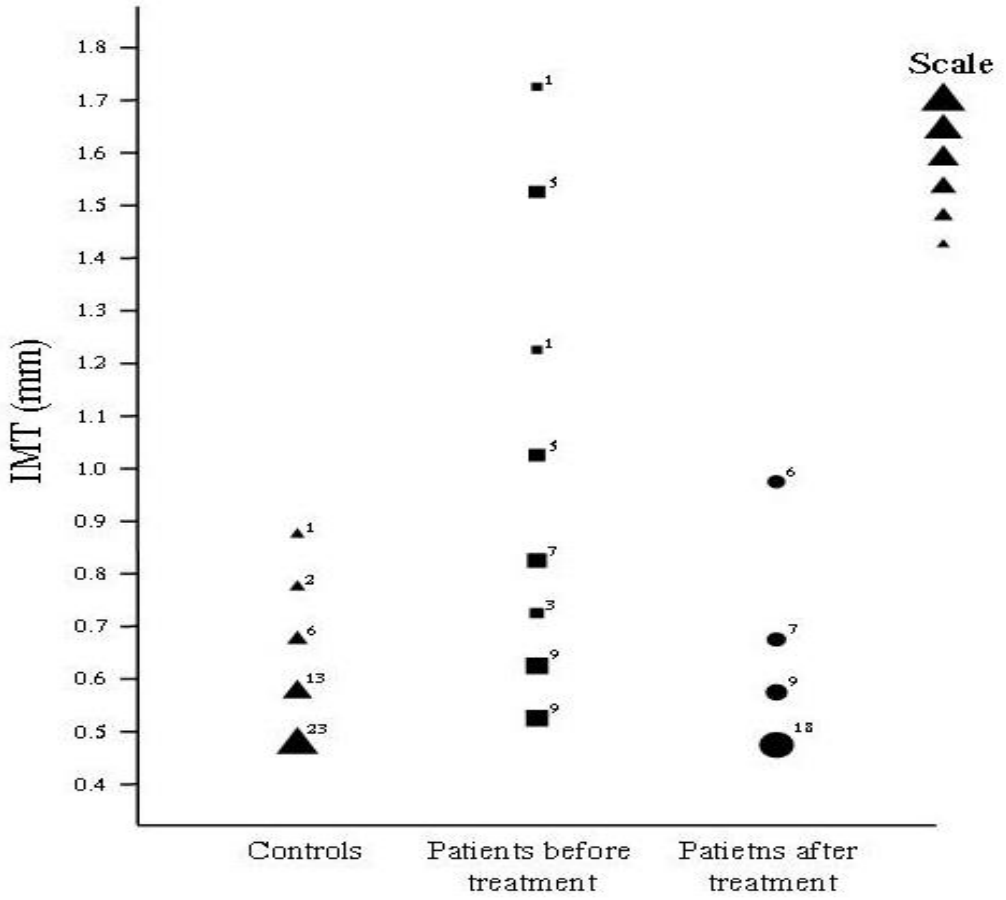
Table 1

Clinical characteristics and lipid profile of patients with early rheumatoid arthritis and controls

	Controls ($N = 63$)	Patients	
		Baseline ($N = 58$)	Post treatment ($N = 56$)
Sex (male/female)	20/43	14/44	13/43
Age (years)	58.4 ± 17.7	53.6 ± 15.3	54.7 ± 14.8
Body mass index (kg/m^2)	25.8 ± 17.7	25.5 ± 3.3	25.8 ± 3.1
IgM rheumatoid factor (+/-)	0/0	45/13	44/13
C-reactive protein (mg/dl)	2.1 ± 1.3	28.15 ± 20.75	4.60 ± 4.20[a]
ESR (mm/h)	5.2 ± 3.1	48.0 ± 19.7	14.6 ± 8.7[a]
DAS-28	-	5.8 ± 0.9	2.7 ± 1.0[a]
TC (mg/dl)	190.4 ± 33.9	216.5 ± 50.3[b]	228.1 ± 42.1[c]
LDL-C (mg/dl)	126.5 ± 31.3	141.6 ± 42.3[b]	140.4 ± 32.4
HDL-C (mg/dl)	51.1 ± 7.4	47.5 ± 11.8[2]	60.7 ± 13.4[a]
NonHDL-C (mg/dl)	139.3 ± 30.2	172.0 ± 46.3[b]	167.4 ± 37.4
Triglycerides (mg/dl)	97.1 ± 28.3	133.0 ± 58.2[b]	131.5 ± 56.1
TC/HDL-C	3.7 ± 0.9	4.9 ± 1.3[b]	3.8 ± 0.8[a]
LDL-C/HDL-C	2.5 ± 0.8	3.0 ± 1.0[b]	2.4 ± 0.6[a]
Apolipoprotein B (mg/dl)	93 ± 19	103 ± 28[b]	105 ± 30
Apolipoprotein A-I (mg/dl)	144 ± 23	127 ± 27[d]	152 ± 22[a]

Values represent the mean ± standard deviation. [a]$p < 0.001$ and [c]$p < 0.05$ compared to the baseline values; [b]$p < 0.001$ and [d]$p < 0.01$ compared to the control group. DAS-28, disease activity for 28 joint indices score; ESR, erythrocyte sedimentation rate; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol.

IMTs measurements before and after treatment



- Common carotid artery IMTs were higher in RA patients compared to controls (0,82±0,29 vs 0,57 ±0,11, p<0,05).
- After 1 year therapy a decrease of the IMTs was noted (0,63±0,196 vs 0,57±0,11, p<0,001).
- Three patients (1 man, 2 women) and 2 controls (1 man and 1 woman) had focal plaques.

Georgiadis AN, et al. Semin Arthritis Rheum 2008;38:13-9

Cardiovascular risk in RA patients

Comparative Study > Arthritis Res Ther. 2007;9(1):R19. doi: 10.1186/ar2129.

Patients with early rheumatoid arthritis exhibit elevated autoantibody titers against mildly oxidized low-density lipoprotein and exhibit decreased activity of the lipoprotein-associated phospholipase A2

Evangelia S Lourida [1], Athanasios N Georgiadis, Eleni C Papavasiliou, Athanasios I Papathanasiou, Alexandros A Drosos, Alexandros D Tselepis

Affiliations + expand

PMID: 17326817 PMCID: PMC1860077 DOI: 10.1186/ar2129

Free PMC article

Cardiovascular risk in RA patients

› Ann Rheum Dis. 2005 May;64(5):765-6. doi: 10.1136/ard.2004.026534. Epub 2004 Sep 30.

Effects of infliximab treatment on insulin resistance in patients with rheumatoid arthritis and ankylosing spondylitis

D N Kiortsis [1], A K Mavridis, S Vasakos, S N Nikas, A A Drosos

Affiliations + expand

PMID: 15458960 PMCID: PMC1755470 DOI: 10.1136/ard.2004.026534

Free PMC article

Clinical Trial › J Rheumatol. 2006 May;33(5):921-3. Epub 2006 Mar 15.

Effects of infliximab treatment on lipoprotein profile in patients with rheumatoid arthritis and ankylosing spondylitis

Dimitrios N Kiortsis [1], Anastasios K Mavridis, Theodosios D Filippatos, Spyros Vasakos, Spyros N Nikas, Alexandros A Drosos

Affiliations + expand

PMID: 16541480

Results

Treatment of RA patients with anti-TNFα improved insulin resistance, but did not altered the lipid profile

Arthritis & Rheumatology

AN OFFICIAL JOURNAL OF THE AMERICAN COLLEGE OF RHEUMATOLOGY

American College of Rheumatology
Empowering Rheumatology Professionals

Original Article

Biologics May Prevent Cardiovascular Events in Rheumatoid Arthritis by Inhibiting Coronary Plaque Formation and Stabilizing High-Risk Lesions

George A. Karpouzas, Sarah R. Ormseth, Elizabeth Hernandez, Matthew J. Budoff

First published: 21 April 2020 | https://doi.org/10.1002/art.41293 | Citations: 2

Conclusion

Our findings indicate that in RA, biologic DMARD use is associated with reduced CVD risk, protective calcification of noncalcified lesions, and lower likelihood of new plaque formation in patients with early atherosclerosis.

Arthritis Rheumatol. 2020 Sep;72(9):1467-1475. doi: 10.1002/art.41293.

Observational Study > Heart Vessels. 2022 Dec;37(12):2128-2136.
doi: 10.1007/s00380-022-02114-y. Epub 2022 Jun 24.

The effects of biologic agents on cardiovascular risk factors and atherosclerosis in rheumatoid arthritis patients: a prospective observational study

G V Papamichail [1], T E Markatseli [2], A N Georgiadis [2], V G Xydis [3], H Milionis [1], A A Drosos [2], P V Voulgari [4 5]

Affiliations + expand

> Clin Rheumatol. 2024 Jan;43(1):481-488. doi: 10.1007/s10067-023-06744-z. Epub 2023 Aug 29.

Antibodies against oxidized LDL and atherosclerosis in rheumatoid arthritis patients treated with biological agents: a prospective controlled study

G V Papamichail [1], A N Georgiadis [2], C C Tellis [3], I Rapti [1], T E Markatseli [2], V G Xydis [4], A D Tselepis [3], A A Drosos [2], P V Voulgari [5]

Affiliations + expand

PMID: 37642764 DOI: 10.1007/s10067-023-06744-z

Table 1 Clinical and laboratory characteristics of RA patients at baseline

Characteristics	Group of RA patients ($n = 59$)	Controls ($n = 31$)	p-value
BMI (kg/m^2)	23.5 ± 3.1	24.8 ± 2.9	0.16
Disease duration (years)	2.8 ± 1.2		
TJC (0–28)	8 ± 2		
SJC (0–28)	6 ± 3		
DAS28 score	3.79 (3.18–4.78)		
VAS pain (mm)	44.6 ± 17.4		
IgM RF (+), *n* (%)	32 (65.3%)		
ACPA (+), *n* (%)	29 (59.2%)		
MTX use, *n* (%)	50 (84.6%)		
LFN use, *n* (%)	9 (15.4%)		
PDN use, *n* (%)	59 (100%)		
PDN dose (mg/day)	3.5 ± 1.2		
TC (mg/dl)	210 ± 59	233 ± 45	0.004
TGs (mg/dl)	115 (91–158)	135 ± 60	0.14
HDL-C (mg/dl)	56 ± 15	61 ± 14	0.001
LDL-C (mg/dl)	137 ± 39	143 ± 35	0.06
CRP (mg/l)	9 (7–14)	2 (1–4)	0.04
ESR (mm/hr)	21 (12–36)	8 (6–12)	0.02
cIMT (mm)	0.9 (0.8–1)	0.6 (0.5–0.7)	0.001
IgG anti-oxLDL (AU)	0.193 ± 0.052		

Results are expressed in mean ± SD or median (IQR), unless otherwise noted

Table 2 Changes over time in disease activity indexes, lipid profile, cIMT, and anti-oxLDL in RA patients treated with anti-TNF and non-anti-TNF for 6 months

Parameters	Baseline	6 months	*p*-value
Anti-TNF users			
Gender (F/M)	26/9	26/9	
Age (years)	55.3 ± 14.8		
DAS-28 score	3.42 (2.89–3.86)	2.89 (2.28–3.31)	0.001
CRP (mg/l)	10 (8–16)	3 (2–5)	0.018
ESR (mm/hr)	26 (15–43)	18 (8–29)	0.001
TC (mg/dl)	208 ± 62	223 ± 49	0.138
TGs (mg/dl)	108 (90–149)	103 (85–139)	0.561
HDL-C (mg/dl)	57 ± 15	66 ± 17	0.001
LDL-C (mg/dl)	138 ± 41	133 ± 36	0.329
cIMT (mm)	0.9 (0.8–1.2)	0.8 (0.6–0.9)	0.001
IgG anti-oxLDL (AU)	0.197 ± 0.054	0.145 ± 0.045	0.002
Non anti-TNF users			
Gender (F/M)	17/7	17/7	
Age (years)	51.8 ± 14.9		
DAS-28 score	3.42 (2.79–3.74)	2.88 (2.38–3.06)	0.001
CRP (mg/l)	4 (2–9)	2 (2–3)	0.001
ESR (mm/hr)	20 (10–26)	6 (4–11)	0.001
TC (mg/dl)	214 ± 56	232 ± 38	0.077
TGS (mg/dl)	123 (98–216)	119 (89–199)	0.548
HDL-C (mg/dl)	58 ± 16	70 ± 17	0.001
LDL-C (mg/dl)	136 ± 38	134 ± 36	0.588
cIMT (mm)	0.9 (0.8–1)	0.7 (0.6–0.8)	0.001
IgG anti-oxLDL (AU)	0.188 ± 0.050	0.142 ± 0.046	0.001

