ORIGINAL ARTICLE

Which Factors are Predictive for Presence of Insulin Resistance in Patients with Rheumatoid Arthritis?

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ABSTRACT

Objective: *To investigate obesity and insulin resistance and associated factors in patients with rheumatoid arthritis (RA).*

Methods: *We included a cohort of patients with RA. In the clinical research, duration of disease, existence of clinical remission (disease activity index [DAS] 28 below 2.6) and amount of the relevant disease-modifying anti-rheumatic drugs were derived from clinical datum. Cumulative corticosteroid dose was calculated by duration of corticosteroid usage and ratio of physiologic dose. Insulin resistance was calculated with the homeostasis model of assessment of insulin resistance.*

Results: *A total of 64 patients aged between 22 and 77 with RA were studied. Insulin resistance was detected in 34.4% (n = 22) of patients. There was a statistically significant correlation between body mass index and DAS28 scores (*r *= 0.469,* p *= 0.000). We found that the incidence of insulin resistance was lower in patients treated with methotrexate at least 1 year (*p *= 0.001). As long as we did not detect insulin resistance, none of the patients (n = 7) treated with tumour necrosis factor (TNF) blockers. Cumulative steroid dose, presence of obesity and DAS28 were the best predictors for insulin resistance according to multivariate linear regression analysis (*R^2c *= 0.242,* F *= 6.39,* p *< 0.001). In this model* R^2c *for cumulative steroid dose was 0.113 (*F *= 7.88* p *< 0.007) and obesity was 0.147 (*F *= 10.67,* p *= 0.02).*

Conclusion: *Obesity and long-standing corticosteroid usage were determinants of insulin resistance in patients with RA. Medications such as methotrexate, TNF blockers may help to reduce insulin resistance.*

Keywords: Insulin resistance, methotrexate, remission, rheumatoid arthritis, obesity

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease associated with increased disability, morbidity and mortality (1). The synovial membrane is the primary site of rheumatoid inflammation. In addition to articular symptoms, extraarticular manifestations are present in approximately 30% of chronic patients with RA. Systemic inflammation can lead to constitutional symptoms such as low-grade fever, fatigue, malaise, myalgias, weight loss and metabolic disorders.

In the last two decades, adipose tissue was promoted to an active endocrine organ and was also implicated in obesity which is a low-grade inflammatory state, such as inflammatory conditions including RA (2).

High levels of leptin, adiponectin and resistin in adipose tissue are associated with an increased inflammatory state in obesity. Moreover, increased insulin resistance and metabolic demand of insulin are considered another problem related to obesity. Some researchers claim that

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there may be a possible aetiological link between obesity and certain autoimmune diseases such as RA (3, 4).

The relationship between obesity and inflammation has been demonstrated in the past decades and those two entities are certainly linked with insulin resistance. Obesity studies in patients with endocrinologic diseases and other conditions related to insulin resistance have pointed tumour necrosis factor (TNF), interleukin IL-6 and IL-8 levels (5, 6). The mechanisms generating low-level inflammation in obesity are not known in depth.

Although patients with RA show a high prevalence of obesity, dyslipidemia or impaired glucose metabolism, few studies have specifically investigated insulin resistance in RA. This study was accomplished for the assessment of obesity and insulin resistance and associated factors in patients with RA.

MATERİALS AND METHODS

Sixty-four enrolled patients who were followed at the Rheumatology Policlinics in the Medicine Faculty Hospital between April 2013 and April 2014 and fulfilled the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) 2010 RA classification criteria, were included in the study. ACR/EULAR RA classification criteria included (a) joint involvement (b) RF and anti-CCP positivity (c) acute phase reactants (d) duration of symptoms (7).

Informed consent was obtained from all patients. The study protocol was approved by the Ethics Committee of Sakarya University. The patients' age, gender and body mass index (BMI) were registered. In the clinical research, the patients' duration of disease, the existence of clinical remission, the relevant disease-modifying anti-rheumatic drugs (DMARD) amount and the existence of family history were taken as notes. Cumulative corticosteroid dose was calculated by duration of corticosteroid usage and ratio of physiologic dose. Body mass index values < 18.5 kg/m^2 are considered underweight, between 18.5 and 24.9 as normal, 25 and 29.9 as overweight and values greater than 30 indicated obesity (8). Thirty-two patients with BMI higher than 30 kg/m^2 were assigned as obesity group. We excluded patients with diabetes mellitus and acute or chronic pancreatic disorders.

