Review

Heberden’s nodes and what Heberden could not see: the pivotal role of ligaments in the pathogenesis of early nodal osteoarthritis and beyond

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Despite its relatively high prevalence, polyarticular nature, limited treatment options and recognized genetic contribution, the study of generalized OA (GOA) has lagged behind that of isolated knee OA. Whilst the pathogenesis of OA has been viewed in relation to either articular cartilage or bone disease, this article offers a viewpoint on why GOA may, in fact, be primarily a disorder of ligaments, and to a lesser extent tendon and joint capsule dysfunction. A relatively fast presentation of GOA, typically in the perimenopausal period, and its recognition on clinical grounds alone makes this type of OA potentially useful for pathogenic studies in OA, in general. The recent high-resolution MRI studies, microanatomical studies and animal models, in addition to established clinical and radiographic data that support this ligament-centric perspective of disease, are reviewed. The earliest structural abnormalities in GOA may be evident in ligaments and the ligament-associated ‘enthesis organ’, where degenerative changes are evident. Ligaments also influence the expression of joint damage including Heberden’s node and joint erosion formation. Joint inflammation in a ‘periarthritic’ pattern is well recognized in GOA, and histological studies have shown that the ligament and capsule could represent the epicentre of such inflammatory changes. A perspective is also offered on how ligaments could play a pivotal role in OA in general; for example, the loss of joint space in knee OA due to meniscal extrusion could ultimately be related to derangement of the medial collateral ligament to which the meniscus is anchored.

KEY WORDS: OA, Heberden’s nodes, Ligaments, Enthesis, MRI, Synovio–entheseal complex, Histopathology, Hand, Inflammation, Fibrocartilage.

Introduction

A myriad of factors contribute to the difficulties in studying the pathogenesis of OA including the generally slow evolution of disease, the heterogeneity of precipitating factors, the variability in its natural history according to the joints involved, different associations with biomechanically related factors (including joint malalignment, joint injury and obesity), and other issues including joint inflammation and genetics [1–6]. However, eventual joint failure is accompanied by significant loss of articular cartilage and consequently, OA has been mainly viewed in relation to this tissue [7]. Where OA commences following an isolated chondral injury, this would indeed appear to be the case, but the view that OA is merely a disease of articular cartilage is no longer widely accepted [8–10]. Nevertheless, the vast majority of both academic and industrial research pertains to understanding articular cartilage degeneration and the development of therapies to prevent the progression thereof [10, 11].

Although end-stage OA represents a disease of the whole organ, the question regarding the anatomical site where disease commences is important. Recognized sites of ‘traumatic’ knee OA initiation include the meniscus, the anterior cruciate ligament (ACL) or articular cartilage, following the mechanical disruption of any of these. This shows how end-stage OA may begin at different anatomical locations [12]. However, data on the primary joint site of ‘non-traumatic’ OA is very limited. Besides articular cartilage, a historical theory that has been recently revised is that, OA is primarily a disease of bone [13, 14].

Why study nodal OA?

The eventual clinical recognition of nodal OA can be traced back to the original description of Heberden’s nodes in the DIP joints in subjects with hand arthritis [15]. The classic clinical presentation of nodal OA is with Heberden’s and Bouchard’s nodes of the DIP and PIP joints, respectively, and also with the involvement of many other joints including the CMC joints, hips, knees and the first MTP joint are also characteristically involved [16] (Fig. 1). However, many patients may have hand OA, which may or may not be associated with other joint involvement. Conversely, many patients with polyarticular OA may have sparing of the hands. Our arguments are initially articulated in relation to hand joint involvement, and then isolated large joint OA is also evaluated from the same perspective of ligament abnormalities as initiators of disease. Whilst fully recognizing the constraint that OA is a heterogeneous disease, the nodal OA spectrum allows one to ask, at what anatomical location does “non-traumatic” OA start? In order to address this question from a novel perspective, and to minimize the effect of disease heterogeneity, we have studied nodal OA using high-resolution MRI and micro-anatomical studies [8, 9]. This category of OA was chosen because it is relatively common and has a strong genetic basis [2, 17]. It attacks multiple, anatomically distinct joints, both large and small, and can involve both the axial and appendicular skeleton. Unlike isolated knee joint OA—for example, that which may have an insidious onset—nodal OA may present over a shorter time frame (e.g. in the perimenopausal period) and may involve multiple joints [18]. However, nodal OA can also appear later in both the sexes.

