Skeletal Radiol (2009) 38:419–423
DOI 10.1007/s00256-008-0637-y

PERSPECTIVE

Osteoarthritis revisited—again!

Iain Watt

Published online: 30 January 2009
© ISS 2009

Introduction

Osteoarthritis (OA) remains the commonest arthritic disease and increasingly commands attention in our ageing populations. Indeed, in recent years, the full impact of osteoarthritis has become apparent. Various estimates suggest that more than 40% of 70-year-old people have the disease, and health care costs may rise to in excess of $100 billion in the USA. Accordingly, a number of major new research programs have been established to reappraise this Cinderella subject including the Osteoarthritis Initiative in the USA. The question still remains as to whether or not the underlying pathological processes that govern the causation and repair mechanisms in the OA joint are understood.

It took many years for research in OA to move away from the "wear and tear" concept of OA. Hyaline cartilage (HC) was deemed to be the important focus in OA, and much research effort and resource was focused upon it in the belief that it represented the cause as well as the manifestation of the disease. However, while much important research data have been forthcoming, and concepts of therapy innovated, HC research has failed to provide the full answers let alone provide the means to arrest the progress of disease. Even the therapies that have spun off from this research have proven little better than placebo in relieving pain, stiffness, and self-reported function [1]. By moving the focus from HC alone to consider it in its natural environment quickly demonstrated that HC was but one component in a complex series of tissue interactions, and hence, the concept that OA is a whole organ disorder has slowly gained popularity. However, even this holistic approach fails to grasp the real problems we have in understanding OA. For, indeed, do we really know what this disease is, or even if it is a single disorder? For example, the distinction between OA per se and the simple affects of ageing may be difficult. Older people loose bone and HC thickness. Minor osteophyte formation at joint margins may simply reflect instability and a repair mechanism. Further, as joints become more congruous, circulation of synovial fluid declines, nutrition may be further compromised and HC thins [2]. Thus, Kellgren and Lawrence [3] grade 1 joints may include older, rather than arthritic joints. Indeed, a correlation has been long reported in finger joints between joint space narrowing, joint margin "spurs" and age [4]. What threshold must we pass before an old joint becomes an OA joint?

OA is not a single disease

It is obvious from clinical observation that OA comprises a series of semi-discrete subsets (hand, knee, hip, and elbow for example). These are not easily explained on the "generalized OA" model that is generally advocated even if local considerations, such as femoroacetabular impingement are identified. Further, OA has marked familial tendencies, and a series of genetic markers are becoming identified. Even then, the manifestations of OA are by no means homogeneous ranging from the frankly destructive but non-generalized erosive hand OA, to slowly progressive hypertrophic hip or knee disease. We know nothing about the controllers of these responses. Clues may be found in the associated crystal expressions within the deranged joints

I. Watt (✉)
Department of Radiology, Leiden University Medical Centre,
Albinusdreef 2, Postbus 9600,
2300 RC Leiden, The Netherlands
e-mail: i.watt@lumc.nl

such as coexistent calcium pyrophosphate dihydrate crystal deposition (CPPD) or the basic calcium phosphates found in rapidly destructive atrophic OA. Current evidence suggests that these are epiphenomena rather that cause and/or effect.

So where does the problem lie?

Traditionally, HC pathology has been seen to be the cause and effect of OA. Other structures have played a subsidiary role, bone a stiff supporter, ligaments merely a means of ensuring a range of healthy movement, and synovial fluid the nutritional supplier and waste removal means of keeping HC healthy. However, increasingly attention is being refocused on these other areas. Preeminent among them is subchondral bone. Indeed, a recent review article from four eminent rheumatologists in the OA field has stated that "there is yet more evidence that OA is not a cartilage disease" and suggested that it was indeed a bone disease [5].

So why is OA a bone disease?

The key clinical feature of OA is the Heberden node. Described in 1803, this hallmark feature is, of course, bony. Further evidence suggests that osteophyte formation does not equate with disease progression. For example, of 86 patients diagnosed as having hip OA on the basis of osteophytosis, only one patient had progressive joint space narrowing 11 years later [6]. The association between osteophyte formation and enthesophytosis is also well documented. From such studies, the concept of "bone forming" individuals has emerged, such that generalized OA and diffuse idiopathic skeletal hyperostosis are closely related [7]. Could it be that the way a joint responds to injury or stress is systemic and not local? That would certainly lend weight to the genetic underpinning of OA. Further, hypertrophic OA patients are not osteoporotic whereas atrophic OA patients are [8]. One could paraphrase *Animal Farm* "bone formation—good (hypertrophic OA), no bone formation—bad (atrophic OA)". Is the tissue response in a deranged OA joint dictated by our systemic ability to form and repair bone? Tantalizing clues come also from the small volume of work on texture analysis of bone in OA. The assumption that osteophytosis and sclerosis are parallel phenomena is incorrect. It is likely that they represent different processes and are inversely related to each other [9]. In osteophytic bone, density is maintained and trabecular reorganization occurs. In sclerotic bone, the converse occurs. Is it too much to suggest the former is a repair mechanism, and the latter shoring up the failure?

