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. 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. 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 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 a1-acid glycoprotein (AGP) or a1-antichymotrypsin (ACT) are glycoproteins and possess glycosylation sites attached by N-glycosidically bound, complex-type oligosaccharide side chains. 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. Glycosylation of acute phase proteins takes place in the liver and is controlled by cytokines.

Affinity immunoelectrophoresis with con A is a simple technique that can be used to study the glycosylation pattern of acute phase proteins. Glycosylation variants of AGP and 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. 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) 1b, IL 6, and tumour necrosis factor a (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. As glycosylation of acute phase proteins does not depend on the expression of genes encoding the polypeptide chains of these proteins, glycosylation 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.

P Z Hrycaj
Department of Rheumatology and Clinical Immunology, University of Medical Sciences, Poznan, Poland

Correspondence to: Dr P Z Hrycaj, Department of Rheumatology and Clinical Immunology, University of Medical Sciences, Winogrady 1/44, 61-662 Poznan, Poland; phrycaj@icp.net.pl

References
authors' reply

We thank Dr Pawel Hrycaj for his comment on our manuscript on determinants of low grade systemic inflammation as assessed by high sensitivity C reactive protein (CRP) in patients with advanced osteoarthritis (OA). 1 We agree with Dr Hrycaj that there is a need to elucidate further low grade systemic inflammation in patients with OA and that research based on biochemical and pathophysiological concepts is promising.

In his letter, Dr Hrycaj compared a variety of markers of inflammatory response in 37 patients with clinically active OA, who were not further characterised, with those in 24 patients with non-active disease (again not further characterised) without presenting or taking into account information on possible determinants of these markers. He found that microheterogeneity of acute phase glycoproteins but not the serum concentrations of acute phase proteins, including high sensitivity CRP, were associated with the clinical severity of disease and concluded that determination of microheterogeneity may possibly be a more sensitive measure of the systemic inflammatory activity of OA than high sensitivity CRP.

Our study,1 based on the concepts and methods of clinical epidemiology, was very different in its aim, design, and use of analytic techniques. We focussed on high sensitivity CRP as marker of subclinical systemic inflammation because this marker has well established epidemiological and clinical determinants,2 little diurnal variation, and varies only moderately within a person, allowing long term monitoring of disease.3 When assessed independent determinants of this marker in a well described population of 770 patients who were recruited in four clinical centres using a standardised protocol and interview. In our analyses, known and suspected determinants of serum levels were taken into account using multivariable regression methods.4 We found that severity of pain was a predictor of serum levels of high sensitivity CRP independent of age, sex, body mass index, smoking, alcohol consumption, and comorbidity (hypertension, coronary artery disease, congestive heart failure, diabetes).

The results presented by Dr Hrycaj are difficult to interpret owing to a lack of information on the selection of patients, on basic characteristics of the two groups compared, and determinants of variability of the proposed microheterogeneity, including diurnal and day to day within-person variability. Furthermore, the data would be much more convincing if they had been analysed with possible differences in the characteristics of the two groups other than the activity of OA taken into account.

Nevertheless, the results presented by Dr Hrycaj appear consistent with our conclusion that severity of pain may be associated with levels of low grade systemic inflammation in patients with OA, and we hope that they will encourage further research in this area.

As in other areas of medical research, an interdisciplinary approach combining the areas of expertise of clinicians, basic scientists, and epidemiologists seems to be most promising.

T Stürmer
Division of Pharmacoepidemiology and Pharmacoeconomics, Division of Preventive Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, USA

H Brenner
Department of Epidemiology, German Centre for Research on Ageing, Heidelberg, Germany

W Koenig
Department of Internal Medicine II – Cardiology, University of Ulm, Ulm, Germany

K P Günther
Department of Orthopaedic Surgery, University of Dresden, Dresden, Germany