The occurrence of nodal OA at multiple sites argues against a stochastic initiating event such as significant joint trauma (either recalled or forgotten). Other key factors such as joint malalignment that may be critical for large joint disease, especially in the knee, are also reduced. Importantly, the diagnosis of nodal OA is mainly clinical based, and does not depend on insensitive
radiographic techniques; therefore, the investigator can recognize nodal OA with some confidence. Furthermore, the small joints lend themselves to high-resolution imaging and easier histological analyses because the entire joint organ can be more readily evaluated using imaging and histological techniques. A further advantage offered by the hand in OA is that disease tends to spread from joint to joint, thus allowing the investigator to study ‘pre-clinical’ disease, since joints that are clinically and radiographically normal at the time of investigation may be likely to develop OA at a later date [19]. Finally, with the exception of the CMC joint disease [20], orthopaedic interventions are not definitive and many patients are thus consigned to chronic pain and suffering [21]. In addition to the aforementioned academic factors, this dearth of understanding and lack of therapeutic modalities make research into nodal OA especially pertinent [22].

GOA as a ligamentous disease—the imaging case
The original description of GOA largely stemmed from the pioneering work of Kellgren and Moore [23] who showed that not only GOA encompassed the spectrum of disease that Heberden noted, but also that a wider territory was involved. Their classification studies made good use of radiography. Although plain radiography has several diagnostic limitations, it is most sensitive in the small joints, where abnormalities are more readily appreciated. Despite clinically florid joint disease, plain radiography may be normal in many cases of GOA at clinical presentation without evidence of joint space narrowing and hence articular cartilage loss. Furthermore, some of the radiographic manifestations of chronic GOA (including new bone formation and periartricular erosions—both of which may be evident in the DIP joints) can be difficult to distinguish from PsA that is an entheseal-associated disease (Figs 3 and 4) [24]. As further outlined subsequently, these features that are reminiscent of PsA are a very important clue for a better appreciation of the micro-anatomical basis for hand OA.

The advent of MRI has changed the understanding of OA. Conventional MRI has provided valuable insights into the role of synovitis and bone marrow oedema in the symptomatology and progression of large joint OA, particularly of the knee [25, 26]. On MRI, bone oedema-like lesions may be a reliable indicator of progressive joint destruction in the case of joint malalignment [27, 28]. However, little has been reported utilizing conventional MRI in the small joints, or indeed in large joints that are affected as part of the GOA spectrum. A major limitation of conventional MRI is the inability to depict subtle changes accurately within the ligaments and capsules due to their small size, and importantly, their relatively short T2 relaxation times. This latter issue results from the highly organized molecular structure of these tissues and results in limited intrinsic contrast using conventional MRI techniques.

Therefore optimization of high-resolution MRI for clinical scanners was carried out in order to facilitate the detailed imaging of small joints [8, 9]. As expected, it was established that chronic symptomatic OA was a disease that affected virtually every joint tissue and in which there was florid joint degeneration, inflammation or both. In chronic disease, the most striking abnormality was disruption of the collateral ligaments of the PIP and DIP joints. Even at clinical presentation, ligament involvement was prominent, but disease of the whole joint organ was also commonplace on MRI [29].