Further, important clues have come from skeletal scintigraphy. ^{99m}Technetium-labeled diphosphonates proved to be highly sensitive to the presence of OA, but, more importantly, abnormal scans had a predictive value. Normal joints on radiograph with abnormal scan developed radiograph changes at follow-up. Further, abnormal joints on radiograph but with negative scans showed no progression. Indeed, it can be argued that skeletal scintigraphy has offered the only reliable prognostic indicator of subsequent joint failure in OA to date. Yet, how then can this be when hyaline cartilage is avascular and not actively calcifying in the adult? While it may be argued that in major weight-bearing joints bones are merely responding to abnormal loading transmitted by diseased cartilage, the same cannot be the case in hand OA in which the efficacy of the bone scan as a predictor was well documented [10]. Quite clearly, the bone scan is demonstrating bony pathology prior to radiographic change. Bone scans in knee OA also suggested subsets, one which seems to correlate with osteophyte formation, the other extending away from the joint surfaces correlated with bone marrow lesions subsequently identified on knee magnetic resonance imaging (MRI) [11]. Two processes, one perhaps bone forming, non-progressive OA, the other indicating significant pathology in subchondral bone supportive of the texture changes already described?

The advent of MRI has revolutionized our understanding of knee OA. The multiplanar display coupled with the ability to discriminate the various tissue types transformed the anatomical appreciation of health and disease. Again, as in the laboratory, HC received prime attention not only with evolving methods of quantifying HC volume and thickness but also in the elaboration of physical characteristic such as T1ρ, T1, and T2 maps. The use of contrast medium, either as delayed gadolinium-enhanced MRI of cartilage or, more recently, employing a pharmacodynamic approach [12], have enabled in vivo demonstration of abnormal cartilage but have not yielded the desired "gold standard hallmark" of disease prediction.

The other major new feature that MRI provided was that of the bone marrow lesions (BML) thought initially to be foci of edema. A few publications have demonstrated clearly that this was not the case and that BMLs are histologically much more complex with fibrosis, cellular infiltration, and bony damage including micro fracturing. Edema was not a significant feature [13, 14]. That is not to say that bone marrow edema does not occur in other conditions, such as acute trauma, but in OA the pathology is different. Initial reports were extremely enthusiastic about the role of BMLs in knee OA. They suggested that BMLs were associated with knee pain [15], could be predictive of progression [16] especially if they enlarged [17] or were

associated with varus or valgus angulation [16]. Later reports, however, were less clear-cut even suggesting that BMLs were not only unassociated with Western Ontario and McMaster Universities index of OA scores (WOMAC™) [18, 19] and other measures of patient symptoms but also fluctuated over a period of time, resolving and/or worsening with new lesions coming and going elsewhere in the same joint [20, 21]. Again, these lesions did not correlate with patient symptoms. As more groups analyze their data, it seems probable that BMLs represent some form of episode within subchondral bone—but what sort?

What are these bone marrow "edema" lesions?

Two recent clues have emerged—firstly, that such lesions may progress to "cysts" [20, 22] and also that at follow up progressive BMLs are associated with damage to overlying hyaline cartilage [23]. To understand these findings, it is timely to go back to some older literature. Studies measuring intraosseous pressure in hip OA and chondromalacia patella showed that not only was intraosseous pressure greatly increased in symptomatic patients but also intraosseous phlebography demonstrated grossly abnormal venous drainage [24, 25]. In other words, all was not well with intraosseous blood flow. That may explain the apparent "cavitation" of BML into "cysts" but how does it correlate with hyaline cartilage pathology granted that it is alleged to be separated from the vascularity of underlying bone. But, is this so? The work of Imhof and others has shown our classical teaching of the impermeable osteochondral junction is not correct [26]. By revisiting the histology of this region, the conclusion is drawn that the terminal vessels in the richly supplied subchondral zone of normal mature bone directly contact the deepest hyaline cartilage layer. Further, it is suggested by these authors that about 50% of the glucose and oxygen requirements of HC are supplied in this way. If these authors are right, half of HC nutrition comes from subchondral bone and a profound local alteration in bone blood flow could have highly significant effects on adjacent hyaline cartilage. Indeed, as mentioned above, the report that pharmacokinetic imaging of hyaline cartilage in health and OA can be performed within 5 min of intravenous gadolinium chelate injection [12] can only be possible if the usually taught pathway of contrast medium from synovium to joint fluid to adsorption by hyaline cartilage is circumnavigated by direct perfusion. Equally of importance is the recent demonstration on dynamic MRI that marked perfusion abnormalities are present in BML areas of subchondral bone, both in the experimental animal and in human OA [27].