Correspondence to: Dr T Stürmer; til.sturmer@post.harvard.edu

References


7. HACA may be related to a shortened duration of response after repeated infliximab doses as was first described in patients with rheumatoid arthritis (RA).7 It is likely that higher levels may have been 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 1/40.8 Formation of HACA may be inversely related to the infliximab dose. HACA were found in 53, 21, and 7% of patients with RA receiving infliximab 1, 3, or 10 mg/kg, respectively, 12 weeks after the last of five infusions of the drug.9 It has been suggested that higher doses may be associated with immunological tolerance.10 HACA appeared to be associated with lower serum infliximab concentrations.4 Concomitant administration of methotrexate (MTX) appears to reduce HACA formation. While infliximab maximal concentration values are similar when it is given with or without MTX, serum concentrations of infliximab decline more slowly when MTX is
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 concomitant MTX and those not. Clinical disease declines rapidly after serum infliximab concentrations drop below 1 mg/l. The mean serum concentration in patients receiving the recommended dosage regimen of infliximab 3 mg/kg at weeks 0, 2, and 6 and every 8 weeks thereafter was 1.5 mg/l at week 30 (that is, 8 weeks after the last dose). Moreover, the rates of formation of HACA were 15, 7, and 0% with the 1, 3, and 10 mg/kg doses in those receiving concurrent MTX. Possibly, MTX, by decreasing the 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.

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 with HACA after treatment. The technique is a valuable tool for identifying and adapting undesirable immunogenic sites on protein therapeutic agents.

Moreover, the presence of anti-HACA antibodies to another anti-TNF drug etanercept (Enbrel) are rarely found (2–4%) and, as they are non-neutralising they do not interfere with the efficiency of etanercept as monotherapy for at least 1 year. The reason for these differences is still unclear. Lower immunogenicity of the receptor-fusion protein may be implied. Finally, it seems to me that one cannot define GCA as a self-limiting disease, unlike polyarthritis rheumatica, as it may have an ocular and aortic form with a risk of progressive vessel and target organ damage. I also think that relapse of the disease may be dramatic (blindness, cerebrovascular accident) and should be considered before the first administration of infliximab as monotherapy, with its unknown duration of action and possibility of exposing the patient to serious complications. However, the problem of relapsing and “disease escaping” mechanisms should be further investigated.

A P Rozin
Bat Galim, Rambam Medical Centre, Pardes 9802 Haifa, Israel 31096

Correspondence to: Dr A P Rozin; a_rozin@rambam.health.gov.il

References

Authors’ reply
We thank Dr Rozin for his interest in our report,1 describing our 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 on this approach.

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-chimERIC 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.2

Secondly, we employed the usual therapeutic regimen with 3 mg/kg body weight of infliximab empirically, and after the first infusion, if the first one had not impressively encouraged us to continue. Furthermore, we emphasised 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.

A P Andonopoulos, N Meirmis, D Dassouss, A Bounas, G Giannopoulos
Department of Medicine – Division of Rheumatology, University of Patras School of Medicine, Patras, Greece

Correspondence to: Professor A P Andonopoulos, Division of Rheumatology, University of Patras School of Medicine, 265 00 Rio, Patras, Greece; andonopi@med.upatras.gr

References
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 enthesitis in patients with seronegative arthropathies 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 enthesitis, 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 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 overdiagnose enthesis if this is based on the presence of calcium deposits alone.

Finally, 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 enthesitis, care needs to be taken in interpreting such data when all the information has not been presented.

R J Wakefield, D Mcgonagle, A L Ton, A Evangelisto, P Emery

Academic Department of Musculoskeletal Medicine, First Floor, Old Nurse’s Home, General Infirmary at Leeds, Great George Street, Leeds LS1 3EX, UK

Correspondence to: Professor P Emery; p.emery@leeds.ac.uk

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 erosions associated with enthesopathy.

As regards 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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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 enthesitis in the heels and knees. We strongly believe that the US examination is a very useful and reliable procedure for the diagnosis of enthesitis of different joints.

M Kamel
Al-Azhar University, Cairo, Egypt

R Mansour, M Abbody
Dr Fakhry and Almeuhawis Hospital, Alhhabar, Saudia Arabia

H Eid
Memotaia University, Egypt

REFERENCES


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 arthrits 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 and injection techniques. The technical complement includes the most comprehensive 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, as the software does not permit selection of more than one answer.

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

H Schulze-Koops