Disease activity score (DAS28) remission criteria, involving C reactive protein (CRP), swollen and tender joint counts and patient's global health assessment were used to determine whether the disease in remission. A score of DAS28 between 2.6 and 3.2 indicates low disease activity, 3.2 and 5.1 moderate and > 5.1 high disease activity (9).

In this study, the assessment of insulin was done with experimental method in which *in vitro* frozen (–20°C) serum samples were re-evaluated. The following parameters were determined from the patients' own charts: fasting plasma glucose, haemoglobin A1C (HbA1C), erythrocyte sedimentation rate (ESR), CRP and haemogram parameters such as white blood cell, platelet, mean platelet volume, platelet distribution width, neutrophil/lymphocyte ratio (N/L ratio) and ferritin levels by standard laboratory methods.

Insulin resistance was evaluated from the homeostasis model of assessment of insulin resistance (HOMA-IR) (10). The HOMA-IR was calculated from fasting plasma glucose and fasting serum insulin concentrations using the following formula (fasting plasma glucose [mg/dL] × fasting serum insulin [mU/L]/405) Therefore, values were considered abnormal when HOMA-IR index was > 2.5.

Statistical analysis

Descriptive statistics were performed and indicated as mean ± standard deviation and median for continuous variables. All qualitative data are expressed as frequencies and percentages. Correlations were investigated by univariate analysis and multivariate linear regression models, when appropriate. Statistical testing of differences in continuous variables between groups was made by Mann–Whitney *U* test. *p* values less than 0.05 were considered significant. All statistical analyses were done using SPSS for windows version 20.0 program.

RESULTS

We included 64 patients with RA in the study. The clinical characteristics of the patients were given in Table 1.

Table 1: Clinical characteristics of 64 study patients with rheumatoid arthritis

Age, mean ± SD years, interquartile range (IQR)	56.23 ± 11.26 [56.50]
Sex, women%	76.6
Cigarette smoking, patients%	32.8
BMI, kg/cm^2, IQR	29.41± 5.26 [28.62]
Disease duration, mean ± SD years, IQR	7.76 ± 7.92 [6.50]
Rheumatoid arthritis family history, patients%	46.8

BMI = body mass index; IQR = interquartile range.

In the obesity group and controls showed homogeneous characteristics in terms of demographical and some clinical characteristics ($p > 0.05$) (Table 2).

The ratio of patients with clinical remission were 37.5% (n = 24) and low disease activity and moderate

disease activity were 20.3% (n = 13) and 42.2% (n = 27), respectively. In evaluation of disease activity by DAS28, there was a statistically significant correlation between BMI and DAS28 scores as shown in Figure (r = 0.469, p = 0.006).

Insulin resistance were detected in 34.4% (n = 22) of patients. We found differences in some laboratory measurements; N/L ratio was statistically significantly lower in obese patients (p = 0.036). HbA1c levels were higher in obese patients (p = 0.033). Insulin resistance was found in obesity group in comparison of controls (z = −2.089, p = 0.037). Furthermore, there were no statistically significant differences between laboratory parameters other than HbA1c, N/L ratio, insulin resistance ($p > 0.05$) (Table 3).

There was no difference between the types of other DMARDs in each group. Methotrexate has been the first choice in both groups. The ratio of medication used in obesity group were as follows: methotrexate, leflunomide, hydroxychloroquine sulphate, sulphasalazine, TNF blockers (two patients adalimumab, one patient golimumab) and rituximab (one patient), 75%, 42%, 31%, 24%, 9% and 3%, respectively. The ratio of medication in the control group were as follows; methotrexate, leflunomid, hydroxychloroquine sulphate, sulphasalazine and TNF blockers (two adalimumab, two etanercept), 75%, 59%, 42%, 42% and 12%, respectively.

There was significant correlation between insulin resistance and cumulative corticosteroid dose (r = 0.336, p = 0.007). We found that the incidence of insulin resistance was lower in patients treated with methotrexate at least 1 year (16% *vs* 50%, r = –0.428, p = 0.001). As long as, we did not detect insulin resistance, none of the patients (n = 7) treated with TNF blockers.

