Systemic inflammation in osteoarthritis

Several studies have shown that the acute phase response may take place in osteoarthritis (OA), suggesting that low grade systemic inflammation may be present in patients with OA.\(^1\)\(^2\) I read with interest the paper by Stürmer et al on high sensitivity C-reactive protein (CRP) in relation to the severity and extent of OA.\(^3\) As assessed by high sensitivity nephelometry, serum high sensitivity CRP was higher in 770 patients with advanced OA than in 567 age and sex matched healthy controls (geometric mean 2.5 mg/l v 1.7 mg/l, respectively). Moreover, severity of pain as measured by a visual analogue scale was associated with mean high sensitivity CRP. Interestingly, neither the bilateral nor the generalised extent of OA, nor any of the dimensions of the Western Ontario and McMaster Universities OA index (WOMAC) were associated with mean high sensitivity CRP concentrations. The authors concluded that the subjective severity of pain is associated with low level systemic inflammation in OA, and measurement of high sensitivity CRP may have some potential for monitoring and/or predicting the clinical course of OA.

In contrast with CRP, some acute phase proteins like α1-acid glycoprotein (AGP) or α1-antichymotrypsin (ACT) are glycoproteins and possess glycosylation sites attached by N-glycosidically bound, complex-type oligosaccharide side chains.\(^4\) Heteroglycans of acute phase proteins share the common core structure but differ in their outer chain sequences. According to the number of these oligosaccharide chains bi-, tri- and tetra-antennary heteroglycans can be distinguished. This structural diversity (termed “microheterogeneity”) results in different reactivity with the lectin concanavalin A (con A). It has been shown that biantennary side chains react strongly with con A. Thus, diverse microheterogeneous forms of acute phase glycoproteins, containing different number of biantennary heteroglycans, differ in their reactivity with con A.\(^5\) Glycosylation of acute phase proteins takes place in the liver and is controlled by cytokines.\(^6\)

Affinity immunoelectrophoresis with con A is a simple technique that can be used to study the glycosylation pattern of acute phase proteins.\(^7\) Glycosylation variants of AGP/ACT can be separated during electrophoresis in a gel containing con A, and the area enclosed by the precipitates representing microheterogeneous variants of AGP and ACT can be measured by planimetry (fig 1). The results are usually expressed as the reactivity coefficients (AGP RC and ACT RC, respectively), calculated according to the formula: total area under the peaks of the con A reactive variants divided by the area enclosed by the peak representing the con A non-reactive variant.

Using affinity immunoelectrophoresis, we studied the systemic inflammatory response in 61 patients with OA classified as having clinically active (patients with rest joint pain, tenderness, joint swelling or effusion, n = 37) and clinically non-active (patients with radiological evidence of OA with no or mild clinical symptoms, n = 24) disease.\(^8\) In contrast with the study by Stürmer et al, patients with advanced OA and severe deformities were not included.

We found a significant decrease in the reactivity of AGP and ACT with con A in patients with clinically non-active disease (p<0.001 and p<0.05 for AGP RC and ACT RC, respectively, fig 2). Concentrations of AGP, ACT, and low sensitivity CRP did not differ significantly between the groups. Serum concentrations of interleukin (IL) 1β, IL 6, and tumour necrosis factor α (TNFα) were either undetectable or low. However, in six of the seven synovial fluids available, IL6 concentrations were higher than in the respective serum samples. For TNFα the same could be shown in one case only.

Our findings suggest that there are changes in the microheterogeneity of acute phase glycoproteins in OA similar to those seen in rheumatoid arthritis and other chronic inflammatory conditions.\(^9\) As glycosylation of acute phase proteins does not depend on the expression of genes encoding the polypeptide chains of these proteins,\(^7\) glycosylation of acute phase glycoproteins may possibly be more sensitive to the cytokine control than their synthesis. Thus, even small fluctuations in the serum profile of cytokines might eventually lead to alterations in the microheterogeneity of acute phase glycoproteins, while having no apparent influence on their serum concentration. Our data suggest that determination of microheterogeneity of acute phase glycoproteins may help to determine systemic inflammatory activity in OA and may possibly be more sensitive than measurement of serum concentration of acute phase proteins, including high sensitivity CRP.

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References


Figure 1 Glycosylation pattern of AGP (A) and ACT (B) in the sera of patients with clinically non-active (left) and clinically active OA (right). Note relative increase in the concentration of con A non-reactive variant 0 combined with decrease in the concentration of the con A reactive variants 1–3 in the serum of a patient with clinically active disease compared with the patient with clinically non-active OA.

