Should bone be a therapeutic target in osteoarthritis?

"*These data imply that we should be choosing lesion-specific therapy for osteoarthritis...*"

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Osteoarthritis is a major public health problem. Traditionally, it was thought that cartilage loss was the primary process and all else followed. However, approaches to prevent cartilage loss have been disappointing. Studies over the last 10 years using high powered imaging techniques have greatly enhanced our understanding and made it clear that cartilage loss is a final common pathway of many processes both within, around and distant from the joint [1]. Therefore, targeting specific processes may be more fruitful. Bone is the area that has the most promise at this point in time as there a number of therapies that can have potent effects on bone.

The role of bone in osteoarthritis

It was hypothesized many years ago by Radin and colleagues that osteoarthritis was a disease of the subchondral bone [2]. Advances in imaging, notably MRI and DXA scanning, have greatly enhanced our understanding of this process. There are a number of facets of bone involved in cartilage damage and/or loss in the knee. These include bone marrow lesions (BMLs) [3], tibial plateau area [4], subchondral bone density (sBMD) [4] and osteophytes [5]. In addition, there is evidence that BMLs [6], bone attrition [7] and osteophytes [8] are also associated with symptoms, although the latter is controversial as the association did not persist after adjustment for MRI determined structural abnormalities. BMLs [9] and tibial bone area [10] also predict knee replacement independent of pain and radiographic changes, suggesting they may be a marker of fast progression. Most of these changes tend to worsen over time, for example, bone size and osteophytes tend to stay the same or increase (albeit slowly), while sBMD declines with age. Little is known about the natural history of bone attrition. BMLs can worsen, stay static or improve over time and this fluctuation is associated with change in symptoms [9]. There is also evidence that BMLs are linked to pain in the hip [Ahedi H, Unpublished Data] and tenderness in the hands [11].

Potential to intervene

Taking these observations into account, there are some key potential targets. We do not know how to alter bone size or bone attrition. sBMD could be altered by antiresorptive agents, but this would potentially be deleterious as it is higher sBMD that precedes cartilage damage [4] and causing enhanced BMD loss would have the additional effect of increasing the risk of osteoporosis and fractures. There are recent statements based on animal models and theoretical issues suggesting bisphosphonates will not be effective in osteoarthritis [12]. However, the available human evidence contradicts this view. Osteophyte progression in the spine can be slowed by alendronate based on a *post hoc* analysis of the original osteoporosis trial [13]. Risedronate appeared to have no effect on the knee [14], but this may reflect measurement issues and the choice of groups to study as this study had no detectable progression in the placebo arm, making it impossible to determine effectiveness. There is also data for BMLs and observational data suggested that they are much less common in those taking bisphosphonates (but not other antiresorptives) [15], while risedronate may slow the progression of BMLs [16]. Recently, a proof-of-principle trial of the potent intravenous agent zoledronic acid was performed where all subjects had BMLs [17]. This showed strong improvement in pain and a 40% reduction in BML size compared with placebo at 6 months. Chondroitin may also have an effect on BMLs [18], and strontium ranelate has also been shown to help pain and slow down radiographic change in knee osteoarthritis [19], but whether this is mediated by its bone effects or a cartilage effect

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remains uncertain. Back pain is also less common with zoledronic acid [20] and this was after adjusting for change in BMD and spinal fracture risk, suggesting an effect on spinal osteoarthritis or possibly Modic change. There is no data for other potent antiresorptives, such as denosumab or odanacatib.

Implications

These data imply that we should be choosing lesion-specific therapy for osteoarthritis, for example, weight loss for the overweight, anti-inflammatory treatment for those with effusion or synovitis, and bone-targeted therapy for those with BMLs (and possibly osteophytes). The zoledronic acid trial previously mentioned suggests the latter can be carried out very efficiently using a 6-month design, thus therapies can be quickly evaluated. It remains controversial whether x-ray should remain the key measure for OA progression. This author's view is that it should be dropped for many reasons: inadequate sensitivity to change, technical issues around measurement and it being a composite measure of a number of joint pathologies (cartilage volume, cartilage defects, meniscal tear and extrusion), making it unsuitable for lesion-specific trials. A suggested approach for BMLs would be a 6-month proof-of-principle trial followed by a longer Phase III trial with both cartilage and knee replacement as outcomes.

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