A relationship between Heberden’s nodes and the collateral ligaments was also evident since the ligament position predicted adjacent ‘weakness’ in the joint capsules. It was at these sites that acute Heberden’s node tissue could be seen to bulge out in a manner reminiscent of Baker’s cyst formation in the arthritic knee joint [30]. The site of soft tissue bulging between ligaments and tendons in early disease appeared to dictate the distribution and pattern of osteophyte formation in established disease, since such bony abnormalities in chronic disease mirrored acute inflammatory changes in early OA [8]. As might be anticipated, the ligament and tendon enthesis were also the site where bony spurs or enthesophytes (another prominent OA joint manifestation) developed (See X-ray in Fig. 3). Indeed, even at clinical presentation, prominent enthesophytes and osteophytes were commonly observed [9]. This supports the concept that aberrant remodelling might dominate the pathophysiological expression of disease, even at first clinical presentation [31].
The position of the ligaments was also a good indicator of the location of MRI-determined bone erosions. These erosions were often immediately adjacent to ligament origins on the proximal sides of both the DIP and PIP joints [8, 9]. Indeed, it was possible to demonstrate using MRI that the term ‘erosive hand osteoarthritis’ is probably somewhat artificial, since on high-resolution MRI, the majority of cases were in fact erosive [32]. This propensity for erosion adjacent to ligaments is not unique to GOA, and may represent a common biomechanical response at sites of bone stressing related to ligament pressure on bone and the effect of immediately adjacent synovitis [33].

Another finding on high-resolution MRI was bone marrow oedema at entheses—i.e. in addition to the more usually recognized subchondral bone oedema [9]. This was somewhat reminiscent of the osteitis that is known to be associated with enthesopathy in SpA, but of course, there is a lack of evidence that bone oedema in OA is due to osteitis [34]. Bone oedema was also noted at the base of both osteophytes and enthesophytes, which probably indicates active bone remodelling. Notably, the MRI-determined perienthesal changes in the small joints in the hand were reminiscent of those evident in the spine in patients with normal X-rays and mechanical back pain (Fig. 2).

Earliest imaging changes in nodal OA and age-related ligament changes

Nodal OA is often asymmetrical at the time of clinical presentation, but characteristically progresses to involve all of the DIP and PIP joints in both hands, in addition to the CMC joint [19]. In subjects with nodal OA, we imaged asymptomatic joints that were radiographically normal, in order to gain insights into what nodal OA might look like in its pre-clinical phase. Whilst most of the joint structures were normal, the most characteristic finding was thickening of the joint collateral ligaments, though no disruption was evident [9].
OA is a disease of ageing and many age-related changes, including decreased proliferation of articular chondrocytes and defects in chondrocyte stem cells have been reported [35, 36]. We assessed normal non-OA subjects and noted two distinct patterns of disease [9]. In those under 40 yrs of age, ligaments appeared uniformly normal on MRI. However, beyond that age, subtle ligament thickening and signal changes were the principal MRI findings. Indeed, it was not possible to distinguish between older normal subjects and clinically uninvolved joints in nodal OA [9]. Although this was not a longitudinal study, these observations nevertheless provide a possible novel ligamentous link between age and OA, but they also raise many questions. In particular, what is it that causes age-related ligamentous thickening to progress to pathological changes that are only recognized in a subset of people? Otherwise, if ligamentous changes are universal with age, then why is it that nodal OA is not seen more commonly than it is? Based on animal studies, a possible genetic difference has been proposed to explain the propensity of some individuals to develop OA, but no direct link to ligament changes have been explored [37]. Furthermore, why does it most often manifest in the perimenopausal period?