Figure 2 Notched box and whiskers plots showing statistical summaries (medians, 95% confidence limits, square root of the number of observations, range, and extreme values) of AGP RC and ACT RC. (A) AGP RC in patients with clinically active OA; (B) AGP RC in patients with clinically non-active OA; (C) ACT RC in patients with clinically active OA; (D) ACT RC in patients with clinically non-active OA.
Infliximab efficiency and failure

I would like to comment on an interesting letter in the Annals about anti-tumour necrosis factor (TNF) monotherapy for giant cell arthritis (GCA). The suggestion that vasculectomy may be cured by anti-TNF treatment alone seems to be reasonable. The factors sustaining autoimmune inflammation may include new target antigen production, immune system activation, and a vicious cycle of lymphocyte cascade activation. This mechanism has been recently suggested after a report of long term remission (6–24 months) of Wegener's granulomatosis as a result of infliximab treatment. But unfortunately, it is not relevant in this case.

The authors considered overcoming infliximab failure with an increased dose and frequency, but such an approach is by no means cost effective and should not be attempted. There is another way of dealing with a loss of infliximab efficiency, which may be explained by examining the generation of human anti-chimeric antibodies (HACA). The following information should be considered:

- Second line treatment should be added at the start of infliximab treatment to prevent HACA production.
- HACA may be related to a shortened duration of response after repeated infliximab doses as was first described in patients with rheumatoid arthritis (RA).
- The assay used to determine HACA is affected by the presence of infliximab itself and HACA levels have to be measured after the drug has been stopped. In the ATTRACT study, 27 patients who discontinued infliximab treatment were tested for the presence of HACA: three (11%) were positive, two with a titre of 1/10 and one with a titre of 1/40.
- Formation of HACA may be inversely related to the infliximab dose. HACA were found in 53, 21, and 7% of patients with related to the infliximab dose. HACA were found in 53, 21, and 7% of patients with rheumatoid arthritis (RA). Moreover, the levels may be explained by examining the generation of human anti-chimeric antibodies (HACA). The following information should be considered:
- Further research should be conducted to investigate the role of HACA in infliximab treatment failure.
present. Eight weeks after the last of 5×3 mg/kg doses, serum concentrations of infliximab were 2 and <0.1 mg/l in those receiving concurrent MTX, and 2 and 0.05 mg/l in those not. Receiving concurrent MTX, the rates of formation of HACA were 15, 7, and 0% 8 weeks after 0.2 mg/kg doses and 2 and 0.05 mg/l, respectively.

Moreover, the formation of HACA was significantly reduced in patients receiving MTX, as the rates of formation of HACA were 15, 7, and 0% after 8 weeks. The serum concentrations of infliximab decreased rapidly after the last infliximab dose and were <1 mg/l. The mean serum concentration in patients receiving the recommended dosage regimen of infliximab 3 mg/kg every 8 weeks was 2 mg/l at weeks 0, 2, and 4, and 0.2 mg/l at week 8. Moreover, the rates of formation of HACA were 15, 7, and 0% with infliximab alone or in combination with MTX, while the rates of formation of HACA were 2 and 0% with MTX alone.

The clinical response rate achieved with infliximab 1–10 mg/kg in combination with MTX was consistently greater than that achieved with infliximab alone.

An HACA-reactive discontinuous epitope has recently been developed in order to create a functional mutant which has significantly reduced reactivity with the sera of patients and reduced immunogenic potential of infliximab, may slow its rate of clearance from the blood. The clinical response rate achieved with infliximab 1–10 mg/kg in combination with MTX was consistently greater than that achieved with infliximab alone.

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Rozin A. Infliximab efficacy in refractory Wegener’s granulomatosis. Rheumatology (2002);41:1124-5.


Authors’ reply

We thank Dr Rozin for his interest in our report, describing the experience with anti-tumour necrosis factor α (infliximab) administration as monotherapy for giant cell arteritis (GCA), because this provides us with the opportunity to express some further thoughts and clarify our position.

It appears that Dr Rozin’s initial concern about the loss of response to infliximab of our two patients with GCA, has to do with the possibility of development of human anti-chimantic antibodies (HACA) in their sera. The development of such antibodies in our patients, who did not receive concomitant methotrexate (MTX) and were treated with relatively low dose infliximab, is quite likely, as this occurrence is well established as Dr Rozin indicates. However, we would like to make the following points on this matter.

Firstly, the design of our trial precluded the use of MTX because our purpose was to investigate the effectiveness of infliximab alone in GCA, and MTX has been used, albeit with questionable results, in the treatment of this disease, mainly as a steroid sparing agent.

Secondly, we employed the usual therapeutic regimen with 3 mg/kg body weight of infliximab empirically, and after the initial impressive response of our patients to this dose we continued with it.

