Arthritis or arthrosis – that is the question?
An overview of concept in osteoarthritis.

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ARTHRITIS VAGY ARTHROSIS – AZ ITT A KÉRDÉS!

1. Az osteophyta-képződés könnyen összetéveszthető az osteoarthritissel (OA). Az utóbbi lényege a hyalinporc pusztulása és a subchondrális rendellenességek kialakulása. Az osteophyta-képződés ellenben az ízület instabillá válása és a hyalinporc elvékonyodása miatt fellépő szöveti regeneráció – mindenekelőtt az öregedéssel párhuzamosan észlelhető – megnyilvánulása. Ennél is nagyobb baj, ha az életkorfüggő elváltozásokat tévesztik össze osteoarthritissel. Ismételten leszögezzük, hogy az ízületi rés öregedéssel járó beszűküléséhez óhatatlanul társul némi osteopohyta-képződés. Ez a jelenség „normális" és bár nem a tökéletes regeneráció jele, semmiképpen sem tekinthető kórosnak.
2. A CPPD az osteophyta-képződéshez és nem OA-hez társul, jóllehet hypertrophiás OA-ben is fennállhat, az alapbetegség megnyilvánulásaként. A pyrophosphat arthropathia minden bizonnyal a „Milwaukee-vállhoz" hasonló mítosz és mint ilyen nem létezik.
3. Az enthesophyták az osteophytákkal együtt fordulnak elő. A beteg szervezete vagy hajlamos csontképzésre – vagy nem! Vajon mely folyamatok szabályozzák ezt a sérülésre vagy mechanikai stresszre adott válaszreakciót? Miképpen befolyásolható és módosítható?
4. Egyre inkább definiálják az ízületi regeneráció és pusztulás ismérveit. Ennek így is kell lennie, ha a támogatandó élettani, ill. leállítandó kórfolyamatok azonosítása a cél. Ideje szakítani azzal a felfogással, miszerint az OA az ízület lassú, progressszív pusztulásához vezető, „egyirányú utca". Ez a nézet megalapozatlan, az OA igenis reagálhat a kezelésre.
5. Az OA több válfaja különböztethető meg. Nem egységes kórkép, hanem hasonló, az ízületek különféle csoportjait – gyakran nem egyidejűleg és különböző mértékben – károsító betegségek együttese.
6. Az OA-t az ízület minden összetevőjét károsító betegségnek kell tekinteni. Ezen kívül, az OA rendszerbetegség, örökletes-familiáris kórkép, mely monoarthritis multiplex képében is megnyilvánulhat.
7. Végül, a radiológia nagymértékben előmozdíthatja az OA kutatását.

The basic misunderstanding implicit in this question is that osteoarthritis (OA) is a degenerative condition, unaccompanied by any inflammatory component – hence osteoarthrosis. But is it, does OA never have an inflammatory component, is it a progressive 'wear and tear' phenomenon? Before that question can be answered another, more fundamental one needs to be addressed – what is OA? It is perhaps surprising and inexplicable that so little is understood about this extremely common disorder. It involves almost everyone in the developed world who has lived long enough to get it, yet it remains poorly researched. True, a great deal of fundamental, important work had been undertaken into hyaline cartilage structure and function. Recently developed cartilage grafting techniques are exciting and offer great hope of future therapy to those millions of patients who suffer the pain, restriction of movement and impaired life style that is the price they pay for OA. However, this treatment option will remain out of reach for most patients and other therapeutic strategies remain limited. Fortunately, the impact and consequences of osteoarthritis (OA) in the ageing population of the industrialized world has been recognised by the recent declaration of the Bone and

Based on an invited lecture to the VIth Magyar Osteologiai Kongresszus, Balatonfüred 2005.