**Microanatomy of ligaments**

To begin to address these questions, it is helpful to look at the functional anatomy of ligaments and the age-related pathological changes occurring in them. From a functional perspective, some ligaments are over-simplistically viewed as reinforcing cables for joint capsules that run from one attachment site to the other (Fig. 5A). Unlike articular cartilage, ligaments are vascularized and when they are injured, there is a typical inflammatory reaction with remodelling and repair [38]. OA is often stated to be a disease of ‘wear and tear’, and one possibility is that the degree of damage of a joint structure could be directly related to its size and the degree of mechanical stress that it experiences during locomotion. Even a cursory view of the small joints of the hand shows that their collateral ligaments are extremely large relative to the size of the joint, and thus, to the area occupied by articular cartilage (Fig. 6) [39]. It is of paramount importance to the ability of the hand to act as both a coarse ‘gripping’ and a fine ‘precision’ tool that the abduction and adduction of the IP joints are prohibited—something that necessitates impressively sturdy collateral ligaments (Fig. 6) [40].

**The ligament and bone**

It is now recognized that many entheses are not simply focal insertions, but part of a stress-dissipating anchorage organ that we have dubbed as the ‘enthesis organ’ [41]. Thus, there may be two ‘buffering’ fibrocartilages at a ligament attachment site, in addition to that present at the enthesis itself (Fig. 5C). These have been termed sesamoid and periosteal fibrocartilages. These enthesis organ structures help illustrate how the ligament and bone are functionally integrated. Ligaments may not run in a straight line between two bones, even when they may seem to. Thus, in the case of the PIP and DIP joints, the collateral ligaments arise from a small pit on the proximal side of the joint and hence must cross a convex bone surface to reach their distal insertion (Fig. 5B) [8]. This leads to a close functional integration between the ligament and adjacent bone at the proximal end of the joint. Furthermore, both ends of the ligament are effectively anchored to an extended trabecular network of bone rather than to the bone cortex that is extremely thin at attachment sites [42]. These anatoniocal observations appear to be clinically relevant, since we have noted that bone oedema as determined by high-resolution MRI, extends from the periligamentous bone to the subchondral plate beneath the articular cartilage [8]. This provides a novel mechanism of how ligament-related dysfunction could affect articular cartilage directly via a bony pathway. Although the earliest anatomical changes seem to be centred on the ligaments, it would be premature to discount a pivotal role for bone in ligamentous-related disease processes in OA; it is just that the first structural abnormalities appear in the ligaments.
A novel mechanism of synovitis in hand OA

Inflammation is a prominent feature of OA in general and including that of the hand [8, 9, 43]. A major perceived mechanism of synovitis in OA relates to the liberation of damaged tissues from articular cartilage [43]. However, on high-resolution MRI in early hand OA, inflammation may be extensive and involve the periarticular tissues even when the cartilage looked relatively normal. The inflammatory changes can be seen in the body of the ligaments themselves but also in the extracapsular tissues [8, 9]. This may also have implications for a possible novel explanation for the mechanism of synovitis and associated cartilage destruction in GOA. Analogous to the bone, there is also a close functional interdependence between periosteal and sesamoid fibrocartilages and the synovium (Fig. 5C). The term ‘synovio-entheseal complex’ (SEC) has been coined to highlight the normal functional and pathological interplay between synovial membrane and an enthesis (Fig. 5C) [44].

When a systematic search for ‘wear and tear’ and inflammation in ligament-related tissues is performed then strong evidence for disease in these sites as contributors to OA can be found. Ligaments have been evaluated for evidence of microdamage and degenerative changes in normal cadaveric joints [9, 33]. This has shown that degenerative changes were virtually universal in the ligament entheses and adjacent fibrocartilages of aged humans [9, 33]. Such changes included fibrocartilage fissuring and fibrillation, chondrocyte hypertrophy, chondrocytic clustering and subchondral cystic changes—i.e. what could collectively be described as ‘enthesis organ OA’ (Fig. 7). These ‘enthesis fibrocartilage OA’ changes probably explain the age-related findings in normal joints on high-resolution MRI.