A significant correlation between insulin resistance and BMI scores was found (r = 0.383, p = 0.002). A moderate correlation was found between insulin resistance and cumulative steroid dose (r = 0.436, p = 0.000). A weak correlation was found between insulin resistance and CRP levels (r = 0.277, p = 0.045). There was no correlation between insulin resistance and other clinical parameters (age, sex, disease duration, cigarette smoking and family history) ($p > 0.05$).

To establish the best model to predict insulin resistance, multivariable linear regression analysis was performed choosing the variables that were significantly correlated by univariate analysis with insulin resistance. Thus, the dependent variable was the insulin resistance and the independent variables were DAS28, cumulative steroid dose and BMI, respectively. The stepwise

Table 2: A comparison of rheumatological features in RA patients with or without obesity

	Obesity group (n = 32)	Control group (n = 32)	p value
Age, mean ± SD years	56.41 ± 9.38	56.06 ± 13.03	0.941
Sex, women%	77.5	75.2	0.615
BMI, kg/cm^2	33.65 ± 3.67	25.17 ± 2.37	0.690
Cigarette smoking, patients%	32.9	32.1	0.400
Disease duration, mean ± SD years	7.87 ± 7.72	8.06 ± 7.85	0.902
Rheumatoid arthritis family history, patients%	37.5	40.6	0.799

BMI = body mass index

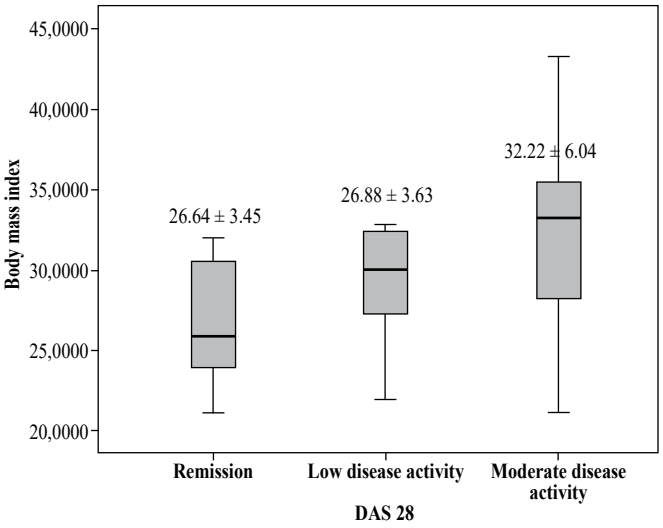

Figure: Correlation between body mass index and disease activity in patients with rheumatoid arthritis.

Table 3: Comparison of laboratory characteristics in patients and control group

	Obesity group	Control group	p value
Fasting glucose (mg/dL)	101.44 ± 16.04	94.25 ± 12.05	0.098
HbA1c (%)	5.61 ± 0.54	5.24 ± 0.70	**0.033**[a]
C reactive protein	6.70 ± 3.58	6.53 ± 6.73	0.113
Erythrocyte sedimentation rate (mm/h)	17.91 ± 14.83	19.10 ± 14.01	0.276
Platelet count	242.91 ± 57.58	240.69 ± 56.95	0.629
Mean platelet volume	7.65 ± 0.83	7.35 ± 0.91	0.086
Neutrophil/lymphocyte	2.08 ± 0.77	2.81 ± 1.38	**0.036**
Ferritin	45.07 ± 54.63	67.46 ± 81.21	0.486
Insulin	10.57 ± 9.64	9.56 ± 4.46	0.224
Insulin resistance (patients%)	46.9	21.13	**0.040**

HbA1c = glycated haemoglobin.
[a]Bold values are significant at the 0.05 level

procedure selected DAS28, cumulative steroid dose, presence of obesity as the best predictors (R^2c = 0.242, F = 6.39, $p < 0.001$). In this model R^2c for cumulative steroid dose was 0.113 (F = 7.88, $p < 0.007$) and obesity was 0.147 (F = 10.67, p = 0.02). When we added HbA1c and N/L ratio to the model, these parameters have been established not a significant predictor of insulin resistance (R^2c = 0.031, F = 0.901, p = 0.412).