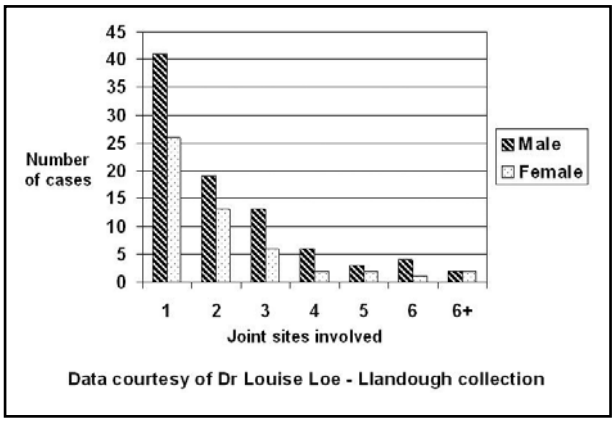


Table 1. Data from a funerary collection show the numbers of joint types involved in OA. Note most skeletons had abnormalities of one or two joint types. There does not seem to be a definite sub-group of GOA patients in this collection.

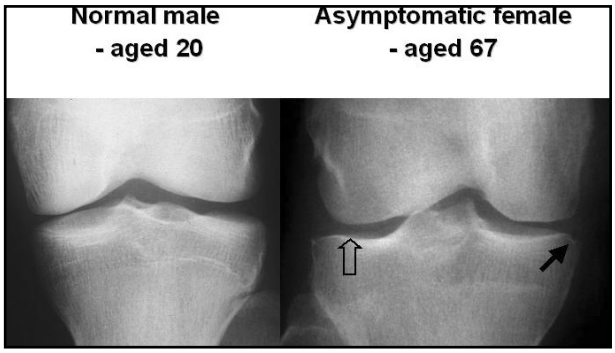


Figure 1. The contrast between the knee x-ray of a normal, asymptomatic 20 year old male (left) and an equally normal asymptomatic 67 year old woman (right) is shown. Whilst the lady has minor rim osteophytes (solid arrow) and slight joint space narrowing (open arrow), it would be overstating the case to diagnose this as OA.

Joint Decade. A major move is underway to understand OA and hence to develop efficacious therapy.

So, is OA inflammatory or degenerative? Is it one disease, or many with a common end result? What do we really know about OA? Let us start at the beginning.

HISTORICAL OVERVIEW – EVOLUTION OF A DISEASE

OA as we know it was described in detail 200 years ago by Heberden (1803) when it was known as arthritis deformans. Later, it was realised that OA was a multiple joint disorder, a polyarthrititis, not just a knee or a thumb, but a generalised synovial joint disorder. Clinically, a hundred years ago, OA became subdivided into two categories – inflammatory and degenerative, each being thought to be a reaction to different forms of joint insult. So, for a century at least, an inflammatory component of OA has been recognised but forgotten. Inflammatory arthritis, as a concept, became subsumed at the turn of the 20th century into what is called now rheumatoid disease even though some cases of OA were clearly erosive (hence erosive OA or EOA). Further, at the same time, different clinical types of the degenerative disease subset were described [1]. Obviously, at a time of heavy manual labour, it was apparent that some cases of OA were post-traumatic but others seemed to run in families, particularly in women. Thus in 1941 the role of heredity became recognised in what was called then hypertrophic arthritis of the finger joints (atrophic arthritis also becoming synonymous with rheumatoid disease later in the early 20th century). It was noted that a greater than expected incidence of Heberden's nodes was found in the mothers and sisters of affected probands [2]. This familial, genetic linkage became forgotten, although with accurate assessment of DNA in recent years a renewed interest in possible hereditofamilial predisposition has become popular again.

By 1952 it was accepted that OA was not limited to one single joint site, or even class of joint, but several and hence the concept of 'primary generalised OA' (or GOA) was described, emphasising that the disease was a systemic disorder. In a series of 103 patients, selected on the basis of Heberden's nodes in their hands, it was found that OA was present in the knee (64), spine (57) and hip (36). The high spinal involvement is of note. But, was this truly OA of the facet or uncinovertebral joints, or, as one may suspect, enthesophytosis around the disc spaces? This apparent association will be returned to below. It is important to note in GOA that not all of the involved joints are symptomatic or even clinically abnormal at one time. The diagnosis of GOA is largely radiographic or based on limited clinical examination. Further, the time and activity curves of various joints becoming active and settling clinically are not known. Indeed, it remains a debate as to whether GOA really exists. It is of interest to look at skeletal collections here. One large series shows that whilst multiple joint types may be involved in OA (hip and knee for example) the involvement of more that two sites and so on seems to decay exponentially (Table 1) [3]. The 1952 paper did describe also, for the first time, joints going through phases of disease evolution [4] subsequently confirmed by other methods . Another 10 years were to pass before another basic truth emerged. This was that X-ray changes whilst predisposing to symptoms did not equate to them. Many patients with radiographic OA did not have symptoms in spite of significant x-ray changes. Even so, it was, and is only too easy to ascribe symptoms to radiological signs. Nonetheless, other risk factors began to be elaborated, apart from trauma, and the linkage was made between obesity and increased pain in knee OA for the first time [5].