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Review Article

Exploring Cardiovascular Risk Factors and Atherosclerosis in Rheumatoid Arthritis

Alexandros A. Drosos *, Aliki A. Venetsanopoulou, Eleftherios Pelechas, Paraskevi V. Voulgari

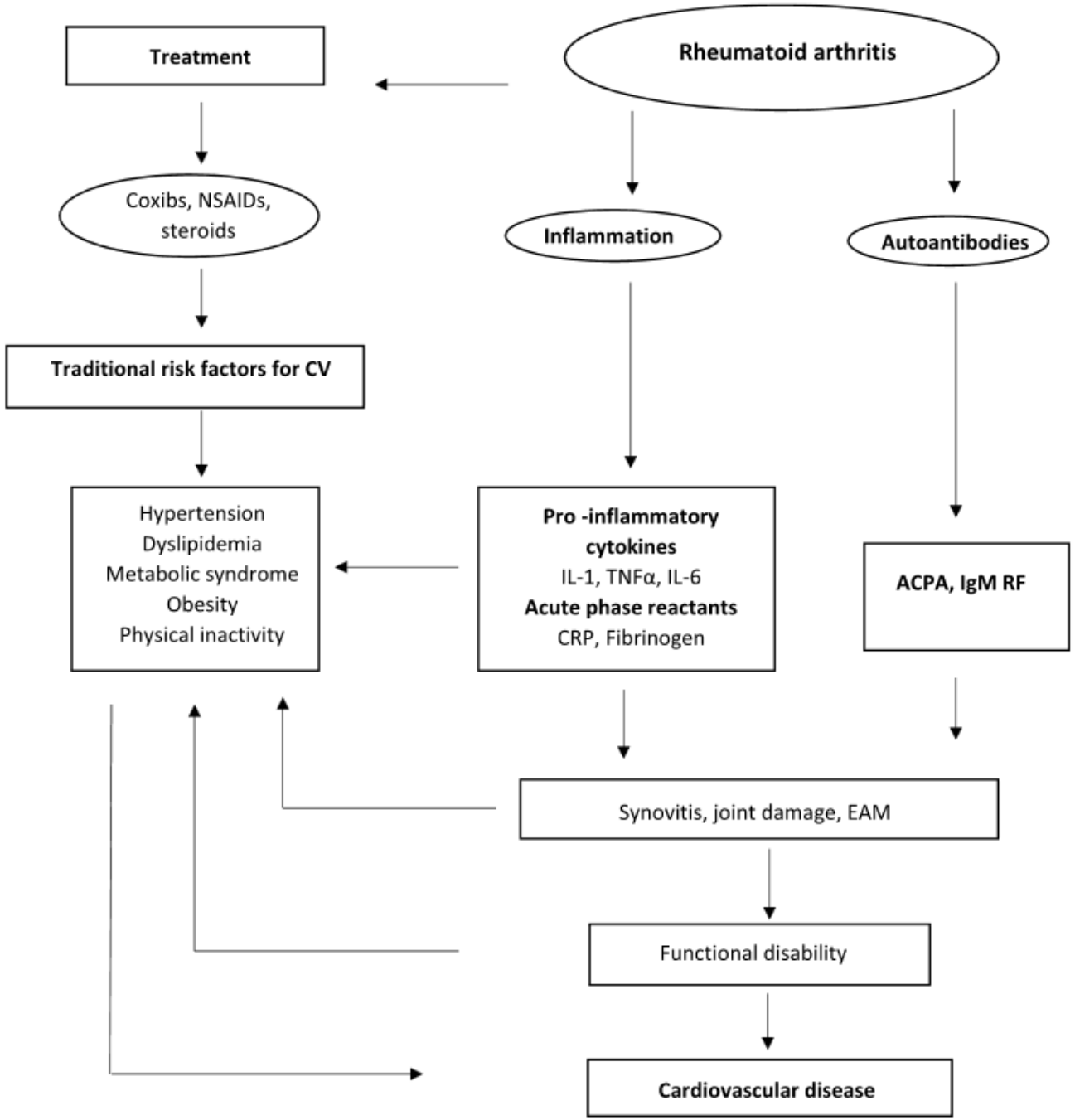
Department of Rheumatology, School of Health Sciences, Faculty of Medicine, University of Ioannina, Ioannina, Greece

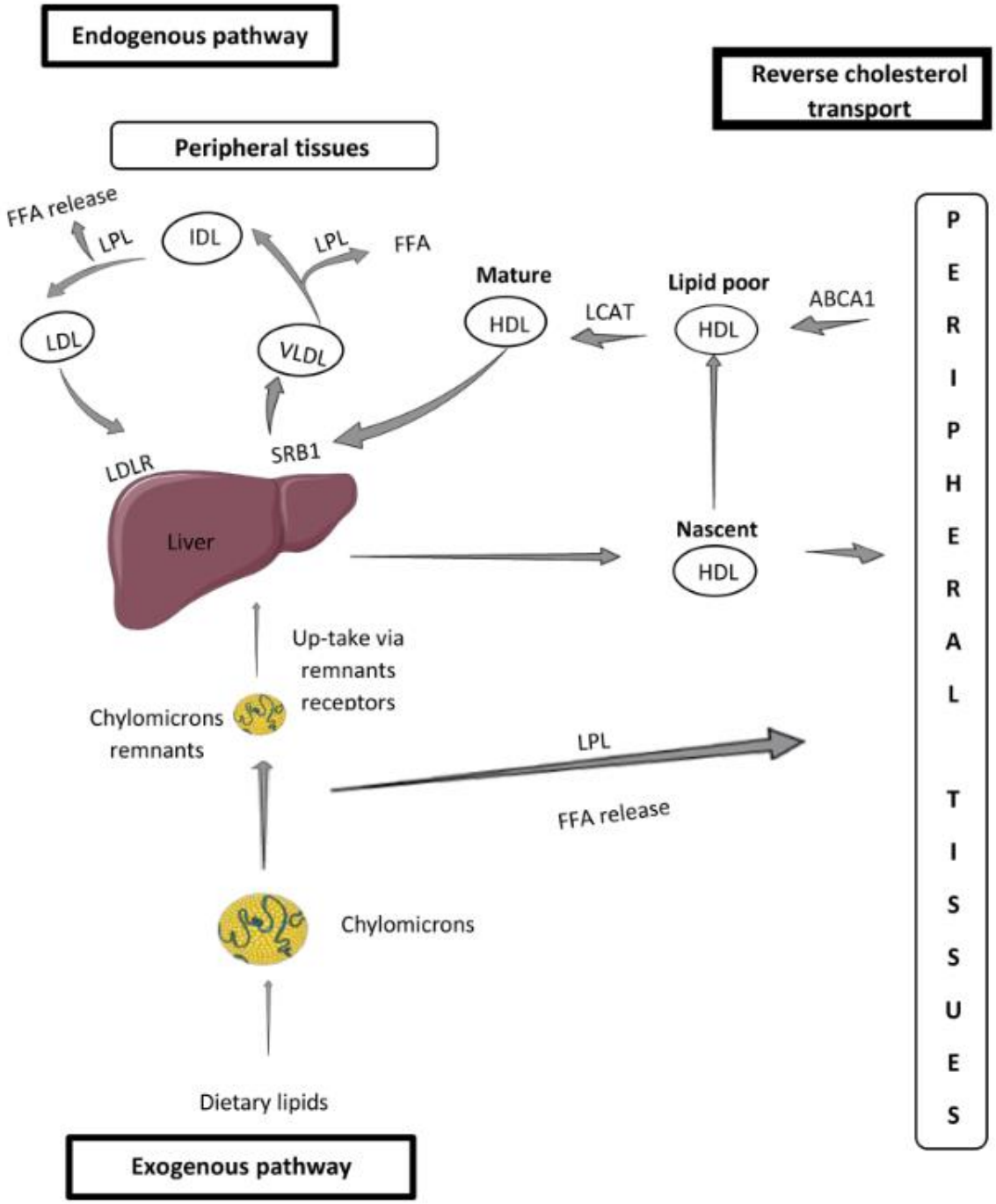
ARTICLE INFO

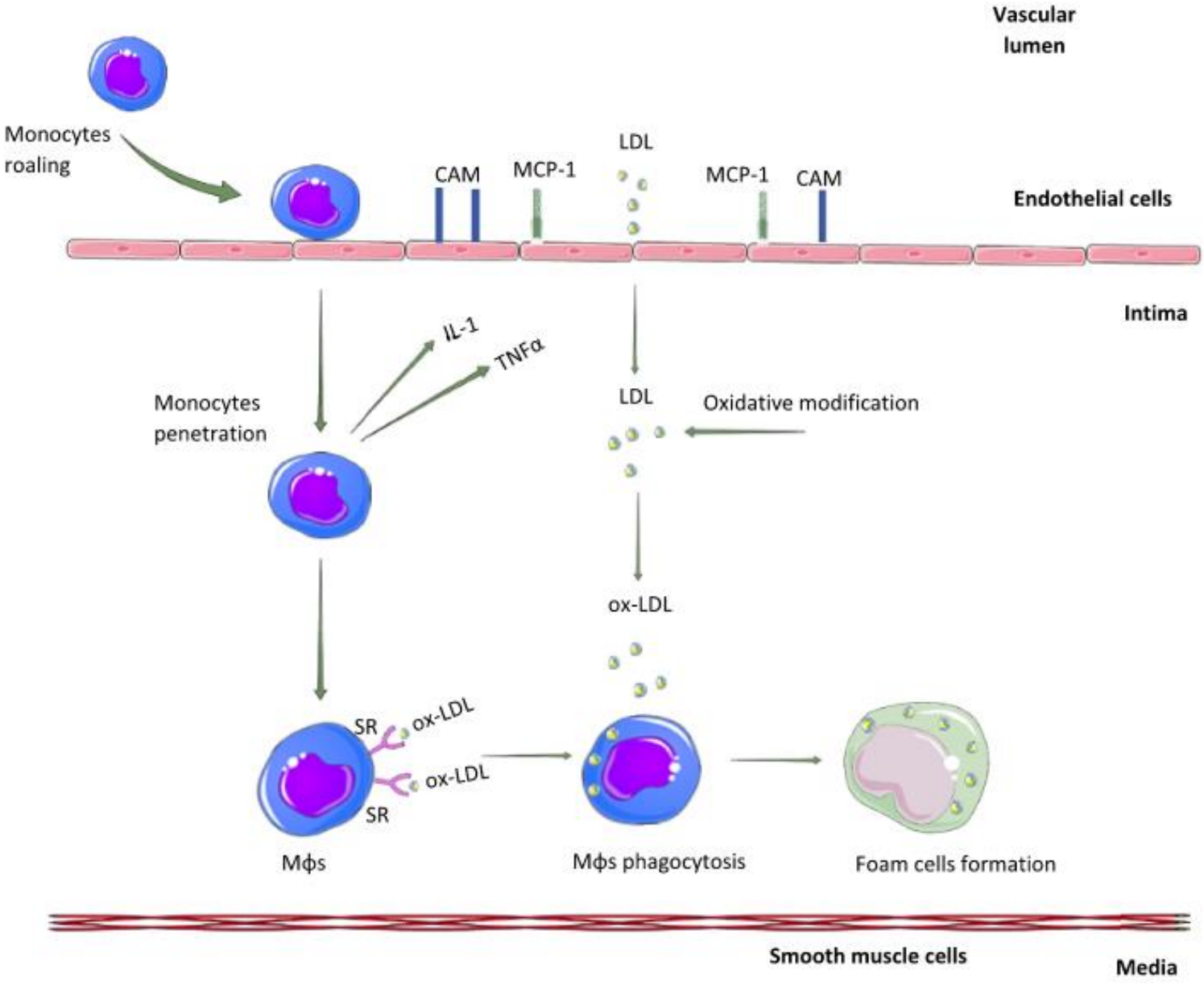
Keywords:
RA
Cardiovascular disease
Coronary disease
Lipid paradox
Systemic inflammation
Biological therapies

ABSTRACT

Rheumatoid arthritis (RA) is a chronic inflammatory disease mainly affecting the peripheral diarthrodial joints symmetrically and also presenting many extra-articular manifestations. Morbidity and mortality in RA patients are higher compared to the general population. Cardiovascular (CV) disease is one of the most common causes of death in these patients. Classical or traditional risk factors for atherosclerosis development occur more frequently in RA patients compared to those without this condition. Studies have showed that RA patients often present comorbidities such as hypertension, dyslipidemia, diabetes mellitus and obesity. However, the high incidence of CV events occurring in RA patients is not explained by the presence of traditional risk factors. Systemic inflammation, as it is expressed with the presence of proinflammatory cytokines and increased acute phase reactants, may contribute to the development of premature atherosclerosis in these patients. In this review, we explore the risk factors for CV disease, the generation of dyslipidemia, the lipid paradox and the role of systemic inflammation in the atherosclerotic process in RA. We discuss also the role of early therapeutic intervention that suppresses inflammation which may have beneficial effects on CV disease in RA patients.