Thirdly, although the development of HACA in our patient’s sera was not unexpected, we cannot be at all sure that this influenced the clinical response of the patients to infliximab. Our point is mainly based on the results of a recent report by Wagner et al, in rheumatoid patients of the ATTRACT study. This showed that HACA were developed in 25% of 295 patients (8.5%), but their presence did not affect the proportion of patients with an American College of Rheumatology (ACR)20 or ACR50 response, after long term infliximab treatment.

Fourthly, we indicated that infliximab administration, probably in higher doses and more frequently, should be kept for patients with GCA (and this is, we think, an important finding of our trial), we cannot preclude its use, in combination with MTX, in the usual 3 mg/kg body weight or higher dosage, in refractory cases of the disease or where chronic corticosteroid administration is contraindicated or is not tolerated. However, appropriately designed studies using this agent in “routine” cases of GCA, probably including serum interleukin 6 in their evaluation of disease remission, are needed to answer the question whether short term infliximab treatment (five infusions), combined with MTX and even corticosteroids, is “curative.”

Finally, we agree with Dr Rozin that “self limiting disease” was not the most appropriate characterisation for GCA. This term was used because most studies have suggested that treatment with steroids is usually stopped within 2 years in most patients, although there is no evidence that such treatment reduces the duration of the disease, and a great deal of controversy exists.

It has been further argued from clinical experience that a partial suppression of the inflammatory process of the disease is sufficient to prevent most vascular complications and justifies the currently used corticosteroid regimens. Dr Rozin is concerned about the possibility of a dramatic relapse of the disease, with blindness or cerebrovascular accident, which should have been considered before the first administration (by us) of infliximab as monotherapy. We would not have given a second infusion, if the first one had not impressively encouraged us to continue. Furthermore, we emphasise that we followed up our patients closely, with a complete physical and ophthalmological evaluation and appropriate laboratory work every 2 weeks, and this should have enabled us to detect in time any undesirable occurrence.

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Ultrasound detection of knee patellar enthesis

We read with interest the report by Kamel et al who highlighted the use of ultrasound (US) and magnetic resonance imaging (MRI) for the detection of patellar tendon enthesis in patients with spondenarthropathies without typical radiographic evidence. Their work adds to the growing body of evidence supporting the clinical use of US in rheumatological practice. US has previously been shown to be better than clinical examination for the detection of enthesis, but data on MRI are more limited. The authors make interesting observations about the position of the abnormalities in the patellar tendon, when compared with the Achilles tendon, possibly relating to joint biomechanics and lines of force. However, we would like to raise a few points on what we regard as important omissions from the paper.

Firstly, the authors do not include the frequencies of the described US or the technical details of the MRI findings and do not state how the modalities correlated with each other. The authors also do not comment on the presence of bone marrow oedema adjacent to the enthesis on MRI. With regard to the plantar fascia, it has been reported that adjacent bone marrow oedema changes are more prominent than soft tissue entheseal changes. No data were presented on the reproducibility of either imaging technique for the detection of enthesis.

Secondly, frequent mention of “early” US findings such as calcification and fatty degeneration is made. However, no correlation with disease activity or symptom duration is recorded for either image modality. Similarly, no correlation between patient age and the findings was made—that is, was calcification an age related phenomenon. Control groups of normal subjects and patients without spondylarthropathy would have strengthened the study.

Thirdly, it would also have been relevant to know if the patients had had any previous corticosteroid injections, as calcified foci are not uncommonly found around the sites of injection, sometimes lasting for many months or years. It is possible, therefore, to over diagnose enthesis if this is based on the presence of calcium deposits alone.

The authors make no mention of power Doppler, which has recently been shown to increase specificity of the grey scale findings for the detection of enthesis. It would have been interesting to correlate this with the MRI findings.

In conclusion, although the findings in this report are interesting and we agree that US is a useful tool in the diagnosis of enthesis, care needs to be taken in interpreting such data when all the information has not been presented.

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References


Authors’ reply

We thank Dr Paul Emery and colleagues for their letter and we are happy that our study has stimulated useful comments. Indeed, the published “Letter” provided only a limited opportunity to describe detailed data. We were not able to publish the full text paper of knee patellar enthesis because of some overlap of the data with our published study on heel enthesis. Table 1 summarises the findings of both ultrasound (US) and magnetic resonance imaging (MRI) examinations of enthesis in each individual case. It also shows the frequencies of these described US and MRI findings and how these imaging modalities correlated with each other. We identified bone oedema in two cases: the two patients had reactive bone oedema secondary to patellar tendon inflammation that was maximal at the entheseal insertion, indicating enthesis associated with enthesis.