Could some of the radiological signs of OA be normal, or perhaps age-related? In 1979 the first report was made that perhaps the individual signs of OA could be normal

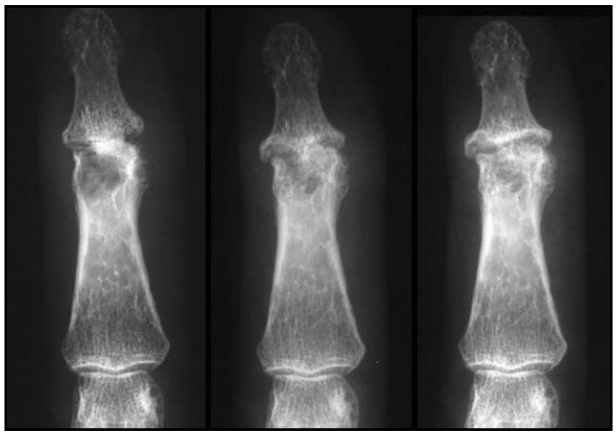


Figure 2. Erosive osteoarthritis. Three views of the same joint show the natural history of this variant of OA. Note that reparative changes occur. True, the joint is not restored to normality, but joint surfaces and some joint space width are restored concurrent with symptom relief.

findings in older normal people. An age-specific correlation was described for joint space narrowing, joint margin spurs and intra-articular "loose" bodies in normal older people [6]. It is an undisputed fact that OA is an age – related disorder. But, as we humans grow older a number of events occur including increasing joint congruity; reduced synovial fluid circulation; deficient hyaline cartilage nutrition; hyaline cartilage thinning; decreasing joint stability; reducing muscle function and reducing trabecular bone mass. Thus, minor marginal osteophytes, and some joint space narrowing, are age-related findings and not clinically significant OA requiring treatment or referral to a surgeon or rheumatologist (Figure 1).

SOME CONFOUNDING DIFFICULTIES

Are osteophytes a 'good' or 'bad' finding? Much focus has been laid on the loss of hyaline cartilage in OA. Does osteophytosis correlate with cartilage loss? Indeed, are they parallel processes? A paper looked at disease progression in 86 patients diagnosed with OA of the hip on the basis of osteophytosis on plain x-ray. Eleven years later, only 1 patient had developed joint space narrowing [7]. In this case osteophyte and joint space narrowing did not correlate. Is osteophyte 'good' therefore, a reparative phenomenon perhaps?

Is OA is one disease? Radiologically and clinically it is clear that it is not, but many. The age of onset of OA hip differs from OA knee, and various distinct clinical and radiological subsets have emerged with possible correlations between specific joint sites (hand and knee as opposed to hip and hand for example). More recently, other subsets have been described, including elbow joint disease, typically presenting clinically as painless restriction of movement in middle aged men, and OA of the post dental joint at C1- 2. Such findings are well known to palaeopathologists but have taken much longer to

