A view on the pathogenesis of osteoarthritis from the shoulders of giants

OA is a common problem with high impact on patients and healthcare costs, accounting for 97% of the increasing number of joint replacements performed in England and Wales [1]: 137 000 hip and knee replacements in 2007 [2]. There is currently a considerable focus on the treatment of OA, including clinical guidelines on the care and management of adults with OA by the National Institute for Health and Clinical Excellence (NICE) [3], Osteoarthritis Research Society International (OARSI) and European League Against Rheumatism (EULAR) guidelines for hip and knee OA [4–6]. These guidelines list a number of treatments to prevent or modify pain and function and recommend that management should include a combination of non-pharmacological and pharmacological interventions to maximize symptom relief. This indicates that we need more effective treatments for the symptomatic treatment of OA and, more importantly, we need effective disease-modifying therapy. Understanding the pathogenesis of a disease will greatly enhance our ability to develop more effective treatments for OA and particularly disease-modifying therapies. There has long been a discussion within the OA community as to whether OA is primarily a disease of bone or cartilage. A review article published in the current issue of Rheumatology by McGonagle et al. [7] is therefore timely in prompting reflection on our current understanding of the OA process and how that understanding can be refined to inform advances in therapy.

McGonagle et al. propose a novel and stimulating hypothesis, describing an important role for ligaments and the ‘enthesis organ’ of the interphalangeal joints of the hand, in the pathogenesis of hand OA, but also, of great importance for clinical practice, at other sites including the knee [6]. Knee OA is the most commonly researched site: this seems appropriate with the recognition that it is the most frequently affected site [8] and the biggest identifiable cause of musculoskeletal pain attendance to Primary Care [9]. How well does their hypothesis bear up to scrutiny?

Hand OA

McGonagle et al. draw on evidence from a number of innovative microanatomical and high-resolution MRI studies, many of which have been performed by this group of authors. The use of high-resolution MRI has allowed the examination of all of the structures of the DIP and PIP joints, thereby allowing the exploration of nodal OA as a potential whole joint disease, as is already happening with the knee. They describe areas of weakness at the margins of collateral ligaments that were associated with ‘Baker’s cyst-like bulges’ at the site of early Heberden’s nodes and they suggest a causal association. Early erosions were also seen at the sites of ligament insertion on the proximal sides of the DIP and PIP joints. They also describe marked thickening and signal changes of the collateral ligaments of the DIP and PIP joints; however, these changes were also seen in uninjured sites of patients with nodal OA and in normal subjects over the age of 40 yrs. Subjects with early hand OA have extensive inflammation of the periarticular tissues in the presence of relatively normal cartilage on high-resolution MRI and the authors suggest that this is unlikely to be secondary to cartilage degradation products and may be a primary feature of OA.

The authors suggest that these findings in the ligaments are the early, possibly the initiating features of nodal OA: a new and potentially very exciting paradigm. Before diverting all of our research attention away from bone and cartilage to ligaments, we should assess the level of the research evidence currently in the peer-reviewed literature to support this hypothesis. These studies were cross-sectional, as is usual in the early stages of exploring a novel research hypothesis, making it impossible to determine temporality or causality. In the reported cross-sectional studies, most of the described changes have also been described in the normal elderly population in addition to early and established nodal OA. The high prevalence of these features in the normal population suggests several possible scenarios: (i) the reported changes are unrelated to OA; (ii) they are predisposing factors to OA but require other risk factors e.g. trauma to lead to OA or (iii) they are early features of OA and most of these subjects will develop OA in the future. If we assume that these changes are associated with OA, using data from cross-sectional studies does not allow differentiation between cause and effect. To answer these important questions will require robustly designed epidemiological studies of longitudinal design. It may be possible to use other imaging techniques, such as high-resolution musculoskeletal ultrasound, which has established reliability in demonstrating OA changes in and around the hand joints [10] and is less expensive and more readily available than high-resolution MRI.

Other sites

Observations of the importance of collateral and cruciate ligament damage for knee OA are uncontroversial, but robust epidemiological data do not exist on early knee OA using modalities capable of visualizing ligamentous changes such as MRI and high-resolution musculoskeletal ultrasound. The data concerning animal models is interesting; however, models of spontaneous OA, although providing valuable information may not be directly related to disease in humans and should be interpreted with caution. There are now several large cohort studies, including the United States National Institute for Health’s OA initiative [11], which are obtaining knee MRI scans that will allow this question to be explored in detail. This may require dedicated scoring methods to address ligament degeneration and inflammation in more detail, which may be addressed by incremental improvement in scoring systems [12], although confirmation of the reliability and validity across other centres is highly desirable.

Spondylosis

There is a danger here of perpetuating the confusion relating to some authors continuing to label spondylosis as ‘OA of the spine’. Although the radiographic change of disc space narrowing is similar to the cartilage loss leading to joint space narrowing in other joints, the anatomy and pathology are different. It would seem speculative to link the changes here to ligaments on current evidence; indeed, there is evidence to the contrary [13].

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Relevance and impact

So, how does this article improve our understanding of the pathogenesis of nodal and generalized OA? By approaching the lesions described by William Heberden the Elder [14] using new imaging techniques, allied to anatomy and animal models, McGonagle’s group are essentially building on the key achievements of forerunners in refining our understanding of the processes involved. The hypothesis is provocative and should stimulate others to reproduce their findings and to explore them further using longitudinal cohort studies in order to establish a robust temporal frame for these changes. In the meantime, we should factor the ligaments into our theoretical frameworks of the pathogenesis of hand OA. However, the generalizability to other key joint sites such as the knee and hip is far from certain. Like many important advances in musculoskeletal and other diseases, this hypothesis article is based on extending the work of those who have gone before, and if this makes us challenge our assumptions and generates new, testable hypotheses, this is laudable. As Isaac Newton remarked to Hooke, ‘If I have seen a little further it is by standing on the shoulders of Giants’ [15].

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References