It was also noted that enthesis fibrocartilage damage was associated with the evidence of a small number of inflammatory cells adjacent to the attachment site. However, inflammatory changes also extended into the ligament fascicles. Extrapolating the above findings offer a novel perspective on the ‘periartirrhis’ pattern of swelling and development of symptoms in acute hand OA (Fig. 7) since an epicentre of inflammation in the ligament or capsule, rather than the synovium, could explain the ‘periartirrhis’ or extracapsular pattern of hand inflammation in GOA (Fig. 8). The degree of enthesis and ligament involvement in OA raises the question that the spectrum of inflammation in OA may be more closely linked to that of the spondyloarthritides than hitherto appreciated. Clearly, this is something that needs to be addressed further.

At the molecular level it has now been established that damage-associated molecular patterns that include intracellular molecules that are released into the extracellular spaces can activate innate immune pattern recognition receptors, including Toll-like receptor-4. Thus, a cascade related to ligament ‘wear and tear’ and microdamage and how this could lead to periarticular inflammation in GOA already exists [44–46].

Ligaments in OA beyond the hands–knee involvement

Investigators in the OA field have tended to argue that the whole spectrum of OA should be viewed from a single principal perspective e.g. articular cartilage, the joint organ or more recently bone [14, 47, 48]. Our arguments are focused on scenarios in which ligaments could play an initiating or modulating role in the nodal OA process. However, we fully acknowledge that traditional OA risk factors including obesity and direct injury to the articular cartilage are still critically important in a significant number of settings. However, in support of the critical importance of ligaments in hand OA, surgeons have recognized the key role that the beak ligament plays in the pathogenesis of CMC joint OA, since its reconstruction is associated with a good outcome [20, 49]. Also, instability of the scapholunate ligament has been associated with CMC joint OA development [50]. However, ligaments are not necessarily initiating factors in all types of OA, but the role of ligaments is likely to be important outside the hand. In isolated knee OA, there is good evidence that ACL disruption or injury is associated with progressive OA [51–53]. Evidence also exists for ACL abnormalities in atraumatic knee OA [54, 55]. Furthermore, it has been suggested that both hypermobility and knee joint malalignment are associated with the subsequent onset of OA [56–58]. Therefore, it seems likely that ligament, tendon or capsular laxity are the major determinants of hypermobility, but could also contribute to joint malalignment, which in itself can contribute to progressive OA [27].

The role of site-specific factors, including the functional anatomy of involved joints is likely to be the key in understanding GOA, and we have illustrated this in relation to the small joints that are most characteristically involved. But how can knee involvement as part of GOA be linked to ligaments? It is well...
recognized that following trauma to the medial collateral ligament (MCL), oedema may be seen associated with the ligament and in the surrounding tissues [59, 60]. However, it is also becoming clear that MRI demonstrates abnormalities in and around the MCL in some patients without a history of traumatic injury. More specifically, Bergin et al. [61] showed that MCL oedema, in the absence of trauma, was associated with degenerative joint disease. The most obvious link other than damage to the collateral ligaments is via the medial meniscus, which is attached to the medial MCL [61, 62]. There is MRI evidence that extrusion of the medial meniscus (a risk factor for knee joint OA progression), is associated with adjacent MCL damage, but cause and effect has not been formally demonstrated [63–66]. Preliminary data has shown abnormal signal adjacent to the MCL itself, suggesting that in some cases, ligament changes could predate those in the meniscus [65]. It must be pointed out that the MCL, but not the lateral collateral ligament, is attached to the adjacent meniscus. There is also evidence that the cruciate ligaments may also play a role in the pathogenesis of knee OA. We have noted that peri-entheseal bone marrow oedema was common in hand OA [8, 9] and now similar abnormalities have been shown by others in the tibial plateau bone adjacent to the ACL [67]. The basis for these important ligament-related findings and OA symptoms and progression awaits further exploration.

Conventional MRI studies have also shown that end-stage knee OA is associated with cruciate ligament rupture [68]. At present, although there are intensive MRI initiatives being developed in order to explore early knee OA, and although OA scoring systems have been developed, these do not specifically include ligaments [69]. This is more a reflection of the insensitivity of conventional MRI for showing ligaments, rather than an oversight by investigators. Nevertheless, there is a need to develop higher resolution imaging methods to ascertain systematically whether the changes in ligamentous, tendinous or capsular structures are early features in GOA with large joint involvement and in isolated knee OA.