DISCUSSION

Obesity and inflammation are clearly related to insulin resistance and evidence of this relationship has been revealed in the last decades. The most important theory is the local cellular hypoxia of adipose tissue and activation of inflammatory cytokines secreted by adipocytes such as resistin, adiponectin and leptin (11). Insulin resistance is a pathological condition characterised by defective insulin signal processing and alteration of the physiological response of peripheral tissues to insulin hormone. It might be inevitable that the high levels of proinflammatory cytokines that release in chronic diseases such as RA would induce an inappropriate tissue response to insulin. Alongside the present studies with conflicting results about insulin resistance in RA, there are no conclusive studies about medications' effects on insulin resistance. The pathogenesis of this condition is not clearly known, but it is needed to perform more detailed research.

Ajeganova *et al* (12) showed that high BMI scores were poor prognostic markers for patient with RA. In recent years, it has been suggested that adiponectin which is secreted from adipose tissue is associated with disease progression in RA (13–15). This molecule may induce osteoclast differentiation by stimulating receptor activator of nuclear factor kappa-B ligand, and also may upregulate vascular endothelial growth factor (16). In clinical research, Harle *et al* (17) concluded that adalimumab therapy did not induce a decrease in adiponectin and leptin levels. Contrary to this information, there are some controversial data about adiponectin and leptin in RA. Towards the results of our study, receiving regular treatment for at least 1 year, it may be generally provided that disease activity of patients with RA was higher in obese patients than controls. To our knowledge, adipose tissue may blockade remission by inducing the production of cytokines such as TNF alpha, IL1 ve IL6.

In the literature, the vast majority of studies about insulin resistance are related to determining cardiovascular risk in patients with RA. Chung *et al* (18) studied insulin resistance in 104 patients with RA and compared the results with those of 124 cases of systemic lupus erythematosus. They found that patients with RA were more likely to develop insulin resistance than lupus patients. Also, this study revealed that BMI score was an independent risk factor unrelated to corticosteroid use. There was no detailed data about calculation of corticosteroid use in the above study. Furthermore, they found that insulin resistance correlated with DAS28 scores, CRP, ESR and extent of coronary calcification. La Montagna *et al* (19) determined high correlation between insulin resistance and subclinical atherosclerosis.

We pointed out one of the important details in this study that the current cumulative steroid dose and daily steroid dose were indicated separately. Moreover, in the development of insulin resistance accumulation of steroid dose may be considered to be more effective. Dessein *et al* (20) studied insulin resistance and beta-cell function in 94 patients with RA. They concluded that HOMA-IR was related to marker for inflammation such as CRP, ESR and diseases activity measured by DAS28. Also, they showed insulin resistance was associated with waist circumference, presence of arterial hypertension and use of diuretics and beta-blockers. Multiple regression analysis indicated that the most significant factor with insulin resistance was abdominal obesity (39–56%), although disease activity was less (5%). Beta-cell function was evaluated with HOMA-B% in this study; cumulative steroid dose was the most important factor of determining beta-cell function. Other studies have also pointed out a positive relationship between CRP levels and HOMA scores in patients with RA and were attributed to an important role of this protein (20, 21).

Contrary to these studies, Garcia Diaz *et al* (22) found no differences in HOMA index between 74 patients with RA and controls. Insulin resistance was not related to disease activity and inflammatory activity. A correlation was found only between insulin resistance and waist circumference.

The main strength and originality of our study are the identification of risk factors and find out which treatments affect insulin resistance in patients with RA. In our study, we found that the cumulative steroid dose and obesity were the most important factors affecting insulin resistance. Also, we claimed that CRP levels and disease activity had relatively less impact on insulin resistance. According to the multiple regression analysis, we showed that HbA1c and N/L ratio are not valuable. One of the advantages of the study was that cumulative steroid dose was to be well quantified.

RA medications that affect insulin resistance in the literature, especially when compared to the multitude of studies on TNF blockers attract attention. There are conflicting results of those studies on TNF blockers. Whereas few studies resolved that there was no improvement in insulin resistance with TNF blockers (23, 24). The majority of studies concluded that there was a reduction of insulin resistance in patients receiving TNF blockers for RA (25, 26). Only seven patients using TNF blockers were included in the study and insulin resistance was not observed in anyone.