OA is not a benign disease

Risk factors for the development of OA are well known and are not benign. Preeminent among these are familial linkages and obesity, themselves interlinked. Bad genes are important and while mechanical loading can be argued to be an obvious etiological factor in hip or knee OA, how can it be in hand OA [28, 29]? Further, hand OA itself is associated with cardiovascular disease [30] and an increased risk of diabetes mellitus [31]. Overall, the comorbidities of OA are significant. They include a greater than expected susceptibility to cardio- and cerebrovascular episodes, hypertension and type 2 diabetes mellitus. Patients seeing their general practitioners with OA present a greater number of comorbidities than any other chronic disease [32]. Further, preoperative hip replacement patients are equally unhealthy [33] and the postoperative death rate is disproportionately higher in OA patients [34]. It would seem that OA is not a benign disease. Thus, several authors have postulated that OA may be a vascular disease [35]. Largely, this has been posited as an atherosclerotic disorder. Indeed, recent work has shown fat and platelet aggregations in hip OA subchondral bone [36]. But the overall picture of intraosseous vascular pathology, hypertension, atherosclerosis, diabetes mellitus, and obesity suggest strongly a firm linkage with Syndrome X or the Metabolic Syndrome. Lipocytes are known to produce an increasingly long series of adipokines with widespread effects including hypertension and cortisol conversion quite apart from fat metabolism. Little is documented about systemic adipokines in OA. However, studies demonstrate that raised levels are present in the synovial fluid of OA joints and that the joint cavity has specific regulatory pathways that may be abnormal [37]. The vascular pathology of Metabolic Syndrome is beyond the remit of this perspective, but documented evidence includes a widespread vasculopathy. One recorded observation is increased arterial vessel wall thickness. For example, carotid artery wall thickness is pathologically increased in metabolic syndrome as assessed on MRI [38]. A pilot study in our group has shown similarly abnormal wall thickness in the popliteal arteries of patients with knee OA [39]. It is, thus, tempting to suggest that the BMLs observed in OA represent vascular lesions which whilst they may be transient may not only necrose and cavitate but seriously affect overlying HC nutrition if they are persistent.

Conclusions

In recent years, our perception of OA has changed significantly. It is increasingly obvious that it is difficult to distinguish between changes in joints occasioned by age

and those of true OA recalling that both are interrelated. Arguably, it is even difficult to know what OA actually is or how to diagnose it! The disease, if indeed it is one disease, is no longer seen as a "wear and tear" disorder or one in which cartilage failure and wear produce joint disruption. The roles of DNA expressions, abnormal joint modeling, underlying subchondral bone changes, ligaments, and vascularization are becoming clearer. Granted the comorbidities it has, OA should be seen also as a serious health risk to the sufferer.

So how do we move forward? Firstly, radiologically and clinically, we need to characterize more clearly the obvious subsets that are known to exist already and to possibly identify others. To set up studies which include a heterogeneous mix is inevitably doomed to failure. Secondly, the distinction between the features of "repair" and "failure" in the damaged joint are far from clear or even widely considered to exist. Imaging provides the unique in vivo ability to look at the processes occurring within the whole joint organ. Global scoring systems such as the Kellgren and Lawrence score are no longer good enough [4]. Even careful assessment of individual signs, such as osteophytes or joint space narrowing, using more detailed scoring systems have their limitations as they do not give credence to the possibility that, for example, an osteophyte may be a good reparative thing. The lessons learnt from skeletal scintigraphy have not been further developed. What was it in bone that caused the activity changes that were so predictive of outcome? Can texture analysis further elaborate early changes before joint failure? The future for MRI is exciting and offers great potential. For example, we need to reexamine Herwig Imhof's seminal work on the osteochondral junction for, if he is correct, our ideas about the health and disease of the osteochondral junction needs a radical rethink. To start this process radiologically, we need far more detailed studies of subchondral bone perfusion and diffusion and to further explore ultrashort echo time imaging. How soon in the OA process are changes occurring here? Can we demonstrate subchondral perfusion and diffusion in vivo with or without the need for contrast medium? The advent of higher field strength magnets at 7T makes this a ready possibility. Thirdly, is it reasonable to include OA in the Metabolic Syndrome for, if so, should it be treated accordingly? We need to extend existing work in the aorta and carotid vessels to those more intimately related to OA joints. Careful clinicoradiological studies should show us whether or not Metabolic Syndrome is associated with BMLs or even severe OA, and if so, which subsets?