Treatment
Rheumatoid arthritis
Coxibs, NSAIDs, steroids
Inflammation
Autoantibodies
Traditional risk factors for CV
Hypertension
Dyslipidemia
Metabolic syndrome
Obesity
Physical inactivity
Pro -inflammatory cytokines
IL-1, TNFα, IL-6
Acute phase reactants
CRP, Fibrinogen
ACPA, IgM RF
Synovitis, joint damage, EAM
Functional disability
Cardiovascular disease


Endogenous pathway
Reverse cholesterol transport
Peripheral tissues
FFA release
LPL
IDL
LPL
FFA
Mature
Lipid poor
ABCA1
LDL
VLDL
HDL
LCAT
HDL
LDLR
SRB1
Liver
Nascent
HDL
PERIPHERAL TISSUES
Up-take via remnants receptors
Chylomicrons remnants
LPL
FFA release
Chylomicrons
Dietary lipids
Exogenous pathway


Vascular lumen
Monocytes roaling
CAM
MCP-1
LDL
MCP-1
CAM
Endothelial cells
Intima
IL-1
TNFα
Monocytes penetration
LDL
Oxidative modification
ox-LDL
SR
ox-LDL
ox-LDL
SR
Mϕs
Mϕs phagocytosis
Foam cells formation
Smooth muscle cells
Media

Conclusions

- **Cardiovascular disease and premature atherosclerosis** are frequently observed in RA patients and is comparable to DM.
- The **lipid paradox observed in RA patients** is a real phenomenon but, needs further investigation. **Anti-oxLDL** antibodies are **present,** but their role should be further investigated.
- **Classical risk factors and systemic inflammation** are responsible for premature atherosclerosis.
- **Early intervention with csDMARDs** especially MTX, and/or biologic therapy reduces structural damage development and may have a beneficial effect on the cardiovascular risk in these patients.

Radiological progression in RA

Review > Clin Exp Rheumatol. 2010 Jan-Feb;28(1):114-23.

Prognostic factors for erosive rheumatoid arthritis

T E Markatseli [1], C Papagoras, A A Drosos

Affiliations + expand

PMID: 20346251

> J Rheumatol. 2011 Jan;38(1):44-52. doi: 10.3899/jrheum.100514. Epub 2010 Oct 15.

Prognostic factors of radiological damage in rheumatoid arthritis: a 10-year retrospective study

Theodora E Markatseli [1], Paraskevi V Voulgari, Yannis Alamanos, Alexandros A Drosos

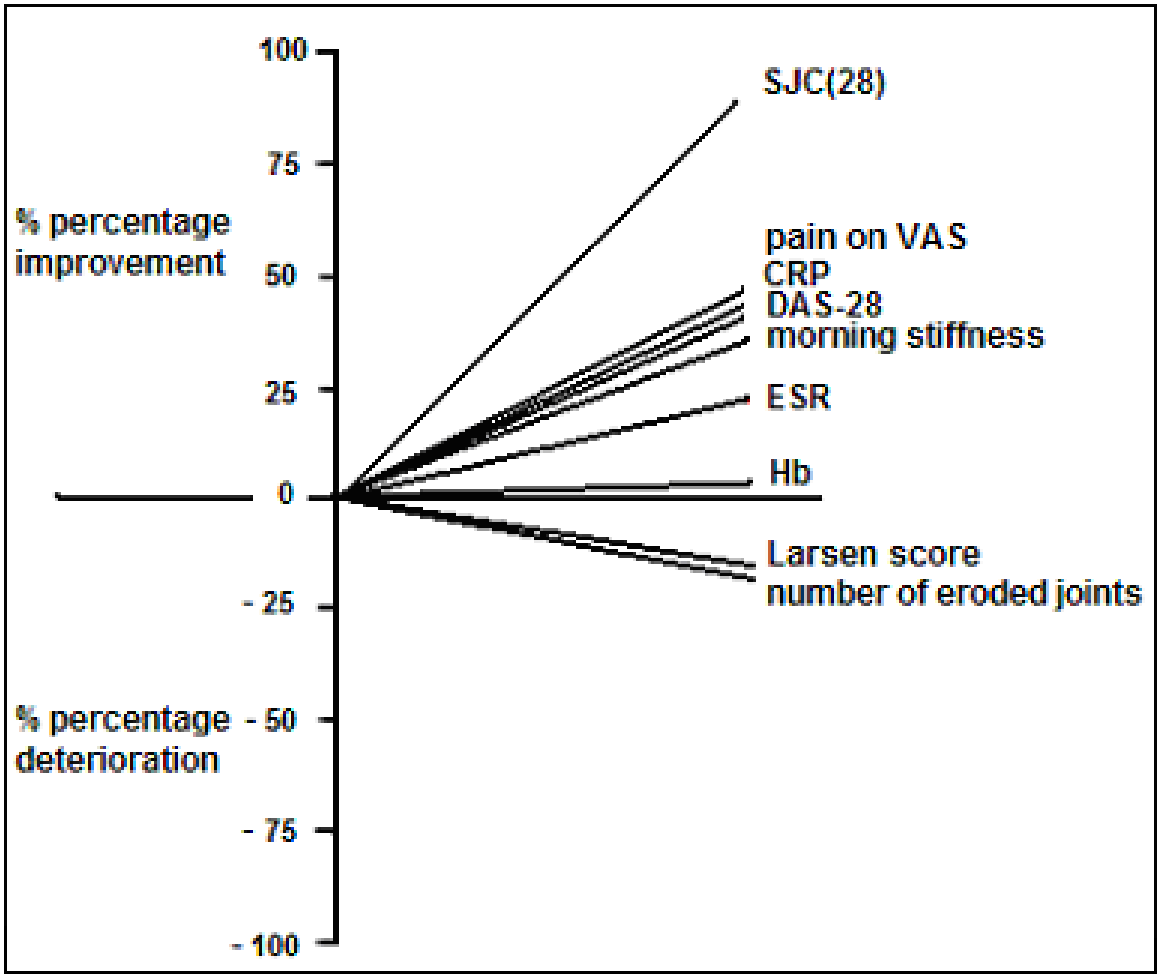
Affiliations + expand

PMID: 20952476 DOI: 10.3899/jrheum.100514

Table I. Potential prognostic factors of radiological damage in rheumatoid arthritis.

Demographic	Genetic
- Age	- Shared epitope
- Sex	- PTPN22 gene
- Disease duration	Autoantibodies
- Smoking	- Rheumatoid factor
- Body mass index	- Anti-cyclic citrullinated peptide antibodies
Clinical	- Anti-peptidyl-arginine deiminase-4 antibodies
- Symmetrical polyarthritis	Bone markers
- Disease activity score	- Matrix metalloproteinase-3
- Health assessment questionnaire score	- RANKL/OPG ratio
- Extra-articular manifestations	- Human cartilage glycoprotein-39
Inflammatory markers	- Cartilage oligomeric matrix protein
- Erythrocyte sedimentation rate	- Collagen cross-linked C-telopeptide
- C-reactive protein	Early imaging damage

Markatseli TE, et al. Clin Exp Rheumatol 2010;28:114-23



Dissociation between clinical and radiological outcome. Improvement is the mean actual change during the 10-year period expressed as a percentage of the value at enrolment. Deterioration is the mean actual change expressed as a percentage of the total change possible.

Markatseli TE, et al. J Rheumatol 2011;38:44-52

Catastrophic RA

Case Reports > Clin Exp Rheumatol. 1999 Jul-Aug;17(4):474-6.

Rheumatoid resorptive arthropathy

P V Voulgari [1], S C Efremidis, A A Drosos

Affiliations + expand

PMID: 10464562

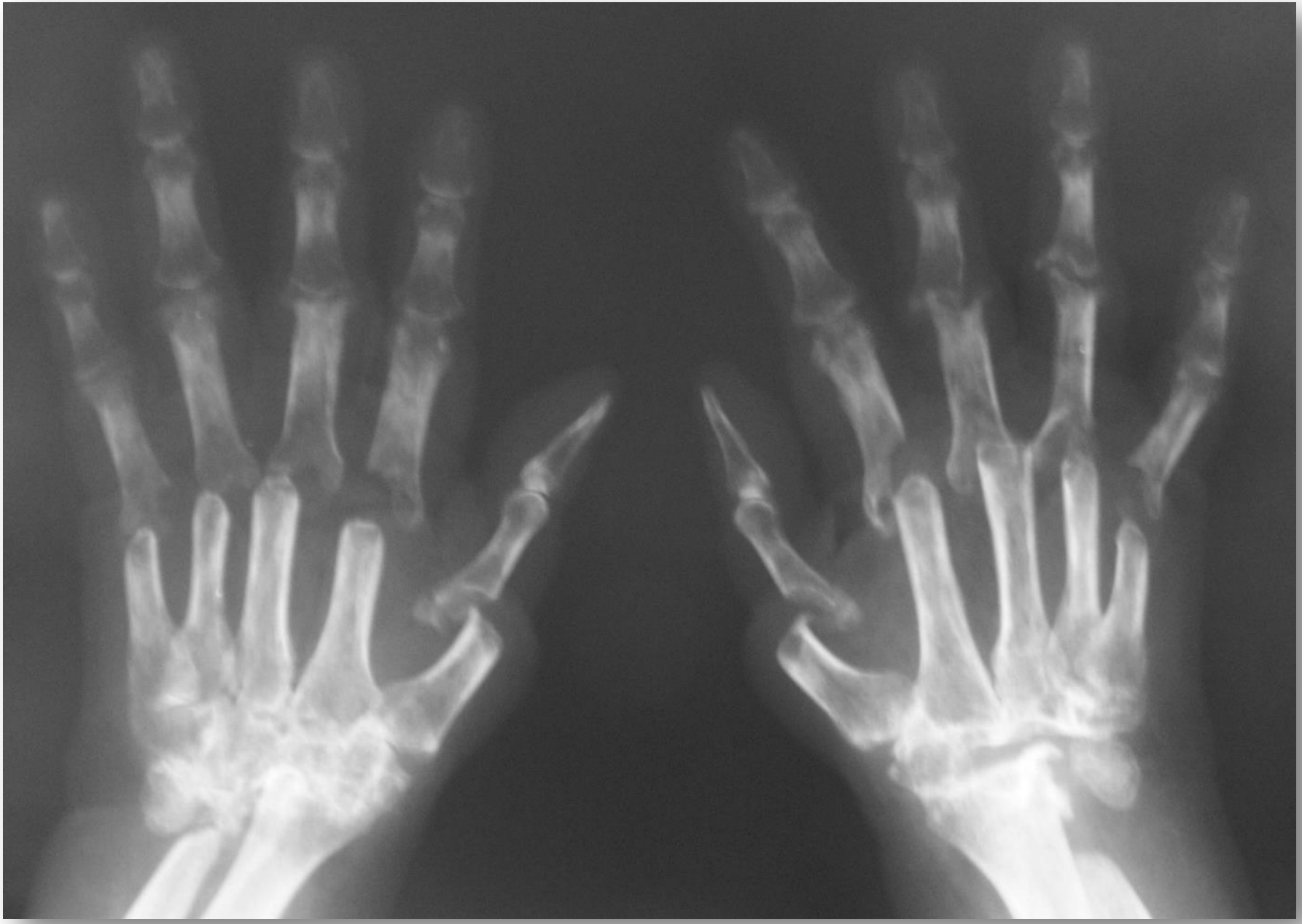
Case Reports > J Rheumatol. 2008 Oct;35(10):2062-3.

