# Correspondence

**INSTRUCTIONS FOR LETTERS TO THE EDITOR**

**Editorial comment in the form of a Letter to the Editor is invited; however, it should not exceed 800 words, with a maximum of 10 references and no more than 2 figures (submitted as camera ready hard copy per Journal Guidelines) or tables and no subdivision for an Abstract, Methods, or Results. Letters should have no more than 3 authors. Full name(s) and address of the author(s) should accompany the letter as well as the telephone number, fax number, or E-mail address.**

*Contact.* **The Managing Editor, The Journal of Rheumatology, 920 Yonge Street, Suite 115, Toronto, Ontario M4W 3C7, CANADA. Tel: 416-967-5155; Fax: 416-967-7556; E-mail: jrheum@jrheum.com Financial associations or other possible conflicts of interest should always be disclosed.**

## Transforming Growth Factor-ß Levels in Synovial Fluid of Osteoarthritis With or Without Calcium Pyrophosphate Dihydrate Crystals

*To the Editor:*

We read with interest the recent article by Derfus, *et al* and the editorial by Terkeltaub[1,2]. The article by Derfus clearly demonstrated the high prevalence of calcium pyrophosphate dihydrate (CPPD) and/or basic calcium phosphate (BCP) crystals in knee joints undergoing total arthroplasty for osteoarthritis (OA). This frequency is impressive but not surprising, because it is in agreement with previous reports[3]. However, the true significance of these crystals in OA joints is still open for discussion. The very instructive editorial by Terkeltaub clearly underlined that the mechanism involved in crystal promotion may be implicated in matrix calcification of OA and subsequently, on disease evolution. In particular, he focused on the role of transforming growth factor-ß (TGF-ß) and interleukin-1ß (IL-1ß), questioning the possibility that the intraarticular measurement of these or other mediators may be useful in the evaluation of severity and prognosis of OA.

In this context we think that it may be interesting to report our experience with determination in OA synovial fluid (SF) of IL-1ß and TGF-ß. In our study, we subdivided patients diagnosed for OA according to Altman criteria (Kellgren and Lawrence grade 2 and 3) into 2 groups: the first group (10 patients) characterized by SF presence of CPPD crystals on polarizing microscopy (OA+); the second (16 patients) without these features (OA-). The mean values of TGF-ß, IL-1ß, and matrix metalloproteinases-1 (MMP-1) are reported in Table 1. As shown, the SF TGF-ß levels were significantly higher in OA+ than in OA- ($p < 0.0001$). Interestingly, MMP-1 levels too were higher in OA+ SF ($p = 0.0003$), while no difference was observed for IL-1ß between the 2 groups. Our results are in keeping with Terkeltaub's hypothesis[1] and seem to confirm the important role of TGF-ß in crystal and calcification promotion. In addition, it is possible that the presence of calcium crystals promote the evolution of OA, as demonstrated by higher levels in OA+ of MMP-1, a substance with well known arthritogenic properties[4]. Results of a recent study by Das, *et al* seem in agreement with such an interpretation: addition of colchicine to the usual therapy with nonsteroidal antiinflammatory drugs and/or intraarticular corticosteroid injections improved the symptoms of OA[5].

In conclusion, the study by Derfus[1] and the editorial by Terkeltaub[2] have increased our awareness of the presence of crystals in SF of OA. This information should promote further studies to investigate their possible role in the evolution of OA.

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## Dr. Rosenthal replies

*To the Editor:*

We agree with Drs. Punzi, *et al* that both the frequency and the significance of calcium crystals in osteoarthritis (OA) are often underestimated. Consequently, the factors permitting crystal formation and the mechanisms of their biologic effects in OA remain poorly characterized. Drs. Punzi, *et al* provide compelling evidence that levels of the calcium crystal promoting factor, transforming growth factor-ß (TGF-ß), are higher in synovial fluids from OA patients with calcium pyrophosphate dihydrate (CPPD) crystals than those without crystals. TGF-ß promotes elaboration of inorganic pyrophosphate, the anionic component of the CPPD crystal, from cartilage[1]. TGF-ß

*Table 1.* IL-1ß, TGF-ß, and MMP-1 in synovial fluid from OA knees with (OA+) or without (OA–) calcium pyrophosphate dihydrate crystals. Values are mean (± SD); data are compared using Mann-Whitney U test.