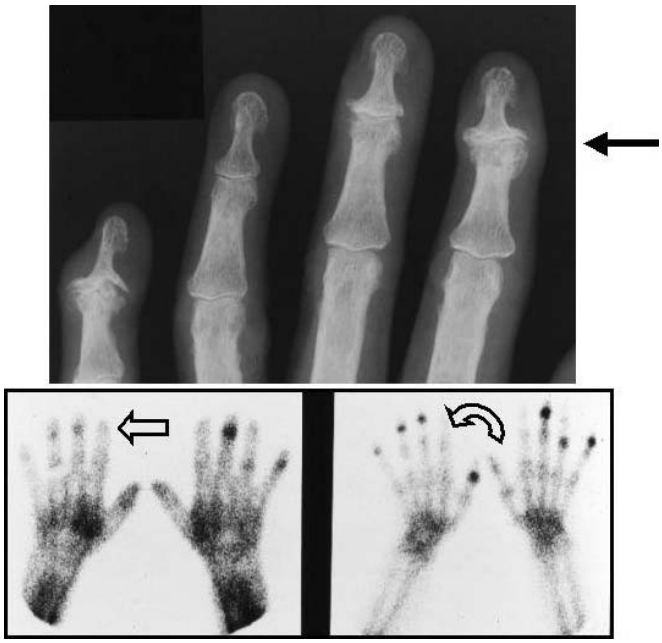
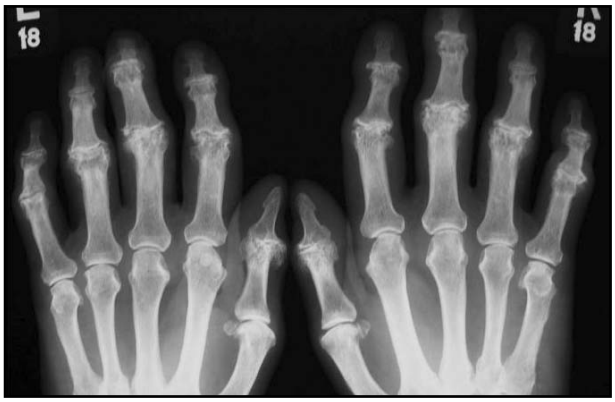
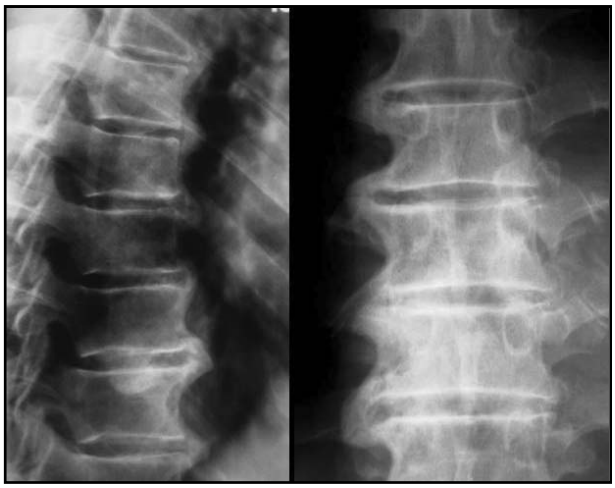


Figure 3. The disparity between plain films and radionuclide bone scanning in OA is shown (99mTc HDP). Note that the index finger appears to have as much OA change as the middle finger on plain film, and yet on both the blood pool phase (left) and delayed phase (right) it is normal. Clearly, a difference exists between structural change and biological activity.

enter current clinical practice. In some cases underlying, predisposing factors can be recognised (old dysplastic hip disease, Perthe's disease or old trauma for example). Yet in the majority of cases such findings are not readily visible and OA would seem to be idiopathic. However, careful scrutiny of OA of the hip or knee suggests that underlying elements of joint dysplasia may contribute to the risk of the development of OA. What is dysplasia in this context? It may be no coincidence that the joints in which we get OA, as humans, are those that have evolved most recently in our evolutionary history. We are uniquely a purely upright, bipedal ape using joints in ways for which they were not designed. For example, consider the use of the hand (the thumb carpometacarpal joint and the terminal interphalangeal joints), the shoulder, the knee, the hip the spinal facet joints. Improbable, well what then are dysplastic hips and knees, the former resembling the waddling gait of the chimpanzee, the latter failing to reflect the alignment needed for the upright, locked knee that we use so effectively?

Does OA progress predictably and slowly – wear and tear? No, the rate of disease progression can vary dramatically. Consider EOA, a hand subset with rapid joint change from destruction to reconstitution and repair [8]. Quite clearly, here are joints going through phases of collapse and failure with subsequent repair (Figure 2). Further, skeletal scintigraphy has shown that EOA is an episodic disease, waxing and waning, with plain film, clinical and scintigraphic features out of synchrony with each other [9] (Figure 3). From such studies has arisen





Figures 4 and 5. This 60 year old lady has both classical EOA in her hands and Forestier's disease (DISH) in her spine. She is forming bone at both osteochondral and enthe-seal sites.

the concept that whilst OA is a systemic disorder it may be visualized better as a monoarthritis multiplex with one joint switching on and then another. Why should this be? The trigger factors that cause individual joints to become involved are unknown at present.