Finally, whatever the future holds, for now, OA is far from a benign disease. As we observed 18 years ago in this journal, most of us are going to get OA, and the sooner the disease and repair processes are understood, the better [40].

References

1. Zhang W, Robertson J, Jones AC, Dieppe PA, Doherty M. The placebo effect and its determinants in osteoarthritis: meta-analysis of randomised controlled trials. Ann Rheum Dis 2008; 67: 1716–1723.
2. Bullough PG. The geometry of diarthrodial joints, its physiologic maintenance, and the possible significance of age-related changes in geometry-to-load distribution and the development of osteoarthritis. Clin Orthop Relat Res 1981; 156: 61–66.
3. Kellgren JH, Lawrence JS. Radiological assessment of osteoarthrosis. Ann Rheum Dis 1957; 16: 388–397.
4. Mäkelä P, Virtama P, Dean PB. Finger joint swelling: correlation with age, gender, and manual labor. AJR Am J Roentgenol 1979; 132: 939–943.
5. Brandt KD, Radin EL, Dieppe PA, van de Putte L. Yet more evidence that osteoarthritis is not a cartilage disease. Ann Rheum Dis 2006; 65: 1261–1264.
6. Danielsson LG. Incidence and prognosis of coxarthrosis. Acta Orthop Scand Suppl 1964; suppl. 66: 1–114.
7. Rogers J, Shepstone L, Dieppe P. Bone formers: osteophyte and enthesophyte formation are positively associated. Ann Rheum Dis 1997; 56: 85–90.
8. Dequeker J. The inverse relationship between osteoporosis and osteoarthritis. Adv Exp Med Biol 1999; 455: 419–422.
9. Sharma S, Rogers J, watt I, Buckland-Wright C. Bone mineral density and fractal signature analysis in hip osteoarthritis- a study of a post-mortem and postoperative population. Clinical Radiology 1997; 52: 872. abstract.
10. McCarthy C, Cushnaghan J, Dieppe P. The predictive role of scintigraphy in radiographic osteoarthritis of the hand. Osteoarthr Cartil 1994; 2: 25–28.
11. McAlindon TE, Watt I, McCrae F, Goddard P, Dieppe PA. Magnetic resonance imaging in osteoarthritis of the knee: correlation with radiographic and scintigraphic findings. Ann Rheum Dis 1991; 50: 14–19.
12. Sanz R, Martí-Bonmartí L, Rodrigo JL, Moratal D. MR Pharmacokinetic modeling of the patellar cartilage differentiates normal from pathological conditions. JMRI 2008; 27: 171–177.
13. Zanetti M, Bruder E, Romero J, Hodler J. Bone marrow edema pattern in osteoarthritic knees: correlation between MR imaging and histologic findings. Radiology 2000; 215: 835–840.
14. Taljanovic MS, Graham AR, Benjamin JB, et al. Bone marrow edema pattern in advanced hip osteoarthritis: quantitative assessment with magnetic resonance imaging and correlation with clinical examination, radiographic findings, and histopathology. Skeletal Radiol 2008; 37: 423–431.
15. Felson DT, Chaisson CE, Hill CL, et al. The association of bone marrow lesions with pain in knee osteoarthritis. Ann Intern Med 2001; 134: 541–549.
16. Felson DT, McLaughlin S, Goggins J, et al. Bone marrow edema and its relation to progression of knee osteoarthritis. Ann Intern Med 2003; 139: 330–336.
17. Felson D, Niu J, Guermazi A, et al. Correlation of the development of knee pain with enlarging bone marrow lesions on magnetic resonance imaging. Arthritis and Rheum 2007; 56: 2986–2992.
18. Sowers MF, Hayes C, Jamadar D, et al. Magnetic resonance-detected subchondral bone marrow and cartilage defect characteristics associated with pain and Radiograph defined knee osteoarthritis. Osteoarthr Cartil 2003; 11: 387–393.
19. Kornaat PR, Bloem JL, Ceulemans RY, et al. Osteoarthritis of the knee: associations between clinical features and MR imaging findings. Radiology 2006; 239: 811–817.