| Groups | No. of Patients | Age, yrs (mean) | Volume, ml | WBC, × $10^3$/mm$^3$ | IL-1ß, ng/ml | TGF-ß, ng/ml | MMP-1, ng/ml |
|---|---|---|---|---|---|---|---|
| OA+ | 10 | 71.40 ± 6.80 | 26.10 ± 9.23 | 0.41 ± 0.08 | 0.40 ± 0.11 | 66.06 ± 21.95 | 53.70 ± 12.24 |
| OA– | 16 | 70.56 ± 8.35 | 24.06 ± 8.48 | 0.45 ± 0.22 | 0.52 ± 0.18 | 18.18 ± 7.00* | 32.25 ± 6.45** |
| Total OA | 26 | 70.88 ± 7.66 | 24.85 ± 8.65 | 0.43 ± 0.18 | 0.47 ± 0.16 | 36.59 ± 27.70 | 40.50 ± 13.86 |

WBC: white blood cells numbers; IL-1ß: interleukin-1 beta; TGF-ß: transforming growth factor-ß; MMP-1: metalloprotease 1.
*$p < 0.0001$; **$p = 0.0003$.

also stimulates production of matrix vesicles capable of forming increased quantities of pathologically relevant calcium crystals[2]. Dr. Punzi, *et al*'s data demonstrating increased levels of metalloproteases in CPPD crystal-containing synovial fluid reinforce the pathologic relevance of similar crystal effects *in vitro*[3]. These fluids were not examined for basic calcium phosphate crystals, and these studies do not sort out issues of cause and effects. However, this work reinforces our opinion that these biologically active structures are important. We firmly believe that calcium crystals deserve a place alongside cytokines, growth factors, and proteases in studies of the pathogenesis and treatment of OA.

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3. MCarthy G, Cheung H, Abel S, et al. Basic calcium phosphate crystal-induced collagenase production: Role of intracellular crystal dissolution. Osteoarthritis Cartilage 1998;6:205-13.

## Dr. Terkeltaub replies

*To the Editor:*

The letter by Punzi, *et al* cites some interesting preliminary data, particularly the distinctions between transforming growth factor-ß (TGF-ß) in osteoarthritis (OA) with and without CPPD crystals grossly detected. The reader should bear in mind that it is possible that crystal trafficking to the synovium might induce increased TGF-ß expression. In addition, the levels of active versus latent TGF-ß at the sites of crystal formation in cartilage may not be accurately reflected by data from joint fluid. Further data on levels of transglutaminase activity (which activates latent TGF-ß) and on matrix metalloproteinases-13 expression would also be informative.

I appreciate the positive remarks by the authors about my editorial and the hypotheses advanced therein. Clearly, further studies on a larger scale will be important to definitively address these questions.

ROBERT TERKELTAUB, MD, VAMC Rheumatology Section/University of California San Diego, San Diego CA, USA.


## Cardiovascular Thrombotic Events and COX-2 Inhibitors: Results in Patients with Osteoarthritis Receiving Rofecoxib

*To the Editor:*

Recent reports have dealt with the issue of whether selective cyclooxygenase-2 (COX-2) inhibitors, including rofecoxib, are associated with an increased risk of thrombotic events[1-3]. We would like to contribute to this topical question by reporting the rate of cardiovascular thrombotic events recorded in a large 24 week open label randomized clinical trial conducted in community derived patients with osteoarthritis (OA) of the knee or hip and aimed at evaluating nonpharmacological treatments[4].

All participating patients were given rofecoxib at a starting dose of 12.5 mg/day for the first month, with the option of increasing to 25 mg/day thereafter if needed for efficacy. As the patients might have been assigned to perform an exercise program, those with a recent history of myocardial infarction (MI) were excluded, as were patients with serious comorbidities and/or a contraindication to rofecoxib use (known hypersensitivity to the drug, active gastrointestinal disease, severe renal or hepatic disorder). The protocol included 4 study visits for all patients. In addition to the screening visit, patients were seen at Weeks 4, 12, and 24. Thrombotic events were recorded as part of ongoing adverse event surveillance. We recorded all untoward events that occurred throughout the study, but considered only events occurring during treatment and within 14 days after discontinuation of rofecoxib.

In all, 2896 patients (2035 women, 861 men) were involved in the safety analysis. Their mean (SD) age was 66.8 (9.9) years and 631 (21.8%) were 75 years or older. There were 913 patients (31.5%) with hypertension and 151 (5.2%) with diabetes. Further, 78 patients (2.7%) had a history of angina and/or MI. Ongoing use of low dose aspirin was recorded in 26 patients (0.9%). The mean (SD) duration of rofecoxib treatment was 139 (62) days. The dosage of rofecoxib was increased to 25 mg/day in 773 patients after the 4th week, and in 1035 after the 12th week of the study.

A total of 6 cardiovascular thrombotic events was recorded. One patient with a history of MI, coronary angioplasty, diabetes, and hypertension experienced a fatal MI while taking rofecoxib. Further, nonfatal strokes occurred in 5 patients during the period of treatment. Accordingly, the annualized incidence rates of MI and stroke were 0.09 (95% CI 0–0.50) and 0.45 (95% CI 0.16–1.05), respectively. Of note, 2 further thrombotic events (one MI and one stroke) were observed after the 14 day window; they occurred at Day 31 and Day 60, respectively, after discontinuation of rofecoxib.