Has OA remained constant, as we see it today? It has been assumed, incorrectly, that OA has been around, unchanged, for millennia. True, almost all mammals get OA, even, it is alleged, dinosaurs. However, hand OA in the monkey and humans involves different joints reflecting different demands and joint functions. But, even within humans, the distribution of OA has changed over the centuries. One study looked at the prevalence of OA in the hip, tibio-femoral and patellofemoral joints of English Saxon and early mediaeval skeletons versus English post-mediaeval skeletons. The sex ratio was about the same, 1.3 male to 1 female, and all were aged 35 + at death (it is difficult with this material to be more precise about exact age). The results showed that the prevalence of hip OA was unchanged but that knee OA became commoner than hip OA due to 3 fold increase in knee OA. Further, the ratio of tibiofemoral OA to patellofemoral OA increased by more that 300%. Simply put tibiofemoral joint OA was rare, but not now. Why? Perhaps of our increasing weight might be a factor as noted above? [10].

Other concepts? Palaeopathology has taught us to examine other concepts about OA. Osteophyte is formed by enchondral ossification of chondrophyte. As indicated, this may be a reparative phenomenon reflecting joint instability in older people secondary to hyaline cartilage thinning. If so, it may be seen as a good, reparative phenomenon. Other patients also form bone; those with Forestier's disease/ DISH do so at their entheses (Figures 4 and 5). Could those that form bone at joint margins do so also at their entheses? Another palaeopathological study confirms a strong correlation between osteophyte and enthesophyte formation – identifying the possibility that some individuals form bone in response to injury or stress. We might even call these persons – bone formers. Yet more interestingly, such patients have normal spinal and hip bone density as opposed to osteopenic non bone-formers. Could it be that the way a joint responds to injury, or unknown pathological changes, reflects the ability of the whole skeleton to react? What happens in an OA knee may be determined by more global, systemic controllers of bone metabolism that those within the joint itself. The challenge to identify those factors that promote repair, bone formation, as opposed to those of bone failure may become the next challenge in OA research.

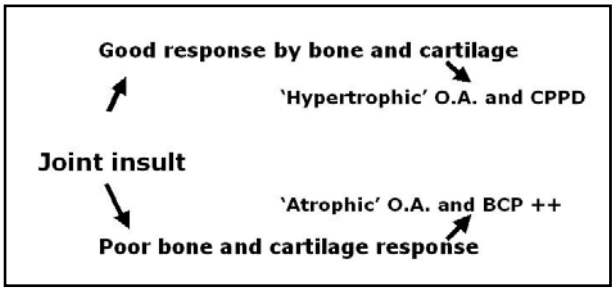


Figure 6. This diagram suggests and makes simple a relationship between joint insult, crystal expression and OA subset.

May other factors may be associated with bone formation? The deposition in joints of calcium pyrophosphate dihydrate (CPPD) is thought to be a marker of a hypertrophic variant of OA (sometimes known as pyrophosphate arthropathy), whereas hydroxyapatite is found in excess in patients with rapidly destructive OA (erroneously called Milwaukee shoulder – see below). Are these crystals markers of disease, their cause or merely co-expressions of underlying processes as yet unknown? A full discussion of the facts and fallacies behind this question is beyond the scope of this paper. However, the original description of 'pyrophosphate arthropathy' only mentioned an apparent association between pseudogout (the clinical expression of acute CPPD crystal shedding) and an unusual arthropathy in some patients. Subsequently, much work has shown that chondrocalcinosis is asso-

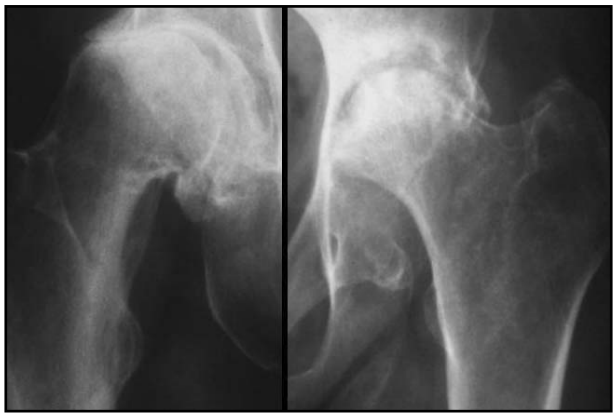


Figure 7. The spectrum of OA is illustrated from slowly progressive hypertrophic OA (left) to rapidly failing atrophic OA (right).

