

Osteoarthritis

Chondrocalcinosis, osteophytes and osteoarthritis

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Crystals, spurs, and osteoarthritis

Association between OA and chondrocalcinosis

An association between osteoarthritis (OA) and radiographic evidence of chondrocalcinosis (CC) has been recognised for years. Crystals of calcium pyrophosphate dihydrate (CPPD) may be found in synovial fluid from patients with OA who are relatively asymptomatic as well as from those who are experiencing an acute flare up of joint pain due to an attack of pseudogout. Whether CC is the cause of OA in such people or develops as a result of changes in metabolism of the chondrocyte or in the extracellular matrix of the articular cartilage is unclear. In any event, conditions associated with CC, such as hyperparathyroidism, Wilson's disease, and haemochromatosis, are well recognised causes of "secondary" OA.¹

Chondrocytes from patients with OA who do not exhibit CC produce as much pyrophosphate as those from the cartilage of patients with CPPD disease.² Furthermore, chondrocytes from human OA cartilage exhibit increased sensitivity to transforming growth factor β (TGF β), which has been shown to induce osteophyte formation in murine knee joints, an effect not seen with insulin-like growth factor 1.³ TGF β also stimulates the secretion of pyrophosphate by chondrocytes, predisposing to formation of pericellular CPPD crystals; the phagocytosis of which results in the synthesis of matrix metalloproteinases by chondrocytes.⁴ These enzymes participate directly in the breakdown of the extracellular matrix of the cartilage and activate latent proenzymes and growth factors that cause further structural damage. Calcium crystals also decrease the synthesis of proteinase inhibitors, such as tissue inhibitors of metalloproteinases, exacerbating tissue damage.⁴

In addition to the effects of CPPD crystals on cartilage cited above, calcium crystals may produce direct mechanical damage to articular cartilage. Addition of CPPD crystals to the solution bathing cartilage plugs that were subjected to mechanical wear in vitro increased proteoglycan loss from the cartilage matrix, suggesting that crystals present in synovial fluid may cause increased wear of

the articular surface in vivo.⁴ Furthermore, calcium crystals are phlogistic; their presence within the joint space and synovium may initiate an inflammatory response.⁵

Radiography of OA

The paper by Neame *et al* in this issue of the *Annals* examines the association between knee OA and CC from an epidemiological perspective.⁶ Subjects in this cross sectional study were defined as having OA on the basis of radiographic evidence of a definite osteophyte and definite joint space narrowing (JSN, a surrogate for thinning of the articular cartilage). The authors found an association between CC and OA in the tibiofemoral and patellofemoral compartments, although patellofemoral CC was relatively uncommon and did not occur in the absence of concomitant tibiofemoral CC.

A strong association was noted between osteophytosis and JSN: a significant relationship existed between CC and both the total osteophyte score and the total number of sites within the joint affected by osteophytosis. In contrast, no association was noted between CC and JSN, leading the authors to conclude that the association between OA and CC is mediated through an association with osteophytes, rather than with JSN. However, given that calcium crystals stimulate the synthesis and release from chondrocytes of potent proteinases that can degrade the cartilage matrix (see above) and that accelerated degeneration of cartilage has been observed in joints of animals with experimentally induced OA after intra-articular injection of CPPD crystals,⁷ the apparent lack of association between CC and articular cartilage damage might have been due to the insensitivity of radiography for detection of CC or of the radiographic protocol employed in the epidemiological study for detection of cartilage loss (that is, JSN).

Possibly, more rigorous radioanatomical positioning than can be achieved with the conventional weightbearing extended anteroposterior view of the knee would have shown an association between CC and JSN. Considerable interest has been focused recently on the

limitations of the standing anteroposterior radiograph for accurate and reproducible assessment of JSN in patients with OA.⁸ The issue concerns the importance of alignment of the central x ray beam with the plane of the medial tibial plateau in assessment of tibiofemoral compartment joint space width, a decrease in which is generally taken as an indication of the radiographic severity of OA and, in serial examinations, of progression of cartilage damage. Fluoroscopically assisted positioning of the joints to align the tibiofemoral compartment (that is, with anterior and posterior margins of the medial tibial plateau superimposed ± 1 mm), as with the technique described by Buckland-Wright,⁹ is associated with a more rapid rate of JSN, and smaller standard deviation of the rate of narrowing, than protocols that are less effective in providing tibial plateau alignment.¹⁰ Because of subject to subject variability in the angle of inclination of the tibial plateau relative to the horizontal plane, (fortuitous) alignment of the medial plateau with the plane of the x ray beam occurs in only about 20–30% of subjects.¹¹ Indeed, in the Nottingham study⁶ the reproducibility of repeated measurements of minimum joint space width on the same image (± 0.31 mm for the left medial tibiofemoral compartment) was considerably greater than the mean annual rate of JSN in serial images of the same joint reported by several investigators (0.1–0.2 mm a year).¹⁰