Catastrophic rheumatoid arthritis

Paraskevi V Voulgari [1], Alexandros A Drosos

Affiliations + expand

PMID: 18843757



Voulgari PV, Drosos AA J Rheumatol. 2008;35:2062-3

Rheumatology International (2019) 39:1331–1341
https://doi.org/10.1007/s00296-019-04326-4

Rheumatology
INTERNATIONAL

REVIEW

Conventional radiography of the hands and wrists in rheumatoid arthritis. What a rheumatologist should know and how to interpret the radiological findings

Alexandros A. Drosos[1] · Eleftherios Pelechas[1] · Paraskevi V. Voulgari[1]

Received: 12 April 2019 / Accepted: 15 May 2019 / Published online: 22 May 2019

Rheumatol Ther (2022) 9:771–779
https://doi.org/10.1007/s40744-022-00426-z

CASE REPORT

A Patient with Symmetrical Polyarthritis. The Value of Conventional Radiography for a Correct Diagnosis

Alexandros A. Drosos · Eleftherios Pelechas · Paraskevi V. Voulgari

Normal hands

posteroanterior

oblique

Radiographic changes

The radiographic changes occurring around a specific joint to be evaluated are:

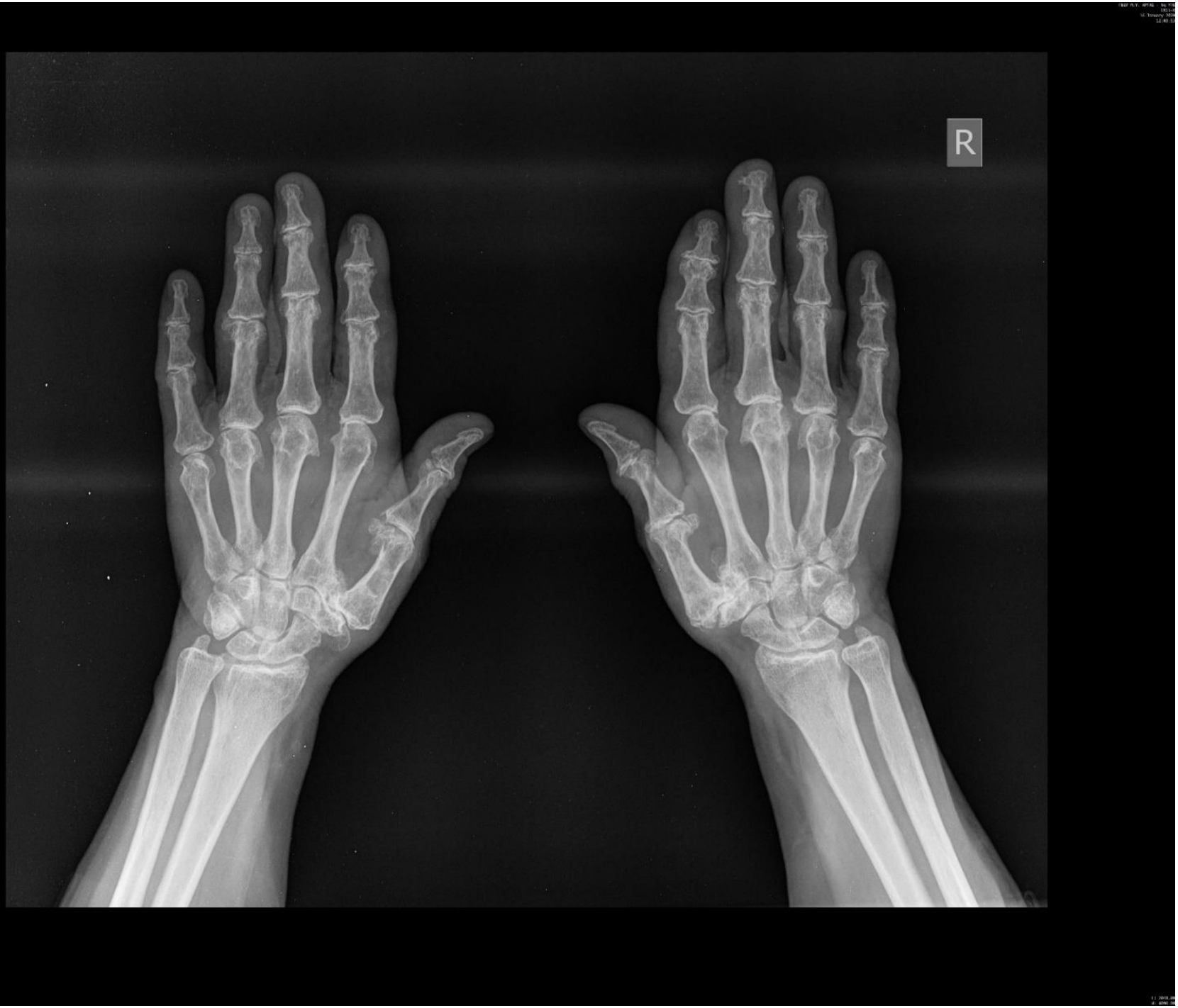
- Soft tissue swelling
- Subluxation/dislocation
- Mineralization
- Calcification
- Bone production
- **Joint space narrowing**
- **Erosions**

Brower AC. Arthritis in Black and White. Saunders (2nd Ed), 1988

Table 1 Imaging changes occurring in hands and wrists in RA patients using conventional radiography

Imaging changes	Early RA	Advanced RA
Soft tissue changes	Symmetrical swelling around the PIPs and wrists	Atrophy
Mineralization	Juxta-articular osteoporosis	Diffuse osteoporosis
Subluxation	None	MCPs (proximal phalanges subluxed ulnarly and palmarly)
Joint space narrowing	Maintained	Uniform loss in PIPs, MCPs and carpal bones
Erosions	Mild, sometimes aggressive	Large, aggressive
Joint distribution	PIPs, MCPs, and pancarpal	PIPs, MCPs, and pancarpal

RA rheumatoid arthritis, *MCPs* metacarpophalangeals, *PIPs* proximal interphalangeals


R

Sarcoidosis

Shanmugam s, Brent LH. J Rheumatol 2008;35:1892

Cervical spine involvement

› Clin Exp Rheumatol. 2005 Sep-Oct;23(5):665-70.

Magnetic resonance imaging findings of the cervical spine in patients with rheumatoid arthritis. A cross-sectional study

A K Zikou [1], M I Argyropoulou, Y Alamanos, N Tsifetaki, C Tsampoulas, P V Voulgari, S C Efremidis, A A Drosos

Affiliations + expand

PMID: 16173243

› J Rheumatol. 2005 May;32(5):801-6.

Radiological cervical spine involvement in patients with rheumatoid arthritis: a cross sectional study

Anastasia K Zikou [1], Yannis Alamanos, Maria I Argyropoulou, Niki Tsifetaki, Constantinos Tsampoulas, Paraskevi V Voulgari, Stavros C Efremidis, Alexandros A Drosos

Affiliations + expand

PMID: 15868612

Table I. Demographic, clinical and imaging findings of patients with established rheumatoid arthritis.

Number of patients	51
Women/men	42/9
Mean age (years) (± SD)	56.5±10.4
Mean disease duration (years) (± SD)	12.4± 8.5
Extraarticular manifestations, no. (%)	19 (37.2)
Clinical findings of cervical spine involvement, no. (%)	30 (58.8)
Radiological findings of cervical spine involvement, no. (%)	40 (78.4)
Magnetic resonance findings of cervical spine, no. (%)	44 (86.2)
IgM rheumatoid factor, no. (%)	33 (64.7)
Disease modifying anti-rheumatic drug therapy	
Methotrexate and prednisone, no. (%)	22 (43.3)
Methotrexate and cyclosporine Aand prednisone, no. (%)	21 (41.1)
Cyclosporine Aand prednisone, no. (%)	8 (15.6)

Zikou AK, et al. Clin Exp Rheumatol 2005;23:665-70

Table II. Magnetic resonance findings of the cervical spine in patients with rheumatoid arthritis.

Magnetic resonance findings	Patients (n = 51)	%
Peridental pannus formation	44	88.0
Dens erosions	12	23.5
Atlantoaxial subluxation	7	13.7
Subaxial subluxations	5	10.0
Fat body caudal to the clivus	5	10.0
Narrowing of the anterior subarachnoid space (level C_2)	4	8.0
Vertebral plate erosions	4	8.0
Cervicomedullary angle < 135°	3	6.0
Brainstem compression	3	5.9
Atlanto-axial impaction	0	0

Zikou AK, et al. Clin Exp Rheumatol 2005;23:665-70

Conventional radiography of RA cervical spine

Figure 2. A 53-year-old patient with a 6 year history of RA: lateral radiograph of the cervical spine shows SAS at C4–C5 level (arrow).

Zikou AK, et al. J Rheumatol 2005;32:801-6

MRI of RA cervical spine

Zikou AK, et al. Clin Exp Rheumatol 2005;23:665-70

Conclusions

- The assessment of joint pathology in patients with clinical manifestations of peripheral arthropathy **should begin with CR.**
- CR is the best imaging, as an **initial screening** test to evaluate any changes occurring in the joints and bones.
- Hand and wrist plain radiographs are simple and valuable imaging tools for the diagnosis of an established arthropathy.
- **Hand and wrist radiographs are the "disease mirror" for arthropathies.**

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CASE-BASED REVIEW

A not-to-miss Cause of Severe Cervical Spine Pain in a Patient with Rheumatoid Arthritis: A Case-Based Review

Alexandros A. Drosos, Eleftherios Pelechas, Athanasios N. Georgiadis, Paraskevi V. Voulgari

Rheumatology Clinic, Department of Internal Medicine, Medical School, University of Ioannina, Ioannina, Greece

Mediterr J Rheumatol 2021;32(3):256-63

https://doi.org/10.31138/mjr.32.3.256

› Clin Rheumatol. 1990 Sep;9(3):333-41. doi: 10.1007/BF02114393.

Methotrexate therapy in rheumatoid arthritis. A two year prospective follow-up

A A Drosos [1], D Psychos, A P Andonopoulos, S Stefanaki-Nikou, E B Tsianos, H M Moutsopoulos

Affiliations + expand

PMID: 2261732 DOI: 10.1007/BF02114393

› Clin Rheumatol. 1990 Sep;9(3):342-5. doi: 10.1007/BF02114394.

Can treatment with methotrexate influence the radiological progression of rheumatoid arthritis?

A A Drosos [1], A H Karantanas, D Psychos, C Tsampoulas, H M Moutsopoulos

Affiliations + expand

PMID: 2261733 DOI: 10.1007/BF02114394

Clinical Trial › Clin Exp Rheumatol. 1997 May-Jun;15(3):263-7.

Influence of methotrexate on radiographic progression in rheumatoid arthritis: a sixty-month prospective study

A A Drosos [1], N Tsifetaki, E K Tsiakou, M Timpanidou, C Tsampoulas, C K Tatsis, K Kotoulas, H M Moutsopoulos

Affiliations + expand

PMID: 9177920

Treatment of RA with synthetic and biological DMARDs (I)

Comment > Clin Exp Rheumatol. 1997 Sep-Oct;15(5):580-1.

D-penicillamine in early rheumatoid arthritis

A A Drosos, P Geogriou, E N Politi, P V Voulgari

PMID: 9307869

Review > Drugs Aging. 2003;20(10):723-36. doi: 10.2165/00002512-200320100-00002.

Methotrexate intolerance in elderly patients with rheumatoid arthritis: what are the alternatives?

Alexandros Drosos [1]

Affiliations + expand

PMID: 12875609 DOI: 10.2165/00002512-200320100-00002

Treatment of RA with synthetic and biological DMARDs (II)

Clinical Trial > Clin Exp Rheumatol. 1998 Nov-Dec;16(6):695-701.

Cyclosporine A in the treatment of early rheumatoid arthritis. A prospective, randomized 24-month study

A A Drosos [1], P V Voulgari, I A Papadopoulos, E N Politi, P E Georgiou, A K Zikou

Affiliations + expand

PMID: 9844762

Clinical Trial > Rheumatol Int. 2000;19(3):113-8. doi: 10.1007/s002960050113.