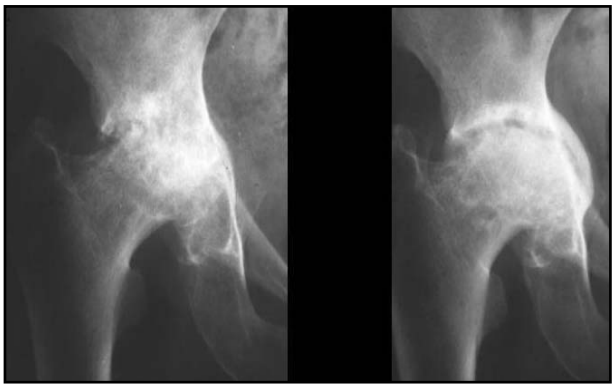


Figure 8. Atrophic OA of the hip. The patient declined surgery. One year later she had lost her pain and a new articular surface and joint space have become reconstituted. Not normal, but repaired perhaps?

ciated with osteophyte formation, but not joint space narrowing [11]. Further, much of the hydroxyapatite found in the joints of atrophic, rapidly progressive OA is 'bone dust' derived from fragmented bone. No excess of proteolytic or other enzymes is found in the joint fluid of these patients. Hence, Milwaukee shoulder as described simply does not exist. The relationship between crystals and OA may be simple (Figure 6). What may matter is the way in which a joint responds to whatever insult, or insults that initiate OA. That response may be either 'good' with active chondrocytes releasing an excess of CPPD (hypertrophic OA), or 'poor' with the release of hydroxyapatite and bone dust (atrophic OA). Thus, it should be possible to identify two groups of radiological changes in the OA joint – those that represent repair, and those of failure. For example osteophyte formation is probably good, whereas subchondral sclerosis, representing trabecular failure, is probably bad. Even in a routine, pre-operative series of patients awaiting joint replacement this spectrum of disease is apparent (Figure 7). Finally, it must not be assumed that a joint may either be hypertrophic or atrophic. The controllers of these processes, whatever they are, may change and repair can occur in an apparently condemned joint (Figure 8).

WHERE DOES RADIOLOGY GO NOW?

Much has been learnt by the careful use of imaging modalities other than plain radiographs. Skeletal scintigraphy, using a bone-seeking radiopharmaceutical, has been shown to be a very sensitive marker of OA activity. Indeed, it was the only imaging modality that had a strong positive and negative predictive value in assessing the risk of developing plain film OA in a joint until recent analysis of MRI findings. However, scintigraphy has a poor spatial resolution and exposes the patient to ionising radiation, limiting its use in longitudinal studies of OA.

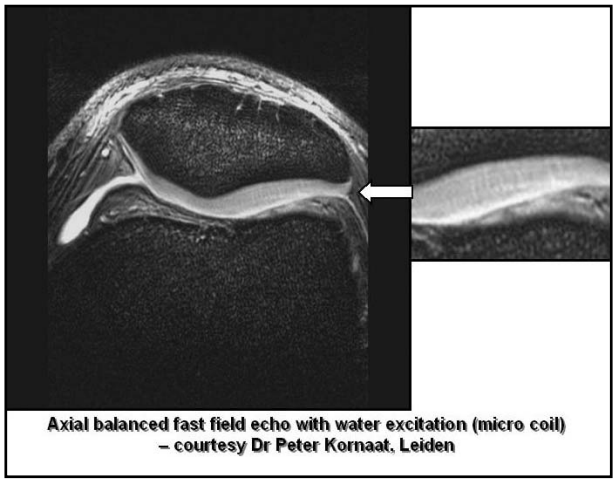


Figure 9. Normal hyaline cartilage anatomy shown by MRI. The magnified field shows the fine, normal detail within hyaline cartilage, including the recently described vertical striations and signal gradient reflecting hydration and hence proteoglycan concentration.