As regard the comment on calcification, the US was sensitive and accurate in detecting the early development of calcific foci in the patellar tendon in 2/16 (12.5%) patients, while MRI failed to recognise their presence (please refer to the previous published figure). The detection of an early calcification process by US was found to be a clinically important sign because it did not correlate with the disease duration. Further, the development of calcific foci in the patellar tendon was less frequent than the calcification of Achilles tendon of heel enthesis. The two patients were aged 26 and 34 years, neither of them had a history of local steroid injection into the knee and so the calcification was not an age related phenomenon, rather it was secondary to a previous local steroid injection. We wonder how our colleagues came to the conclusion that we used the presence of calcium deposition as a clue to making a diagnosis of enthesis. This was not mentioned in our letter or in our previous reports dealing with the diagnosis of enthesis.

The interobserver variability of sonographic readings was assessed by video recording the US examination and comparing the images obtained sequentially by three independent observers (sonographer, radiologist, and rheumatologist), who were unaware of the patient’s name or clinical diagnosis. Agreement between readers’ interpretation was statistically assessed using the weighted k ranges from 0 (no agreement beyond chance) to 1.0 (perfect agreement beyond chance). The interobserver variability was negligible and yielded an excellent coefficient of r = 0.89 (baseline), r = 0.82 US, and r = 0.74 MRI. Therefore, the presented US data were statistically significant and clinically reproducible.

We are currently combining US examination with power Doppler for some cases when we expect proliferation of synovial tissue and/ or other related soft tissue components. It was not practical to include detailed data in a “Letter”. These data deserve to be published in a separate report.

Table 1 Ultrasound and MRI findings in patients with knee enthesis

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</tbody>
</table>

p, Proximal; D, distal; +, increased; , present; —, absent.
As our colleagues mentioned in their letter, we presented interesting data that describe the anatomical and pathological variations of enthesis in the heels and knees. We strongly believe that the US examination is a very useful and reliable procedure for the diagnosis of enthesis of different joints.

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BOOK REVIEW
Rheumatology, third edition

It is a particular challenge to present a new edition of a textbook that has been praised as the “model for other textbooks” and “a departure from everything that has preceded it”. The new international team of editors of Rheumatology has accepted this task and has succeeded brilliantly. The third edition of Rheumatology is an admirable Reference that brings together comprehensive, up to date coverage, more than 1600 full colour photographs, tables and charts, and practical clinical guidance for the practising and academic rheumatologist and arthritus related healthcare professional in a well organised, highly visual format. It is consistent in content, style, and format, and colour coded sections add to its easy and enjoyable use.

Almost 300 international experts, many of them new in the author team, have contributed to this edition. They represent the entire spectrum of clinical and academic rheumatology and of biomedical, clinical, and epidemiological research. Acknowledging the immense progress in the treatment of rheumatic disease over recent years, the authors have extensively revised the section on principles of therapy and the introductory section. Almost half of the chapters have been completely rewritten and 58 chapters have been added. Essential new information is provided on basic biomedical science, clinical therapeutics, disease and outcome measurement, and patient management and rehabilitation. There is a strong focus on evidence based medicine throughout, and increased importance is given to non-drug treatment, bone disorders, management of paediatric and geriatric patients, orthopaedics, and the latest pain management techniques.

In summary, these two volumes are an exquisite textbook, a reference book for the clinical rheumatologist as well as for the general practitioner, and, again, an admirable “model for other textbooks”.

A standard textbook of 2003 would not suffice, however, if it did not make use of modern technology to improve its teaching and educational opportunities, its accessibility, and its up to date relevance. Needless to say, the third edition of Rheumatology is a true “e-dition”. It includes a CD ROM with more than 3000 images and tables that can be downloaded into PowerPoint presentations. The CD ROM also serves as the launch pad for a fully searchable website that contains the entire content of the book and downloadable images. Other valuable features of the state of the art website include frequent updates to the content of the book, outcome measurements and self testing tools, patient information material, and additional images as well as videos of injection techniques. The electronic material complements the book in a most valuable manner.

There are only a few minor weak points that should be mentioned, although they do not detract from the overall value of the book. The index is comprehensive but, despite the hard work that has been carried out to improve it, still sometimes presents difficulties for the reader. Referencing is correct but the many levels below the individual main alphabetical subjects make finding the correct subject a challenge. The self assessment centre contains questions that cannot be answered correctly, as the software does not permit selection of more than one answer even if the text in the question stated that more than one answer was correct. Finally, after going through questions of several sections, the program may quit unexpectedly, requiring a restart of the section.

The third edition of Rheumatology is excellent value, a beautiful addition to any medical library, and the true Reference for the rheumatologist, the arthritus related healthcare professional, and the basic scientist, and all of us who are interested in disorders of the musculoskeletal system.

H Schulze-Koops

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Email: gedel.cm@t-online.de
Website: www.eular.org

EULAR 2004
9–12 June 2004; Berlin, Germany
Contact: EULAR Secretariat
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P Z Hrycaj

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