Influence of cyclosporin A on radiological progression in early rheumatoid arthritis patients: a 42-month prospective study

A A Drosos [1], P V Voulgari, A Katsaraki, A K Zikou

Affiliations + expand

PMID: 10776690 DOI: 10.1007/s002960050113

> J Rheumatol. 2002 Feb;29(2):261-6.

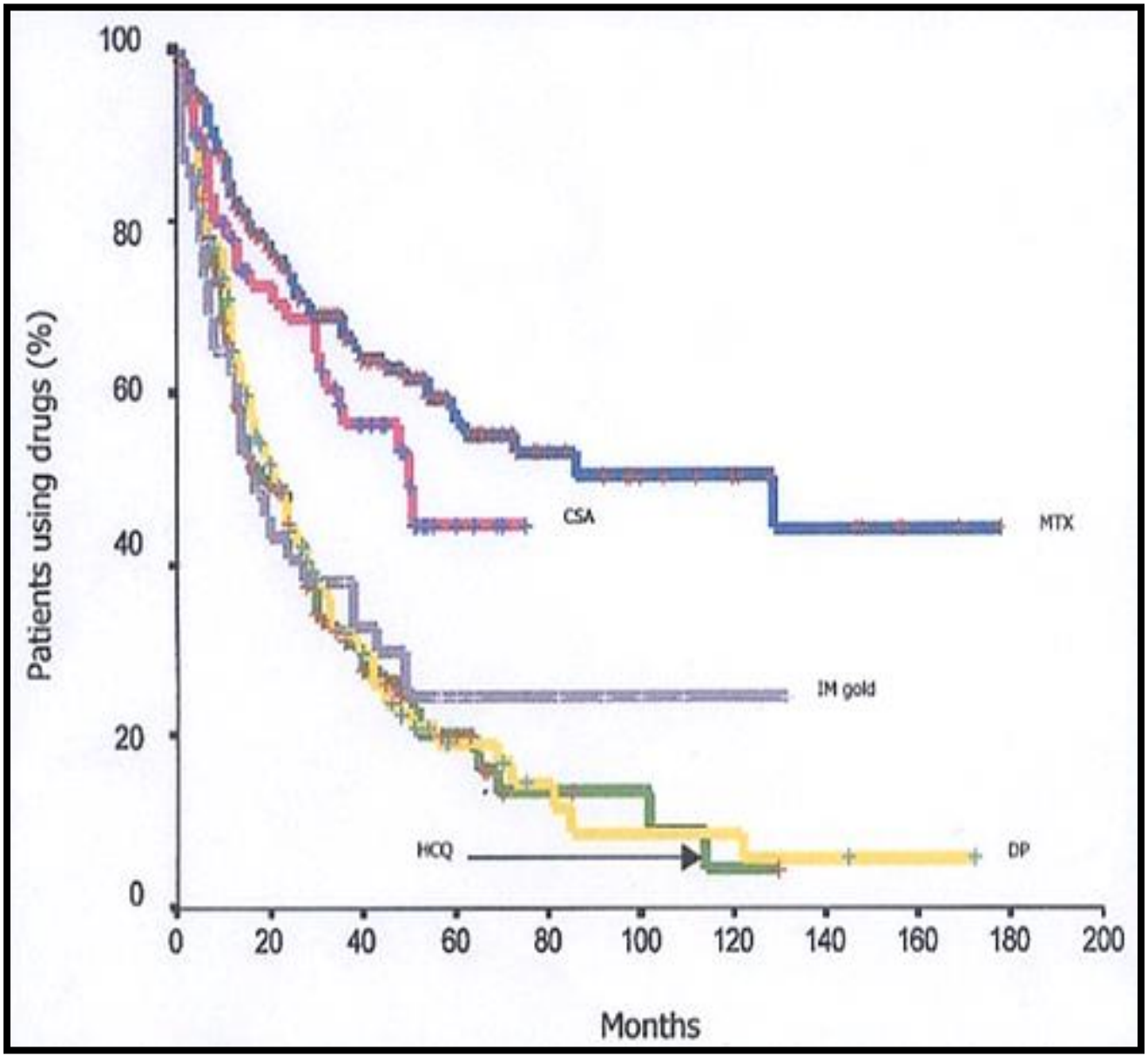
Disease modifying antirheumatic drugs in early rheumatoid arthritis: a longterm observational study

Nikolaos G Papadopoulos [1], Yannis Alamanos, Ioannis A Papadopoulos, Niki Tsifetaki, Paraskevi V Voulgari, Alexandros A Drosos

Affiliations + expand

PMID: 11838843

Drug Survival Time-overall, n=637



Papadopoulos NG, et al. J Rheumatol 29: 261-266, 2002

Treatment of RA with synthetic and biological DMARDs (III)

Clinical Trial > Ann Rheum Dis. 2002 Sep;61(9):822-5. doi: 10.1136/ard.61.9.822.

Infliximab treatment in combination with cyclosporin A in patients with severe refractory rheumatoid arthritis

T I Temekonidis [1], A N Georgiadis, Y Alamanos, D V Bougias, P V Voulgari, A A Drosos

Affiliations + expand

PMID: 12176808 PMCID: PMC1754214 DOI: 10.1136/ard.61.9.822

Free PMC article

> Am J Med. 2005 May;118(5):515-20. doi: 10.1016/j.amjmed.2005.01.029.

Infliximab therapy in established rheumatoid arthritis: an observational study

Paraskevi V Voulgari [1], Yannis Alamanos, Spyros N Nikas, Dimitrios V Bougias, Themistoklis I Temekonidis, Alexandros A Drosos

Affiliations + expand

PMID: 15866254 DOI: 10.1016/j.amjmed.2005.01.029

Treatment of RA with synthetic and biological DMARDs(IV)

› Ann Rheum Dis. 2004 Jan;63(1):102-3. doi: 10.1136/ard.2003.006981.

Treatment of resistant rheumatoid arthritis by intra-articular infliximab injections: a pilot study

S N Nikas, T I Temekonidis, A K Zikou, M I Argyropoulou, S Efremidis, A A Drosos

PMID: 14672902 PMCID: PMC1754709 DOI: 10.1136/ard.2003.006981
Free PMC article

Comparative Study › Ann Rheum Dis. 2006 Feb;65(2):257-60. doi: 10.1136/ard.2005.039099.
Epub 2005 Jun 23.

Efficacy and safety of switching from infliximab to adalimumab: a comparative controlled study

S N Nikas [1], P V Voulgari, Y Alamanos, C G Papadopoulos, A I Venetsanopoulou, A N Georgiadis, A A Drosos

Affiliations + expand

PMID: 15975964 PMCID: PMC1798023 DOI: 10.1136/ard.2005.039099
Free PMC article

Review › Autoimmun Rev. 2010 Jun;9(8):574-82. doi: 10.1016/j.autrev.2010.04.002.
Epub 2010 Apr 28.

Strategies after the failure of the first anti-tumor necrosis factor alpha agent in rheumatoid arthritis

Charalampos Papagoras [1], Paraskevi V Voulgari, Alexandros A Drosos

Affiliations + expand

PMID: 20433955 DOI: 10.1016/j.autrev.2010.04.002

Treatment of RA with synthetic and biological DMARDs (V)

Assessment with MRI the structural damage before and after treatment with anti TNF therapy

› Joint Bone Spine. 2005 Dec;72(6):557-61. doi: 10.1016/j.jbspin.2004.08.014. Epub 2005 Mar 30.

Magnetic resonance imaging quantification of hand synovitis in patients with rheumatoid arthritis treated with infliximab

Maria I Argyropoulou [1], Anastasia Glatzouni, Paraskevi V Voulgari, Vassilios G Xydis, Spyros N Nikas, Stavros C Efremidis, Alexandros A Drosos

Affiliations + expand

PMID: 16376805 DOI: 10.1016/j.jbspin.2004.08.014

Clinical Trial › J Rheumatol. 2006 Feb;33(2):219-23.

Magnetic resonance imaging quantification of hand synovitis in patients with rheumatoid arthritis treated with adalimumab

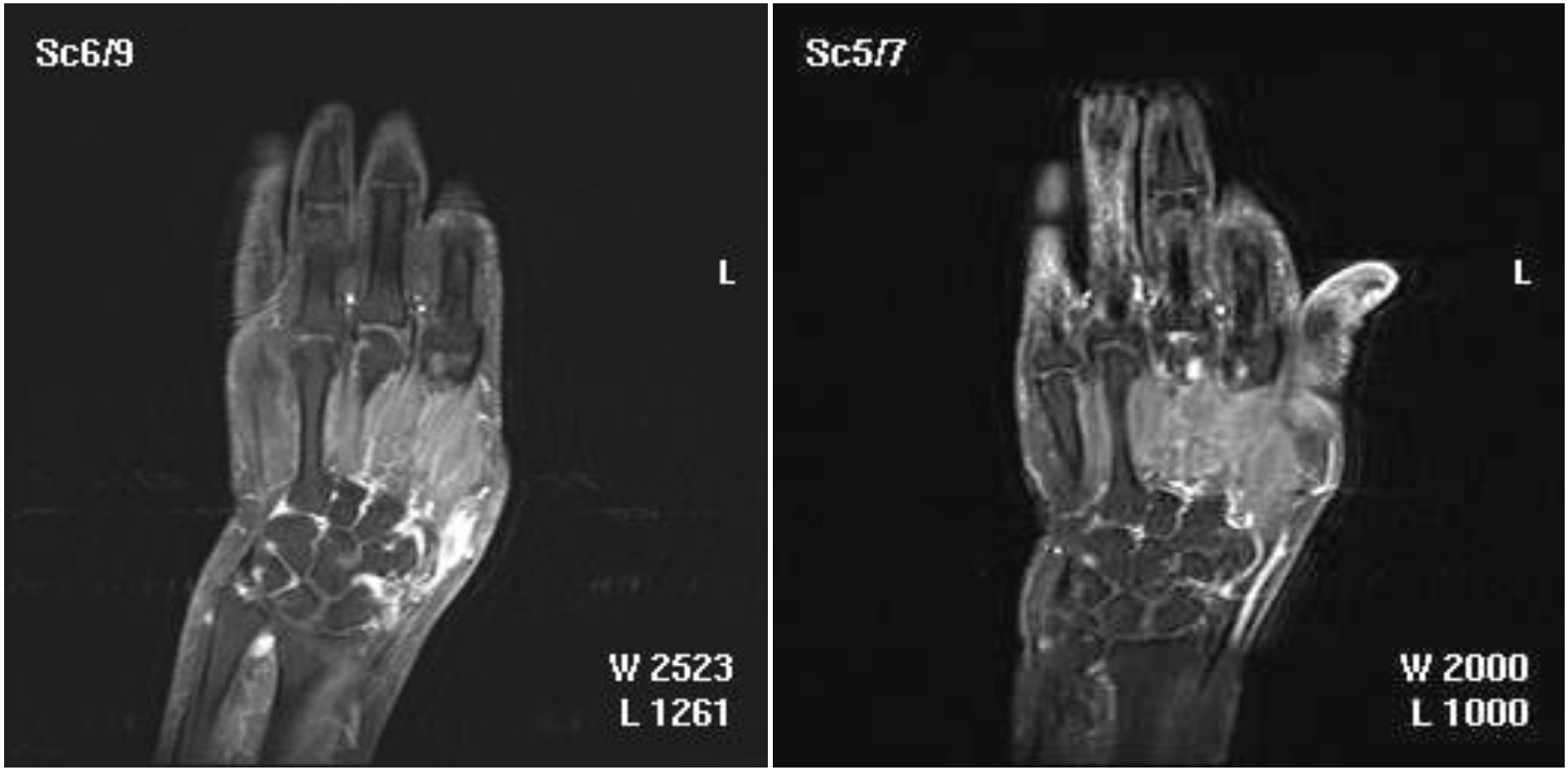
Anastasia K Zikou [1], Maria I Argyropoulou, Paraskevi V Voulgari, Vassilios G Xydis, Spyros N Nikas, Stavros C Efremidis, Alexandros A Drosos

Affiliations + expand

PMID: 16465650

FAT suppressed T1 SE

before infliximab **after infliximab**



Argyropoulou MI, et al. Joint Bone Spine 72: 557-561, 2005

Coronal fat suppressed T1 weighted contrast enhanced scan of the dominant hand showing the enhancing inflammatory tissue before (A) and after (B) treatment with adalimumab. A significant decrease of enhanced inflammatory tissue was observed after therapy.