Although comparison of raw event rates across mutiple studies is hazardous, the annualized thrombotic cardiovascular event rate observed in our study is comparable with that found in controls (weighted mean 0.92%/year, range 0.67% to 1.71%/year) who participated in 4 randomized controlled trials of aspirin for primary prevention[5]. It is also in agreement with the incidences of the Anti-Platelet Trialists' Collaboration (APTC) combined endpoints that were observed in the rofecoxib OA development program[6]. The incidence of APTC endpoints [(1) cardiovascular, hemorrhagic, and unknown death; (2) MI; and (3) cerebrovascular accident] was similar between the rofecoxib (0.96/100 patient-yrs) and nonselective NSAID (1.42/100 patient-yrs) treatment groups on the one hand, compared to the rofecoxib (1.36/100 patient-yrs) and placebo (1.93/100 patient-yrs) groups[6]. In spite of its limitations, including the absence of a control group, ignorance of possible silent MI, and duration of treatment limited to 24 weeks, our study provides further indirect evidence for a lack of excess of cardiovascular thrombotic events in OA patients receiving rofecoxib 12.5–25 mg/day. This should be confirmed by large controlled clinical trials with a longer followup period.

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## Diabetes Mellitus Type 1 and Stiff Hips

*To the Editor:*

We describe a patient who has diabetes mellitus type 1, DISH (diffuse idiopathic skeletal hyperostosis), Dupuytren's contractures, and elements of the syndrome of limited joint mobility or diabetic cheiroarthropathy, who has developed a restricted range of motion of both hips.

A 47-year-old man with diabetes mellitus type 1 diagnosed at the age of 21 and DISH diagnosed at age 44 presented with increasing difficulty with walking secondary to hip and back pain and generalized stiffness. He had bilateral Dupuytren's contractures. A previous surgery for the left hand had failed, as the contracture returned after surgery. He also described a year-long history of progressively worsening stiffness of both hips. The stiffness, constant throughout the day, was accompanied by pain and was severe enough that he was spending most of his time in bed. He denied any history of trauma and had not had any episodes of reflex sympathetic dystrophy. He also denied a history of depression, anxiety, or other psychiatric problems. Over the previous 5 months, the pain in his hips had become increasingly severe, especially with movement.

Examination revealed obvious palmar contractures involving the 4th digits of both hands as well as contractures of metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints of the same digits. He had a prominent prayer sign and decreased extension of the wrists, with no evidence of diabetic sclerodactyly. He had only 85° to 90° of extension and abduction in both shoulders. His hips were in 15° of flexion even while he attempted to lie supine, and he was unable to fully extend his hips so that even when he stood, he was flexed 15° at the hips with lumbar hyperextension. Left hip examination revealed 15° of internal rotation, 30° external rotation, 20° abduction, and 10° adduction. The right hip had 15° internal rotation, 20° external rotation, 10° abduction, and 10° adduction. Attempts at passive range of motion produced pain, particularly at the extremes of his limited range of motion. Active motion appeared to be less painful but more restrictive. Low back examination revealed slight point tenderness along the spine without paraspinal tenderness. There was only 5° of spine extension, and spine flexion was markedly limited as well; attempts at both flexion and extension were painful.

Thoracic and lumbar spinal radiographs revealed flowing anterior osteophytes typical of DISH. There was relative preservation of intervertebral disc spaces of the involved regions, and there was no evidence of apophyseal joint ankylosis, sacroiliac joint erosions, sclerosis, or intraarticular bony ankylosis. Bilateral hip radiographs revealed only minimal narrowing of the joint spaces. Magnetic resonance image (MRI) of hip joints with gadolinium was unremarkable. A computerized tomographic (CT) arthrogram showed a normal joint capsule. Blood tests revealed an elevated Westergren erythrocyte sedimentation rate of 43 mm/h (normal 0–15), elevated IgA of 514 mg/dl (normal 70–400), and negative HLA-B27. He had reasonable control of his diabetes, with the highest hemoglobin A1C over the past year of 7.8%. He had preserved renal function (blood urea nitrogen 19, creatinine 0.8) and annual ophthalmologic examinations reportedly revealed no evidence of proliferative retinal microvascular disease.

The syndrome of limited joint mobility (SLJM), also known as diabetic cheiroarthropathy, diabetic hand syndrome, or stiff hand syndrome, is characterized by joint contractures. The flexion contractures of SLJM occur predominantly in the PIP and MCP joints, although eventually there may be decreased range of motion in larger peripheral joints as well as the axial skeleton[1]. The pathogenesis of this disorder is not entirely understood; however, it has been postulated to involve contractile myofibroblasts producing increased amounts of collagen in response to microvascular ischemia[2]; this theory is supported by the correlation between SLJM and the presence of microvascular disease[1,2].