Neutralisation of TNF by TNF blockers can decrease cytokines which stimulates the development of insulin resistance. Furthermore, we found that the incidence of insulin resistance was lower in patients treated with methotrexate at least 1 year (16% *vs* 50%, $r = –0.428$, $p = 0.001$).

In light of our study, corticosteroids and obesity can be seen substantially responsible for insulin resistance in these patients. We also evaluated the remarkable effect of methotrexate for the elimination of insulin resistance. They are relatively novel findings for patients with RA. It is noteworthy that usage of methotrexate and TNF blocker can prevent the development of insulin resistance.

As a contradiction, low-dose continuous corticosteroid use have suggested as DMARDs in RA (27). This condition will create a confusing situation for clinicians. These data suggest that their effects of insulin resistance and impaired glucose metabolism counteract their beneficial effect on inflammation. In the light of this information, we may recommend to clinicians that short-term use of corticosteroids because of side effects on glucose metabolism and burden of disease more than conventional DMARDs and TNF-blocker.

CONCLUSION

Obesity and long-standing corticosteroid use were determinants of insulin resistance in these patients. Also, higher BMI was associated with increased disease activity of RA. Steroids can inhibit the activity of the disease otherwise it can lead to metabolic problems. We conclude that medications such as methotrexate, TNF blockers can be more physiological and less metabolic side effects than steroids in RA treatment.

AUTHORS' NOTE

There was no conflict of interest.

REFERENCES

1. Rall LC, Roubenoff R. Rheumatoid cachexia: metabolic abnormalities, mechanisms and interventions. Rheumatology (Oxford) 2004; **43:** 1219–23.
2. Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante Jr AW. Obesity is associated with macrophage accumulation in adipose tissue. J Clin Invest 2003; **112:** 1796–808.
3. Harpsoe MC, Basit S, Andersson M, Nielsen NM, Frisch M, Wohlfahrt J et al. Body mass index and risk of autoimmune diseases: a study within the Danish National Birth Cohort. Int J Epidemiol 2014 ; **43:** 843–55.
4. Labitigan M, Bahče-Altuntas A, Kremer JM, Reed G, Greenberg JD, Jordan N et al. Higher rates and clustering of abnormal lipids, obesity, and diabetes mellitus in psoriatic arthritis compared with rheumatoid arthritis. Arthritis Care Res (Hoboken) 2014; **66:** 600–7.
5. Roytblat L, Rachinsky M, Fisher A, Greemberg L, Shapira Y, Douvdevani A et al. Raised interleukin-6 levels in obese patients. Obes Res 2000; **8:** 673–5.
6. Hotamisligil GS, Arner P, Caro JF, Atkinson RL, Spiegelman BM. Increased adipose tissue expression of tumor necrosis factor-alpha in human obesity and insulin resistance. J Clin Invest 1995; **95:** 2409–15.
7. Neogi T, Aletaha D, Silman AJ, Naden RL, Felson DT, Aggarwal R et al. The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis: phase 2 methodological report. Arthritis Rheum 2010; **62:** 2582–91.
8. Physical Status the Use and Interpretation of Anthropometry: In Report of a WHO expert committee. World Health Organ Tech Rep Ser 1995; **854:** 1–452.
9. Wells G, Becker JC, Teng J, Dougados M, Schiff M, Smolen J et al. Validation of the 28-joint Disease Activity Score (DAS28) and European League Against Rheumatism response criteria based on C-reactive protein against disease progression in patients with rheumatoid arthritis, and comparison with the DAS28 based on erythrocyte sedimentation rate. Ann Rheum Dis 2009; **68:** 954–60.
10. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. Diabetes Care 2004; **27:** 1487–95.
11. Andersson CX, Gustafson B, Hammarstedt A, Hedjazifar S, Smith U. Inflamed adipose tissue, insulin resistance and vascular injury. Diabetes Metab Res Rev 2008; **24:** 595–603.
12. Ajeganova S, Andersson ML, Hafström I; BARFOT Study Group. Association of obesity with worse disease severity in rheumatoid arthritis as well as with comorbidities: a long-term followup from disease onset. Arthritis Care Res (Hoboken) 2013; **65:** 78–87.
13. Crowson CS, Matteson EL, Davis III JM, Gabriel SE. Contribution of obesity to the rise in incidence of rheumatoid arthritis. Arthritis Care Res (Hoboken) 2013; **65:** 71–7.
14. Ebina K, Fukuhara A, Ando W, Hirao M, Koga T, Oshima K et al. Serum adiponectin concentrations correlate with severity of rheumatoid arthritis evaluated by extent of joint destruction. Clin Rheumatol 2009; **28:** 445–51.
15. Klein-Wieringa IR, van der Linden MP, Knevel R, Kwekkeboom JC, van Beelen E, Huizinga TW et al. Baseline serum adipokine levels predict radiographic progression in early rheumatoid arthritis. Arthritis Rheum 2011; **63:** 2567–74.
16. Luo XH, Guo LJ, Xie H, Yuan LQ, Wu XP, Zhou HD et al. Adiponectin stimulates RANKL and inhibits OPG expression in human osteoblasts through the MAPK signaling pathway. J Bone Miner Res 2006; **21:** 1648–56.
17. Härle P, Sarzi-Puttini P, Cutolo M, Straub RH. No change of serum levels of leptin and adiponectin during anti-tumour necrosis factor antibody treatment with adalimumab in patients with rheumatoid arthritis. Ann Rheum Dis 2006; **65:** 970–1.
18. Chung CP, Oeser A, Solus JF, Gebretsadik T, Shintani A, Avalos I et al. Inflammation-associated insulin resistance: differential effects in rheumatoid arthritis and systemic lupus erythematosus define potential mechanisms. Arthritis Rheum. 2008; **58:** 2105–12.
19. La Montagna G, Cacciapuoti F, Buono R, Manzella D, Mennillo GA, Arciello A et al. Insulin resistance is an independent risk factor for