20. Kornaat P, Kloppenburg M, Sharma R, et al. Bone marrow edema-like lesions change in volume in the majority of patients with osteoarthritis: associations with clinical features. Eur Radiol 2007; 17: 3073–3078.
21. Brem MH, Schlechtweg PM, Bhagwat J, et al. Longitudinal evaluation of the occurrence of MRI-detectable bone marrow edema in osteoarthritis of the knee. Acta Radiol 2008; 49: 1031–1037.
22. Carrino JA, Blum J, Parellada JA, Schweitzer ME, Morrison WB. MRI of bone marrow edema-like signal in the pathogenesis of subchondral cysts. Osteoarthr Cartil 2006; 14: 1081–1085.
23. Roemer FW, Guermazi A, Javaid MK, Lynch JA, Niu J, Zhang Y, Felson DT, Lewis CE, Torner J, Nevitt MC. Change in MRI-detected subchondral bone marrow lesions is associated with cartilage loss—the MOST study a longitudinal multicenter study of knee osteoarthritis. Epub ahead of print; Ann Rheum Dis. doi:10.1136/ard.2008.096834.
24. Arnoldi CC, Linderholm H. Venous engorgement and intra-osseous hypertension in osteoarthritis of the hip. JBJS 1972; 54-B: 409–421.
25. Björkström S, Goldie IF, Wetterqvist H. Intramedullary pressure of the patella in Chondromalacia. Arch Orthop Traumat Surg 1980; 97: 81–85.
26. Imhof H, Sulzbacher I, Grampp S, Czerny C, Youssefzadeh S, Kainberger F. Subchondral bone and cartilage disease. A rediscovered functional unit. Invest Radiol 2000; 35: 581–588.
27. Aaron RK, Dyke JP, Ciombor DM, et al. Perfusion abnormalities in subchondral bone associated with marrow edema, osteoarthritis and avascular necrosis. Ann NY Acad Sci 2007; 1117: 124–137.
28. Oliveria SA, Felson DT, Cirillo PA, Reed JI, Walker AM. Body weight, body mass index, and incident symptomatic osteoarthritis of the hand, hip and knee. Epidemiology 1999; 10: 161–166.
29. Kalichan L, Kobyliansky E. Age, body composition, and reproductive indices as predictors of radiographic hand osteoarthritis. Scand J Rheumatol 2007; 36: 53–57.
30. Jonsson H, Helgadottir GP, Aspelund T, et al. Osteoarthr Cartil 2008; 16 Supplement 4: S128.
31. Dahaghin S, Bierma-Zeinstra SM, Koes BW, Hazes JM, Pois HA. Do metabolic factors add to the effect of overweight on hand osteoarthritis? The Rottendam Study. Ann Rheum Dis 2007; 66: 916–920.
32. Schellevis FG, van der Velden J, van de Lisdonk E, van Eijk JT, van Weel C. Comorbidity of chronic diseases in general practice. J Clin Epidemiol 1993; 5: 469–473.
33. Marks R, Allegrante JP. Comorbid disease profiles of adults with end-stage hip osteoarthritis. Med Sci Monit 2002; 8: CR305–CR309.
34. Visuri T, Pulkkinen P, Paavolainen P, Koskenvuo M, Turula KB. Causes of death after hip arthroplasty in primary arthrosis. J Arthroplasty 1997; 12: 397–402.
35. Conaghan PG, Vanharanta H, Dieppe PA. Is progressive ostoearthritis an atheromatous vascular disease? Ann Rheum Dis 2005; 64: 1539–1541.
36. Cheras PA. Vascular abnormalities play key roles in osteoarthritis: implications for detection and treatment. Osteoarthr Cartil 2008; 16 Supplement 4: S55.
37. Presle N, Pottie P, Dumond H, et al. Differential distribution of adipokines between serum and synovial fluid in patients with osteoarthritis. Contribution of joint tissues to their articular production. Osteoarthr Cartil 2006; 14: 690–695.
38. Alizadeh Dehnavi R, Doornbos J, Tamsma JT, et al. Assessment of the carotid artery by MRI at 3T: a study on reproducibility. J Magnet Reson Imag 2007; 25: 1035–1043.
39. Kornaat P, Sharma R Geest van der R, Lamb H, Bloem J, Kloppenburg M, Watt I. Positive association between increased popliteal artery vessel wall thickness and generalized osteoarthritis; is OA also part of the Metabolic Syndrome? Abstract Skeletal Radiology 2008; 37: 586.
40. Watt I, Dieppe P. Osteoarthritis revisited. Skelet Radiol. 1990; 19: 1–3.