Ligaments in the spine

The presence of both articular cartilage and synovium in the majority of GOA-targeted joints supports the paradigm of joint synovitis contributing to cartilage loss, as there is clear evidence that joint synovitis is associated with progressive joint deterioration at other sites [43]. However, ‘wear and tear’ also manifests prominently in the intervertebral discs of the highly mobile segments of the cervical and lumbar spine as spondylisis. The lumbar spine intervertebral joints are devoid of both articular cartilage and synovium, and progressive joint damage with disabling symptomatology may be evident at this site in isolation, or as part of isolated OA, or as part of GOA (Fig. 2). Therefore, neither articular cartilage nor synovium is a requirement for either initiation or progression of joint degeneration. Degenerative disease of the cervical or lumbar spine have been classified not as OA, but as ‘lumbar and cervical spondylisis’, ‘cervical/lumbar degenerative joint disease’ or ‘degenerative disc disease’. These latter classification schemes have been applied when disease was isolated to these regions but, we suggest that it is time to consider that similar or even identical microanatomical factors could play a role in GOA with spinal involvement or in isolated degenerative arthritis at these sites. If spinal disease can be independent of both articular cartilage and synovium, then it is quite possible that the same holds true for peripheral synovial joints. Indeed, oblique view radiographs of the hands in established GOA clearly show new bone formation at tendon insertions where entheseophytes can be pronounced (Fig. 3). Indeed, such clinical observations formed part of the logic to formally explore the role of ligaments in GOA with hand involvement in the typically affected DIP and PIP joints in the first instance [8, 9].

Lessons from animal models of OA

Of course, there is no animal model of GOA and it is quite possible that this reflects the unique anatomy and biomechanics of the human hand and musculoskeletal system in general. Notwithstanding this limitation, there are several experimental models pointing to the role of ligaments as initiators of OA. Many experimental models of OA are induced by traumatic disruption of the ACL [70, 71], but this type of OA is probably most closely related to that which follows ACL injury in man [71]. However, several non-traumatic OA ligament-related models do exist. Notably, there is OA that develops after the injection of type I collagenase [72]. Since type I collagen is the major structural fibre of ligaments, tendons and joint capsules, this clearly supports the ligament concept. Recently, a novel model for spontaneous ‘non-traumatic’ OA has been described in the Dunkin-Hartley guinea pig [73]. This type of OA is associated with early changes in
This article reviews recent developments in relation to nodal OA and puts the case for the importance of ligaments in disease. Longitudinal studies formally demonstrating that the ligament abnormalities, and not just gross injury, that lead to joint failure, are needed. A search for ligament-related candidate genes could lead to new insights into the genetics of OA. There is also a need to understand why some patients with GOA have disabling symptoms, yet others are symptom free. It would be premature to talk about therapy, but for GOA it is likely that understanding ligament-related factors represent an important first step towards new therapy. Perhaps an ascertainment of the feasibility of ligament-related factors represent an important first step towards new therapy. Perhaps an ascertainment of the feasibility of ligament-related factors represent an important first step towards new therapy.

Conclusions

This perspective argues for a pivotal role for joint ligaments in the phenotypic expression of GOA but many of the arguments herein are equally relevant to tendon insertions and immediately adjacent tissues, since these are functionally linked with ligaments. Indeed, we have noted similar high-resolution MRI findings in tendons [8]. It must be acknowledged that it may be equally important to ascertain the role of ligaments in GOA progression as it is in disease initiation. To conclude, Heberden’s sharp clinical observation skills over 200 yrs ago, which is combined with modern imaging and histopathological studies into ligaments, could open up a new avenue for an understanding of the pathogenesis of OA and, ultimately for therapy development.

Future directions

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Role of ligaments in early nodal OA