atherosclerosis in rheumatoid arthritis. Diab Vasc Dis Res 2007; **4:** 130–5.
20. Dessein PH, Joffe BI, Stanwix A, Botha AS, Moomal Z. The acute phase response does not fully predict the presence of insulin resistance and dyslipidemia in inflammatory arthritis. J Rheumatol 2002; **29:** 462–6.
21. Dessein PH, Norton GR, Woodiwiss AJ, Joffe BI, Solomon A. Independent role of conventional cardiovascular risk factors as predictors of C-reactive protein concentrations in rheumatoid arthritis. J Rheumatol 2007; **34:** 681–8.
22. Garcia Diaz Jde D, Lopez de Guzman A, Sivera Monzo L, Cuende Quintana E. Significado de la resistencia a la insulina en la enfermedad vascular asociada a la artritis reumatoide. Med Clin (Barc) 2008; **130:** 197–8.
23. Rosenvinge A, Krogh-Madsen R, Baslund B, Pedersen BK. Insulin resistance in patients with rheumatoid arthritis: effect of anti-TNFα therapy. Scand J Rheumatol 2007; **36:** 91–6.
24. Martinez-Abundis E, Reynoso-von Drateln C, Hernandez-Salazar E, Gonzalez-Ortiz M. Effect of etanercept on insulin secretion and insulin sensitivity in a randomized trial with psoriatic patients at risk for developing type 2 diabetes mellitus. Arch Dermatol Res 2007; **299:** 461–5.
25. Oguz FM, Oguz A, Uzunlulu M. The effect of infliximab treatment on insulin resistance in patients with rheumatoid arthritis. Acta Clin Belg 2007; **62:** 218–22.
26. Huvers FC, Popa C, Netea MG, Van den Hoogen FH, Tack CJ. Improved insulin sensitivity by anti-TNFalpha antibody treatment in patients with rheumatic diseases. Ann Rheum Dis 2007; **66:** 558–9.
27. Engvall IL, Svensson B, Boonen A, van der Heijde D, Lerner UH, Hafström I; BARFOT study group. Low-dose prednisolone in early rheumatoid arthritis inhibits collagen type I degradation by matrix metalloproteinases as assessed by serum 1CTP—a possible mechanism for specific inhibition of radiological destruction. Rheumatology (Oxford) 2013; **52:** 733–42.