What is the association between osteophytosis and OA? Although it is generally considered that radiographic evidence of definite osteophytosis is a requisite for the radiographic diagnosis of OA,¹² it has been suggested that osteophytes alone—in the absence of other bony changes of OA in the radiograph (for example, subchondral sclerosis, subchondral cysts)—may merely reflect aging, and not OA.^{13,14} Furthermore, radiographic decreases in the interbone distance in the tibiofemoral compartment may be related to age,¹⁵ raising the possibility that, had age been taken into account in the Nottingham study, a relationship between CC and joint space width might have been revealed.

Chondrocalcinosis as a risk factor for OA

Is CC a risk factor for the progression of knee OA? Can the presence of CC be used to predict which subjects with radiographic evidence of OA will progress radiographically or clinically (for example, with increasing severity of joint pain and diminution of function)? Although the presence of CPPD crystals in synovial fluid from patients with knee OA was associated with increased disability,¹⁶ and an association has been reported between the presence of CPPD crystals in

synovial fluid and severe radiographic changes of OA,^{17,18} others have not found an association between CC and radiographic severity of OA.¹⁹ However, these studies were all cross sectional, rather than longitudinal and, as mentioned above, the sensitivity of radiography for the detection of CPPD crystals in articular structures is poor.

In their paper, Neame *et al* note that increases in osteophytosis and bone remodelling were the most common changes found in patients with knee OA and CC who were followed up longitudinally.⁶ It is important to remember that the pathogenetic mechanisms underlying osteophytosis are different from those that result in the well recognised changes in subchondral bone in OA, in which both the formation and resorption of bone are accelerated. Furthermore, the increased turnover of subchondral bone can be inhibited by antiresorptive agents, such as bisphosphonates.

Might this be of therapeutic benefit? In an experimental canine cruciate deficiency model of OA,²⁰ in which bone turnover was markedly inhibited by administration of bisphosphonates, no effects of treatment on structural damage in the OA joint were seen. Nor did bisphosphonate treatment inhibit the prominent osteophyte formation seen in this model. However, osteophyte formation occurs by endochondral ossification—that is, it is not linked to bone resorption, in contrast with osteogenesis in subchondral bone in OA which can be modified pharmacologically—for example, by bisphosphonates. The failure of an antiresorptive drug to inhibit osteophyte formation, therefore, is not surprising. It should be noted, however, that the duration of treatment in the canine study was relatively brief. A placebo controlled clinical trial in humans is now under way whose objective is to examine whether an antiresorptive agent is effective in preventing the progression of structural damage in patients with knee OA.

Diuretics and chondrocalcinosis

Finally, the association observed by Neame *et al* between diuretic use and CC is interesting.⁶ No such association was found between CC and the use of other antihypertensive agents. Because magnesium is a cofactor for pyrophosphates

that convert pyrophosphate to orthophosphate²¹ and increase the solubility of CPPD crystals,²² the authors suggest that the association might have been due to iatrogenic hypomagnesaemia. It might be possible to test this hypothesis in the large prospective study of the natural history of OA soon to be initiated with support from the National Institutes of Health (NIH) and the pharmaceutical industry, in which an attempt will be made to identify surrogate biomarkers for incident OA and for the progression of established OA in 5000 subjects over a four year period of observation. For this purpose a cohort of subjects will be established that would be well suited to a prospective analysis examining whether diuretic treatment predisposes to CC, osteophytosis, or incident or progressive OA. Thus, the careful epidemiological observations of Neame *et al* relative to the relationship between CC and OA⁶ generate hypotheses that, if tested, might help answer the questions: Who gets OA and why? And, who gets clinically important OA and why?

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