DISH is a diagnosis that relies principally on the radiographic appearance of the thoracic spine[3]. However, it is a systemic disease, and in peripheral joints a stiffening arthropathy can also be seen[4]. Among other features, a painless reduction of internal rotation of the hips has been described, but there are no adequate controlled studies on the clinical features of extraspinal DISH[4]. There is an association between hyperinsulinemia and DISH[4,5], and it appears that insulin acts as a growth factor leading to connective tissue proliferation and eventual deposition of new bone[4]. DISH has been associated with diabetes mellitus type 2, impaired glucose tolerance, and obesity[6]; however, cases have also been described in association with type 1 diabetes mellitus[6].

Adhesive capsulitis is another rheumatologic disorder that has been associated with diabetes mellitus[2]. This disorder has usually been described as occuring primarily in the shoulder joint, although adhesive capsulitis of the hip and ankle have also been described[7]. At first we felt our patient had an adhesive capsulitis of bilateral hips, but the finding of a normal joint capsule on CT arthrogram excluded this diagnosis.

This patient exhibits some rheumatologic disorders common to people with diabetes mellitus, namely DISH, SLJM, and Dupuytren's contractures. In general, he has a tendency toward joint stiffening without actual pathology in the joints, as evidenced by his persistent Dupuytren's contractures, even after surgery. He had markedly reduced range of motion with stiffening and pain in bilateral hip joints; however, the radiographs and MRI do not reveal enough pathology to account for this stiffening. This may indeed be a large-joint manifestation of SLJM. It may also be a peripheral joint manifestation of DISH. In either case, this decreased range of motion appears to be related to stiffening of the soft tissues surrounding the hips.

Our patient failed to improve after an intensive inpatient physical therapy program in a rehabilitation hospital. Multiple sessions of passive stretching in a Hubbard tank did not increase his hip range of motion. Therefore, the emphasis in rehabilitation became fall prevention and joint protection. He received isometric muscle strengthening of the hip girdle and back muscles and instructions on floor-to-stand transfers should a fall occur. He was able to walk 300 feet with the assistance of bilateral Lofstrand crutches. The occupational therapy department reviewed his dressing program and other activities of daily living and dispensed the appropriate assistance devices such as a dressing stick and reachers. He was able to achieve a reasonable level of comfort with only a modest reduction in his expectations of total function.

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# Book Review

**Modern Therapeutics in Rheumatic Diseases**

George C. Tsokos, Editor. Totowa, New Jersey: Human Press, 2002, hardcover price $145.00 US.

I have just finished my training in rheumatology at the University of Toronto and am preparing for the Royal College Certification examinations. Over the years, rheumatology has become a specialty with quite a breadth of knowledge. To study efficiently I needed a source that succinctly outlined the pathogenesis of common rheumatic disease, as well as mechanisms of therapy and the evidence of their utility.

*Modern Therapeutics in Rheumatic Diseases* brilliantly encompasses these aspects. The book is divided into chapters by disease experts in their field. The sections generally begin with pathogenesis of the condition and outline potential areas of intervention. Afterwards the role of specific therapeutics is concisely outlined, along with direct reference to the pertinent studies. With the dramatic therapeutic advances in rheumatoid arthritis, the first 11 chapters are dedicated to this condition and include a section on potential experimental therapeutics. I especially enjoyed chapters 12–17, which dealt with osteoarthritis. In these chapters, both existing and experimental interventions such as anti-nitric oxide agents, anti-apoptotic therapy, and gene therapy for osteoarthritis are thoroughly reviewed.

This book could not have been published at a better time from the rheumatology trainee's point of view. It is written in a coherent and concise manner, which serves as an excellent source for all aspects of therapeutics in the rheumatic diseases. Furthermore, the frequent use of diagrams and graphs allowed emphasis of key points. This publication links the basic science of rheumatic diseases to a comprehensive text of therapeutic mechanisms and efficacy.

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# Correction

de Klerk E, van der Heijde D, Landewé R, van der Tempel H, Urquhart J, van der Linden S. Patient compliance in rheumatoid arthritis, polymyalgia rheumatica, and gout. J Rheumatol 2003;30:44-54. Reference 5 was incomplete; it should be: 5. de Klerk E. Measurement of patient compliance with drug therapy: An overview. In: Vingerhoets A, editor. Assessment in behavioral medicine. New York: Taylor and Francis Inc.; 2001:215-44. We regret the error.

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# The Journal of Rheumatology

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