Zikou AK, et al. J Rheumatol 33: 219-223, 2006

Biological treatment and Side Effects (II)

Case Reports > J Rheumatol. 2002 Nov;29(11):2466.

Gingival hyperplasia associated with cyclosporin A

Paraskevi V Voulgari [1], Alexandros A Drosos

Affiliations + expand

PMID: 12415611

Case Reports > Clin Rheumatol. 2007 May;26(5):787-8. doi: 10.1007/s10067-005-0197-7. Epub 2006 Jan 19.

Urticaria and angiedema–like skin reactions in a patient treated with adalimumab

S N Nikas [1], P V Voulgari, A A Drosos

Affiliations + expand

PMID: 16421645 DOI: 10.1007/s10067-005-0197-7

Case Reports > Clin Exp Rheumatol. 2015 Sep-Oct;33(5):734-6. Epub 2015 May 1.

Tuberculous pyomyositis in a rheumatoid arthritis patient treated with anakinra

Michael P Migkos [1], George A Somarakis [1], Theodora E Markatseli [1], Maria Matthaiou [2], Paraskevi Kosta [3], Paraskevi V Voulgari [1], Alexandros A Drosos [1]

Affiliations + expand

PMID: 25936426

Gingival Hypertrophy induced by CsA

Voulgari PV, Drosos AA. J Rheumatol 2002;29:11

Biological treatment and Side Effects

Case Reports > Ann Rheum Dis. 2008 Apr;67(4):567-70. doi: 10.1136/ard.2007.075663.
Epub 2007 Aug 29.

Granuloma annulare induced by anti-tumour necrosis factor therapy

P V Voulgari [1], T E Markatseli, S A Exarchou, A Zioga, A A Drosos

Affiliations + expand

PMID: 17728330 DOI: 10.1136/ard.2007.075663

> Scand J Rheumatol. 2009;38(5):328-31. doi: 10.1080/03009740902922612.

Immune-mediated skin lesions in patients treated with anti-tumour necrosis factor alpha inhibitors

S A Exarchou [1], P V Voulgari, T E Markatseli, A Zioga, A A Drosos

Affiliations + expand

PMID: 19579151 DOI: 10.1080/03009740902922612

Case Reports > Clin Exp Rheumatol. 2009 Nov-Dec;27(6):996-8.

Induction of psoriatic skin lesions in a patient with rheumatoid arthritis treated with rituximab

T E Markatseli [1], E S Kaltsonoudis, P V Voulgari, A Zioga, A A Drosos

Affiliations + expand

PMID: 20149320

ARTHRITIS & RHEUMATISM
Vol. 52, No. 8, August 2005, pp 2513–2518
DOI 10.1002/art.21233

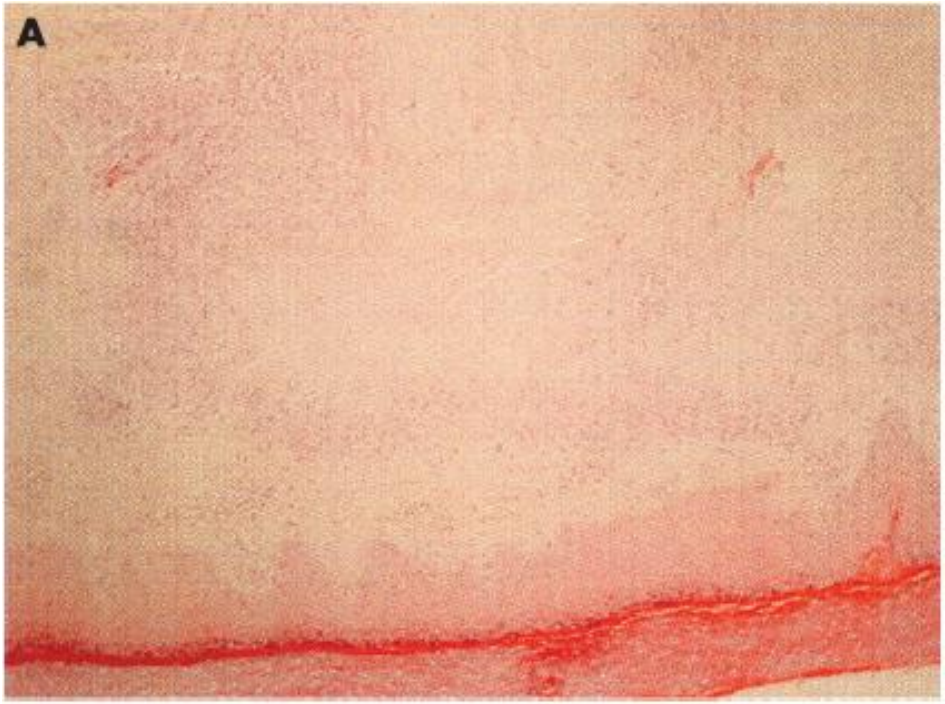
Psoriasis Induced by Anti–Tumor Necrosis Factor Therapy

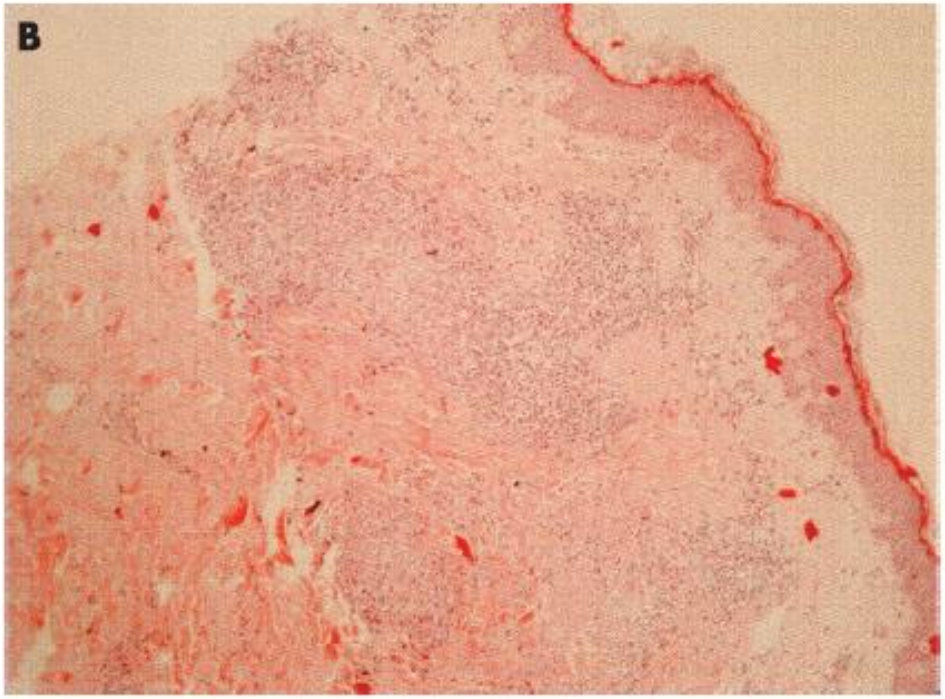
A Paradoxical Adverse Reaction

P. P. Sfikakis,[1] A. Iliopoulos,[2] A. Elezoglou,[1] C. Kittas,[1] and A. Stratigos[1]

Figure 1 Generalised form of granuloma annulare. Widespread symmetric erythematous skin eruptions covering the fingers, hand and forearms bilaterally. Informed consent was received for the publication of this image.

Voulgari PV, et al. Ann Rheum Dis. 2008;67:567-70.





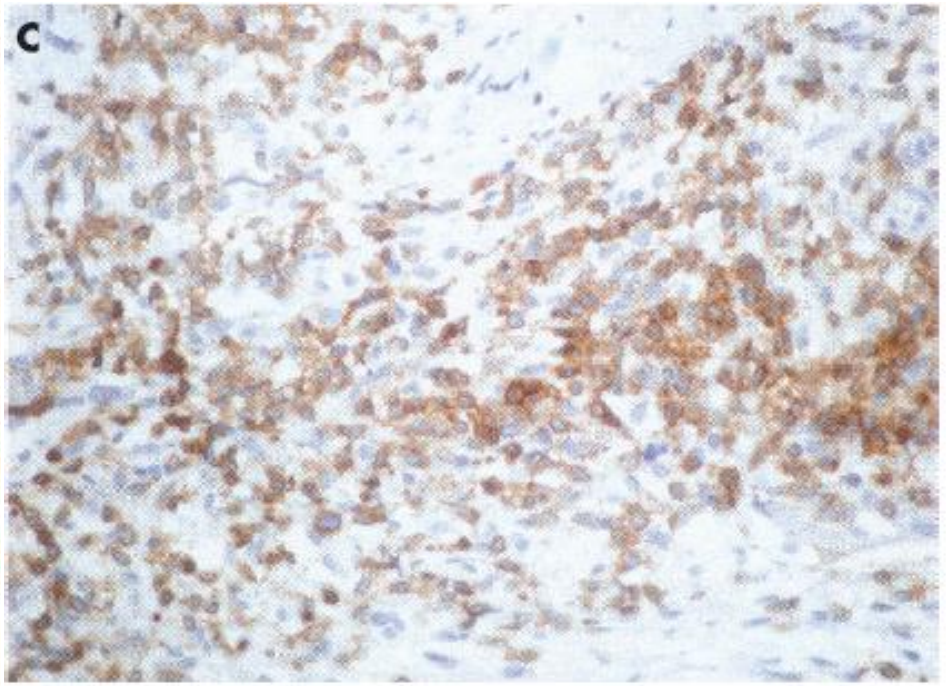
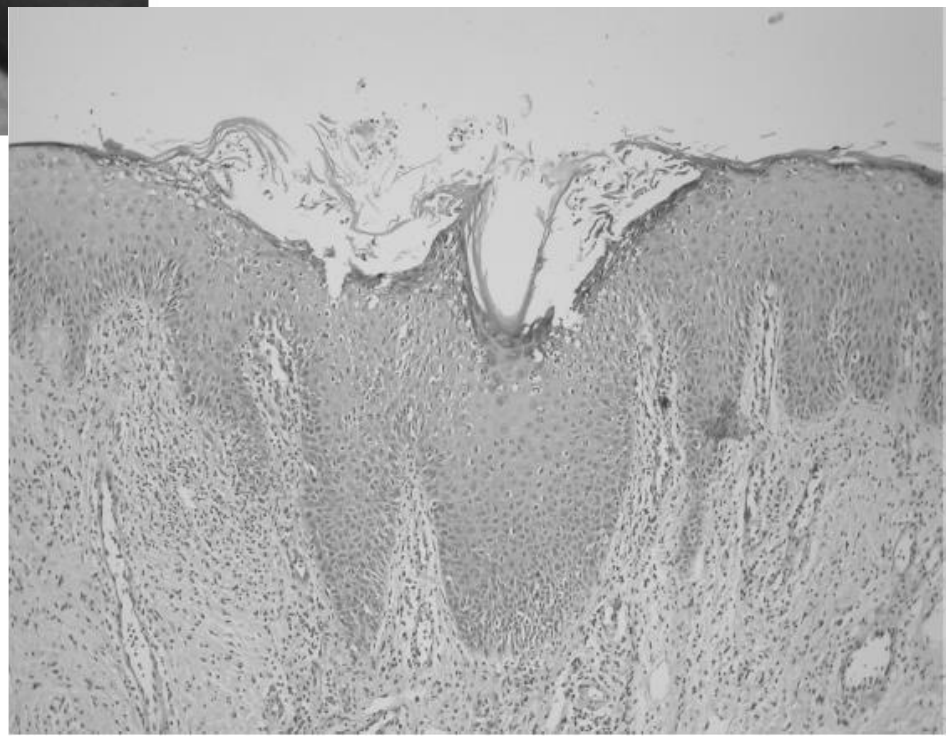


Figure 2 Palisading granuloma: a central core of degenerate collagen surrounded by a radially arranged infiltrate of histiocytes and lymphocytes (haematoxylin and eosin×100) (A). Diffuse infiltrates of histocytes and lymphocytes in the dermis around of small foci degenerated collagen (haematoxylin and eosin×100) (B). Immunohistological picture showing the presence of CD3+ T lymphocytes (× 200) (C).