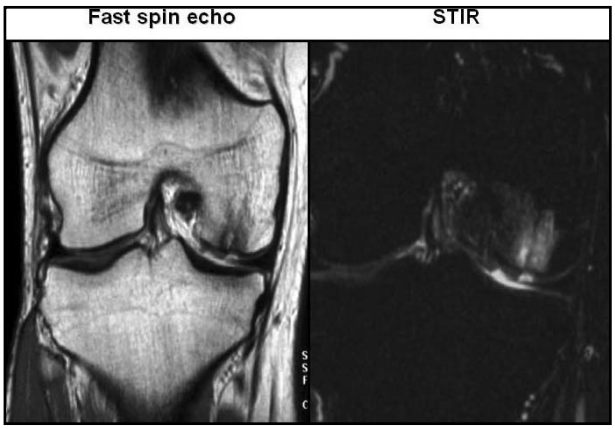


Figure 10. A fast spin echo image (left) and a STIR sequence (right) demonstrate both a hyaline cartilage defect of the medial femoral condyle and underlying marrow change. The latter, usually described as 'oedema', is thought to have an adverse prognostic significance, both in terms of patient symptoms, but also in disease progression.

MRI, on the other hand, is excellent at showing hyaline cartilage (Figure 9) and quantifying volumes and thickness as well as all other structures within a given joint, or group of joints. However, quantification of such findings remains a laborious and time consuming activity. Further, whilst it is relatively straightforward to assess normal, young, healthy knees; in advanced OA it is a different story! Clearly, MRI scanning is not cheap and use cannot be justified routinely, certainly not when assessing multiple joint sites. Longitudinal data suggest that hyaline cartilage imaging does not have a definite prognostic value. Indeed, the rate of loss of hyaline cartilage in OA is very variable, disappointingly slow and relatively slight. Further, it seems unassociated with clinical symptoms or signs. On the other hand, subchondral 'oedema', as shown on fat-suppressed sequences, may be a useful sign indicating the likelihood of disease progression within an individual compartment of the knee [12] (Figure 10). However, others dispute the validity of this. Much work is needed to sort out positive and negative predictive signs, as well as reproducibility and reliability studies. Nonetheless, inflammatory changes in synovium and subchondral bone are now thought to be bad signs whereas sclerosis, osteophytosis and eburnation are not. MRI may assist in distinguishing the signs of arthritis from arthrosis in OA, the former predicting disease activity and progression, the latter indicating inactive changes.

Two publications have focussed on the need for a scoring methodology in MRI of OA of the knee. These have yet to be validated in large scale clinical trials, but are promising. The key element in these too is to include all of the joint structures in the scoring system to reflect the contribution of synovitis as well as hyaline cartilage and subchondral bone to the evolution of OA.

Conclusions

1. It is easy to confuse osteophytosis with OA. OA is all about hyaline cartilage loss and subchondral pathology. Osteophytes represent repair secondary to joint instability and hyaline cartilage thinning, especially as we grown older. Worse, we tend to confuse these age-related changes with OA. To restate, minor osteophyte formation arises as joint space width reduces as we grow older. It is 'normal', not perfection, but normal!

2. CPPD correlates with osteophyte not OA. CPPD coexists with hypertrophic OA as a co-expression of underlying disease. Arguably, pyrophosphate arthropathy is a myth as much as Milwaukee shoulder and does not exist.

3. Enthesophytes correlate with osteophytes. As humans, we are either bone-formers – or we are not! What the processes that govern this response to injury or stress? How do we modify and adapt them?

4. The features of joint repair and failure are becoming defined – and must be so if the processes are to be identified that are to be encouraged, and those to be suppressed. We must stop seeing OA as a 'one-way' journey to slowly progressive joint failure. It is not, and may be treatable therefore.

5. OA has multiple clinical subsets. It is not a single disorder, but a group of similar diseases affecting different joint groups, often at different times with differing outcomes.

6. OA must be seen as a whole joint disease. Further, OA is a systemic, hereditofamilial disorder that may seen as a monoarthritis multiplex.

7. Lastly, radiology has much to offer in OA research.

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