Voulgari PV, et al. Ann Rheum Dis. 2008;67:567-70



Markatseli TE, Et al. Clin Exp Rheumatol. 2009;27:996-8

MEDITERRANEAN JOURNAL OF RHEUMATOLOGY | 32 2 2021

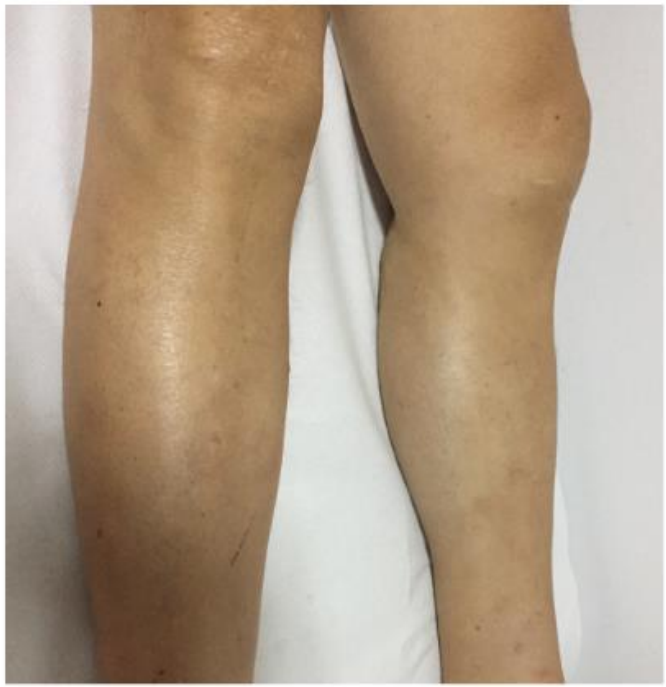
REVIEW

Biologic Therapies and Autoimmune Phenomena

Alexandros A. Drosos, Eleftherios Pelechas, Evripidis Kaltsonoudis, Theodora E. Markatseli, Paraskevi V. Voulgari

Rheumatology Clinic, Department of Internal Medicine, Medical School, University of Ioannina, Ioannina, Greece

Figure 1. A 26-year-old woman with seropositive rheumatoid arthritis refractory to methotrexate received adalimumab 40mg every 14 days subcutaneously. She responded very well, but 6 months later she developed erythematous eruptions affecting her face in a butterfly distribution and with blister formation.



Biological Therapies: Induced Autoimmune Adverse Manifestations

Alexandros A. Drosos*, **Eleftherios Pelechas, Paraskevi V. Voulgari**

Department of Internal Medicine, Rheumatology Clinic, Medical School, University of Ioannina, Ioannina, Greece

Figure 2: A 60-year-old man with seronegative rheumatoid arthritis treated with etanercept developed erythematous skin lesions affecting the face in a butterfly distribution, 4 months after initiation of the treatment. Note also the periocular and forehead erythema.

Figure 1: A 62-year-old woman with seropositive rheumatoid arthritis treated with infliximab. Six months after treatment, she developed diffuse erythematous skin eruptions in sun exposed areas affecting the face, forehead and the upper region of the chest.

Review > Curr Rheumatol Rev. 2022;18(1):72-82. doi: 10.2174/1573397117666211102094330.

TNF-induced Lupus. A Case-Based Review

Anastasia Skalkou [1], Eleftherios Pelechas [1], Paraskevi V Voulgari [1], Alexandros A Drosos [1]

Affiliations + expand

PMID: 34727862 DOI: 10.2174/1573397117666211102094330

Figure 1. A 62-years-old female with erythematous eruptions in a butterfly rash pattern after treatment with adalimumab. Note also a mild periocular and forehead erythema. Figure 1a, b: malar eruption or "butterfly rash" (erythema and oedema of cheeks, sparing the nasolabial folds). Figure 1b shows the skin findings in more detail.

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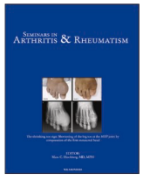

Cutaneous immune-related phenomena in patients with inflammatory arthritides treated with biological therapies: Clinical and pathophysiological considerations

Aliki I. Venetsanopoulou [a], Konstantina Mavridou [b], Paraskevi V. Voulgari [a], Alexandros A. Drosos [a,*]

[a] Rheumatology Clinic, Department of Internal Medicine, Medical School, University of Ioannina, Ioannina, Greece
[b] Department of Dermatology, University Hospital of Ioannina, Ioannina, Greece

a b

Rheumatology International (2023) 43:1751–1754
https://doi.org/10.1007/s00296-023-05364-9

Rheumatology
INTERNATIONAL

CASE BASED REVIEW

TNFα inhibitor biosimilar associated with polychondritis. A case-based review

Aliki I. Venetsanopoulou[1] · Paraskevi V. Voulgari[1] · Alexandros A. Drosos[1,2]

Received: 7 April 2023 / Accepted: 5 June 2023 / Published online: 15 June 2023

Fig. 1 A picture of auricular chondritis presenting redness and swelling of the cartilaginous part of the right ear

Fig. 2 Six months later, a normal right ear, without any redness or swelling

Biological treatment and Side Effects (III)

› Arthritis Res Ther. 2014 Jun 17;16(3):R125. doi: 10.1186/ar4582.

Neurological adverse events in patients receiving anti-TNF therapy: a prospective imaging and electrophysiological study

Evripidis Kaltsonoudis, Anastasia K Zikou, Paraskevi V Voulgari, Spyridon Konitsiotis, Maria I Argyropoulou, Alexandros A Drosos

PMID: 24938855 PMCID: PMC4229940 DOI: 10.1186/ar4582
Free PMC article

Review › Autoimmun Rev. 2014 Jan;13(1):54-8. doi: 10.1016/j.autrev.2013.09.002.
Epub 2013 Sep 12.

Demyelination and other neurological adverse events after anti-TNF therapy

Evripidis Kaltsonoudis [1], Paraskevi V Voulgari, Spyridon Konitsiotis, Alexandros A Drosos

Affiliations + expand

PMID: 24035809 DOI: 10.1016/j.autrev.2013.09.002

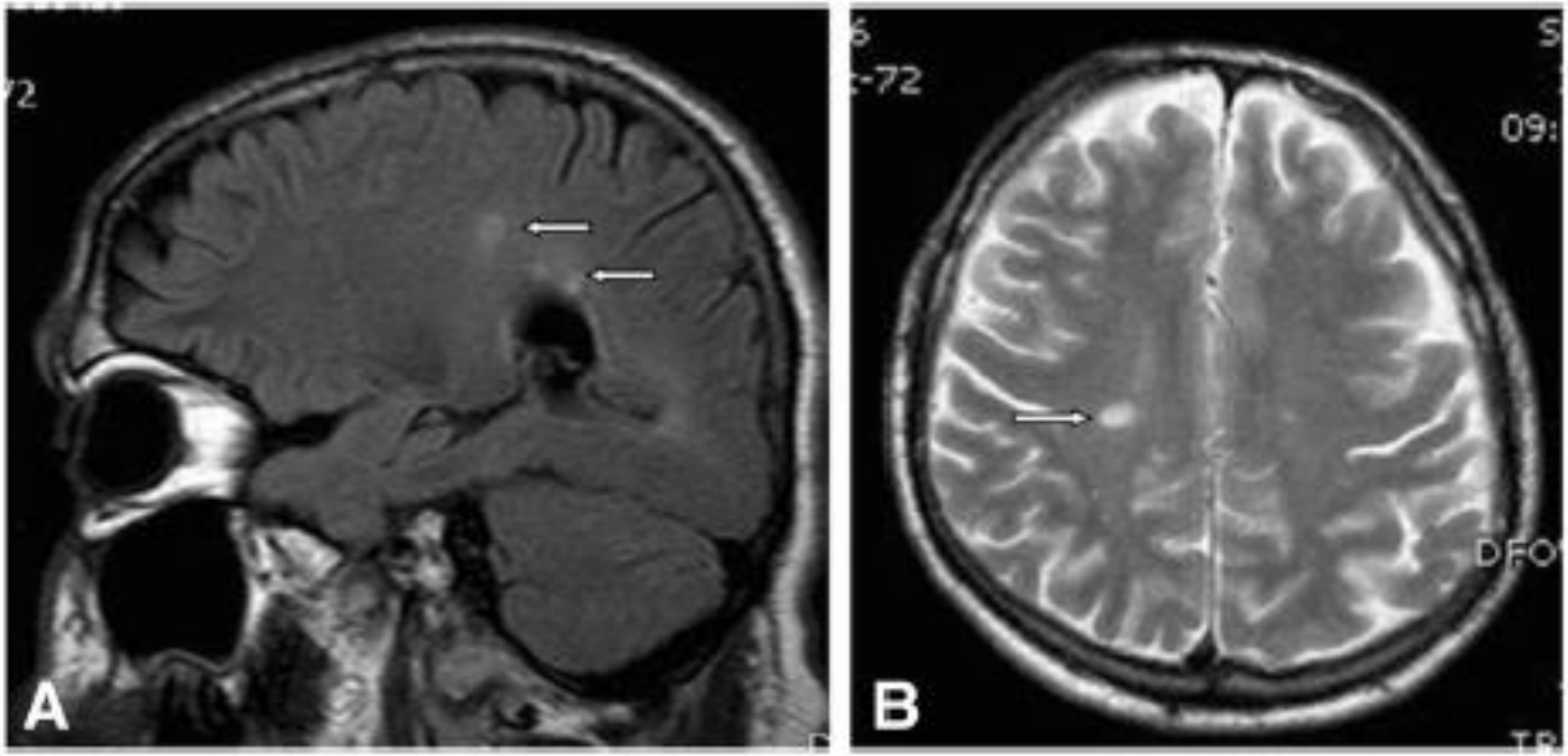

Figure 1 Sagittal fluid attenuated inversion recovery (FLAIR) (A) and axial T2-weighted (B) scans demonstrating ovoid hyperintense lesions in the deep periventricular white matter (arrows).

Kaltsonoudis E, et al. Arthritis Res Ther. 2014;16:R125.

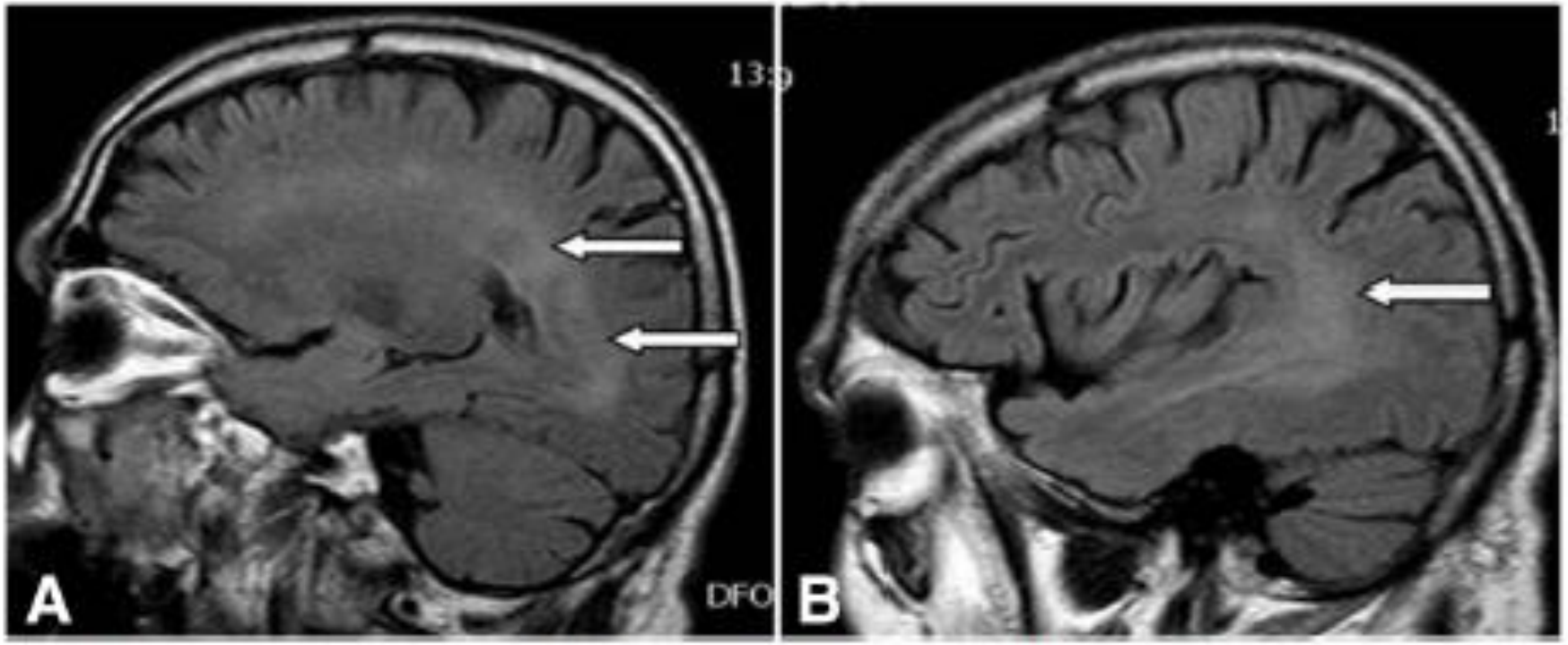

Figure 2 Sagittal fluid attenuated inversion recovery (FLAIR) scans (A, B) show bilateral diffuse hyperintense signal in the periventricular white matter of the parietal, occipital and temporal lobes (arrows).

Kaltsonoudis E, et al. Arthritis Res Ther. 2014;16:R125.

Biological Treatment Registry

› Clin Exp Rheumatol. 2012 Jan-Feb;30(1):31-8. Epub 2012 Mar 6.

Survival of TNF-alpha antagonists in rheumatoid arthritis: a long-term study

T E Markatseli [1], Y Alamanos, I Saougou, P V Voulgari, A A Drosos

Affiliations + expand

PMID: 22153557

Comparative Study › Semin Arthritis Rheum. 2014 Feb;43(4):447-57.
doi: 10.1016/j.semarthrit.2013.07.011. Epub 2013 Sep 6.

Comparative effectiveness and survival of infliximab, adalimumab, and etanercept for rheumatoid arthritis patients in the Hellenic Registry of Biologics: Low rates of remission and 5-year drug survival

Irini Flouri [1], Theodora E Markatseli [2], Paraskevi V Voulgari [2], Kyriaki A Boki [3], Ioannis Papadopoulos [4], Loukas Settas [5], Dimitrios Zisopoulos [6], Fotini N Skopouli [7], Alexios Iliopoulos [8], George K Bertsias [1], Pierre Geborek [9], Alexandros A Drosos [2], Dimitrios T Boumpas [10], Prodromos Sidiropoulos [11]

Affiliations + expand

PMID: 24012040 DOI: 10.1016/j.semarthrit.2013.07.011

Biological Treatment Registry

› Clin Exp Rheumatol. 2016 Nov-Dec;34(6):999-1005. Epub 2016 Oct 7.

Treatment with the first TNF inhibitor in rheumatoid arthritis patients in the Hellenic Registry of Biologic Therapies improves quality of life especially in young patients with better baseline functional status

Nadia Boubouchairopoulou [1], Irini Flouri [2], Alexandros A Drosos [3], Kyriaki Boki [4], Loukas Settas [5], Dimitrios Zisopoulos [6], Fotini N Skopouli [7], Ioannis Papadopoulos [8], Alexios Iliopoulos [9], John Kyriopoulos [1], Dimitrios T Boumpas [10], Konstantinos Athanasakis [1], Prodromos Sidiropoulos [11]

Affiliations + expand

PMID: 27749220

› Clin Exp Rheumatol. 2017 Jul-Aug;35(4):579-585. Epub 2017 Mar 3.

Biologic treatment for rheumatic disease: real-world big data analysis from the Greek country-wide prescription database

Petros P Sfikakis [1], Vasiliki-Kalliopi Bournia [2], Prodromos Sidiropoulos [3], Dimitrios T Boumpas [4], Alexandros A Drosos [3], George D Kitas [5], George Konstantonis [5], Stamatis N Liossis [3], Menelaos N Manoussakis [4], Lazaros Sakkas [3], Maria Tektonidou [2], Athanasios G Tzioufas [6], Panayiotis G Vlachoyiannopoulos [6], Chara Kani [7], Panayiotis Paterakis [7], Panayiota Litsa [7], Dimitrios Vassilopoulos [4]

Affiliations + expand

PMID: 28281458

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Unmet needs in the treatment of rheumatoid arthritis. An observational study and a real-life experience from a single university center

Evripidis Kaltsonoudis, Eleftherios Pelechas, Paraskevi V. Voulgari, Alexandros A. Drosos*

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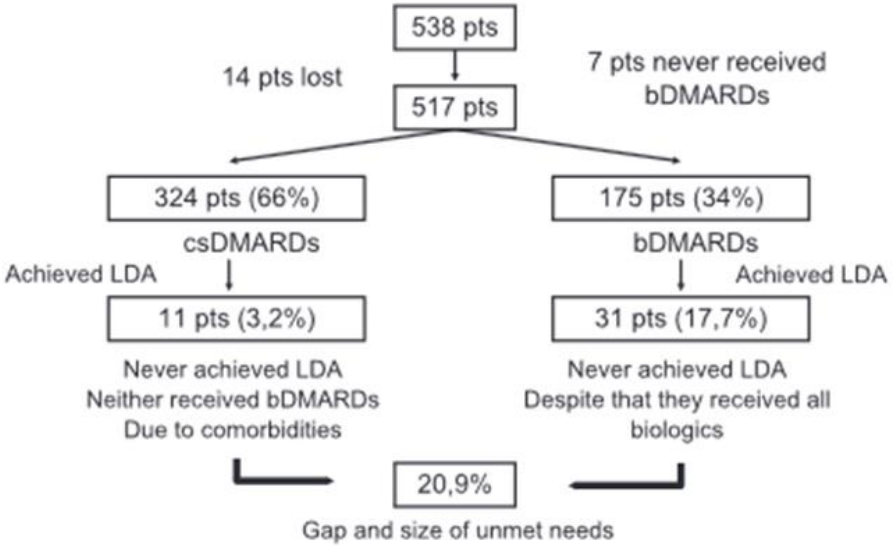

csDMARDs: conventional synthetic disease modifying anti-rheumatic drugs; bDMARDs: biological disease modifying anti-rheumatic drugs; LDA: low disease activity

Fig. 1. Treatment flow chart of early RA patients.

RA treatment

- **Treatment decisions and strategies are very crucial** to obtain a rapid disease control and to achieve possible remission or LDA.
- To this end, the **first approach** should include **early and correct diagnosis and early intervention**.
- The **second step** should **include all the cs, b, ts DMARDs** in an appropriately designed manner to each patient, according to ACR/EULAR guidelines.
- In this direction, **the treat to target strategy and close monitoring is the ideal approach**.

Clinical Rheumatology (2020) 39:1363–1368
https://doi.org/10.1007/s10067-020-05001-x

PERSPECTIVES IN RHEUMATOLOGY

Treatment strategies are more important than drugs in the management of rheumatoid arthritis

Alexandros A. Drosos[1] · Eleftherios Pelechas[1] · Paraskevi V. Voulgari[1]

Received: 22 January 2020 / Revised: 10 February 2020 / Accepted: 14 February 2020 / Published online: 22 February 2020

Abstract

The treatment of inflammatory arthritides has been changed dramatically in the past two decades with the introduction of the biological (b) disease-modifying anti-rheumatic drugs (DMARDs) as well as the targeting synthetic (ts) DMARDs that can be used as monotherapy or in combination with conventional synthetic (cs) DMARDs. The concept of treat to target (T2T) and tight control monitoring of disease activity represents a therapeutic paradigm of modern rheumatology. In rheumatoid arthritis (RA), this treatment approach has proven to be effective in many clinical trials and is now a well-established approach. The most common treatment strategies rely on the combination of csDMARDs (mainly methotrexate, sulfasalazine and hydroxychloroquine). This comes from different studies which compare the outcomes of combination therapies versus csDMARD monotherapy or versus methotrexate plus biologics in early RA patients. Here, we review the literature of the most important T2T studies for RA patients. The results showed that a tight control strategy appears to be more important than a specific drug to control RA. T2T approach aiming for remission or low disease activity can be achieved in early RA patients using less expensive drugs in comparison to newer drugs and this may need to be recognised in the future recommendations for the management of RA.

ΠΓΝΙ Αύγουστος 2017

*«Η ιατρική χρειάζεται **διακόνους** με απέραντη διάθεση για **σκληρή δουλειά, υπευθυνότητα, συμπόνια** για τον αδύναμο, **γενναιοδωρία, μεγαλοψυχία, ανιδιοτέλεια** και **σεβαστό** στα δικαιώματα του πάσχοντος και πάνω απ΄ όλα ενημέρωση και διάβασμα ώστε να είστε ικανοί να προσφέρετε την πλέον σύγχρονη διάγνωση και αποτελεσματική θεραπεία…»*

*«**Η ιατρική θέλει ανθρώπους που να την αγαπούν με πάθος**. Θέλει δηλαδή εραστές, θέλει άτομα που να μην αισθάνονται ότι εργάζονται αλλά να αγωνιούν να πάνε το πρωί στη δουλειά τους για να προσφέρουν στο συνάνθρωπο.»*

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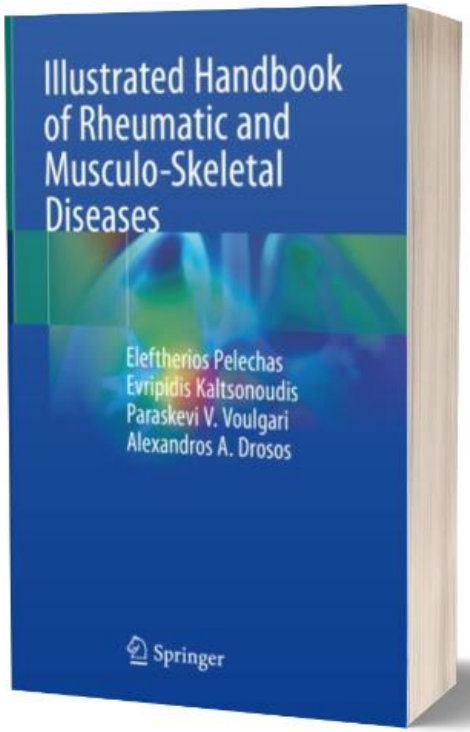

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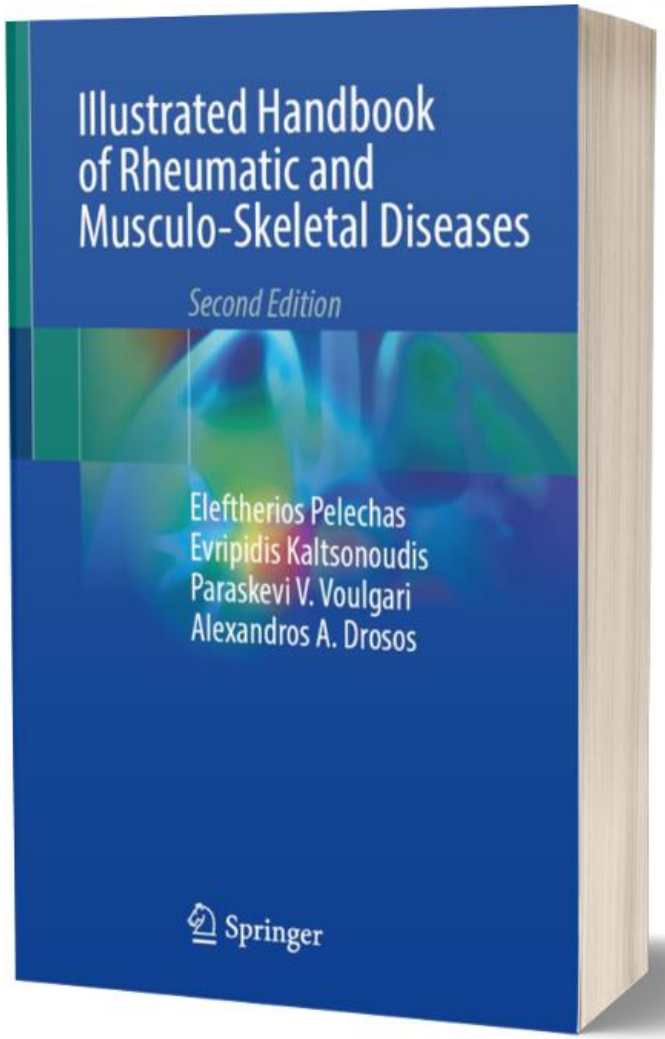

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