

HYPOTHESIS

Is progressive osteoarthritis an atheromatous vascular disease?

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Growing evidence from epidemiological studies suggests that osteoarthritis (OA) is linked to atheromatous vascular disease. This hypothesis article proposes that OA, or at least OA structural progression, may be an atheromatous vascular disease of subchondral bone. Further epidemiological studies, imaging investigations of relevant blood vessels, and trials of the effects of statins on the prevention and treatment of OA are needed to examine this hypothesis.

venous outflow obstruction⁸ and hypercoagulability in both animal and human studies, described by Ghosh and Cheras.⁹ The complexity of OA vascular abnormalities may be compounded by angiogenesis associated with inflammation in OA.¹⁰

Vascular disease in subchondral bone may accelerate the OA process either by altering cartilage nutrition¹¹ or through direct ischaemic effects on bone, if the subchondral bone is actually the first tissue affected and cartilage damage is secondary. Large segments of avascular bone necrosis, of the sort seen in association with steroid use, are relatively uncommon, but Bullough's group has demonstrated that multiple small bone infarcts are common in advanced OA.¹²

Osteoarthritis (OA) is a massive problem for both individual patients and society. It is difficult to define, but there is a common clinical phenotype characterised by pain related to use and structural abnormalities of all tissues in the synovial joint, including cartilage, subchondral bone, synovium, capsule, and ligaments.¹ Vascular disease and OA are both extremely common, age related conditions. It is perhaps unsurprising, therefore, that vascular changes have been associated with the pathology of OA. In this hypothesis we argue that this association may be causal and that investigations of this hypothesis should be undertaken in OA.

“Vascular disease in subchondral bone may accelerate the OA process”

Magnetic resonance imaging (MRI) can detect areas of “bone marrow oedema”, and the limited histological evidence available suggests that these are zones of fibrosis, necrosis, and remodelled bony trabeculae.^{13 14} Recent large OA studies have demonstrated the high prevalence of this MRI abnormality.¹⁵ Imhof and colleagues suggested that the venous outlet syndrome in the subchondral region results in ischaemia of the bone and adjacent cartilage subunit.¹⁶ They and others suggested that the MRI subchondral bone changes seen in OA are similar to those seen in avascular necrosis.

Peter Simkin has recently presented a different hypothesis that links subchondral bone vascular changes to the pathogenesis of cartilage damage.¹⁷ He emphasises the venous outlet obstruction and intraosseous hypertension and suggests that this alters the mechanical properties of the bone, leading to a reduced ability of the bone to act as a shock absorber, with subsequent increased susceptibility to cartilage breakdown.

SECONDARY VASCULAR DISEASE: LONG DESCRIBED IN OA

For the past 20 years or so the articular cartilage has been the main focus of interest in OA; however, the condition was first called *osteoarthritis* because of the prominence of the bone reaction. Early investigators emphasised the role of subchondral bone as an important driver of cartilage damage,^{2 3} and at the cellular level bone cells can also influence cartilage metabolism.⁴ Recent animal and human studies have confirmed the importance of subchondral bone, at least for disease progression.⁵ In human studies of the evolution of OA, increased activity in the subchondral bone is a very early event.⁶ Articular cartilage is avascular, receiving its nutrition from the subchondral bone or the synovial fluid. But the subchondral bone is a richly vascularised tissue, and microvascular changes predominantly affecting the venous circulation are a well described part of the early pathology of bony tissue in OA.³

An ischaemic process *secondary* to OA structural pathology was first suggested over a century ago.⁷ Other proposed vascular mechanisms (again, secondary to the OA process) include

LINKS BETWEEN PRIMARY ATHEROMATOUS VASCULAR DISEASE AND OA

Using radiographic definitions of OA, evidence for decreased survival in people with OA was first described many years ago.¹⁸ It was thought that this might relate to the use of treatments such as

Abbreviations: MRI, magnetic resonance imaging; NSAIDs, non-steroidal anti-inflammatory drugs; OA, osteoarthritis

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non-steroidal anti-inflammatory drugs (NSAIDs), a possibility highlighted by the recent NSAID controversy.¹⁹ However, we believe that reduced survival may be due to the association between OA and cardiovascular disease. A high prevalence of both cardiovascular risk factors²⁰ and vascular comorbidity^{21, 22} have been described in OA.

The association between hyperlipidaemia and OA has not always been clear. However, hospital based studies, such as the Ulm cohort of 809 people having hip or knee surgery because of OA, show a positive association with hypercholesterolaemia and widespread joint involvement²³—so it may be that hyperlipidaemia is linked to severe or generalised OA only.

Cardiovascular mortality may also be linked to the severity and extent of OA, perhaps with a “dose effect”, as described in two recent studies. In one population it was found that the more widespread the radiographic evidence of OA was in the population, the more likely people were to succumb to cardiovascular deaths,²⁴ and in a large Finnish cohort it was demonstrated that in men, OA in any finger joint (generally regarded as a marker of “generalised” OA) predicted cardiovascular death.²⁵

“Reduced survival in OA may be due to its association with cardiovascular disease”

Several explanations are possible for these associations between OA pathology and cardiovascular disease. Firstly, it may be that the presence of OA decreases the amount of exercise a person takes, thus increasing their likelihood of developing cardiovascular problems. Secondly, the link may relate to the common association with obesity. Although the studies mentioned carried out adjustments for body mass index, it remains possible that confounding related to some association such as girth might explain these findings. Sayer and colleagues have put forward an interesting alternative hypothesis. They studied the relationships between weight and hand OA throughout life in a community based cohort.²⁶ They confirmed the association of hand OA with obesity, but found that low, rather than high, weight at birth was a risk factor for OA. Low birth weight is also a risk factor for cardiovascular disease in adult life, so they hypothesise that the association between the two conditions is through a common origin in poor fetal growth and altered “programming” of tissue development. Others have hypothesised that OA is a stromal cell differentiation disorder involving altered lipid metabolism.²⁷ Alternatively, atheromatous vascular disease might cause OA.

ATHEROMATOUS VASCULAR DISEASE AS A CAUSE OF OA PROGRESSION

The debate about which tissue is damaged first in OA has been going on for many years. Articular cartilage and subchondral bone are not the only contenders, ligaments and muscles have recently entered the discussion.²⁸ But asking which tissue comes first may not be the right question. One of the main concerns in OA is *progression* of structural damage.²⁹ Most early OA lesions appear to remain contained and asymptomatic, but in some people they progress, and this can lead to the severe joint destruction of the sort seen before joint replacement. The data on cardiovascular disease and OA associations mentioned above indicate that the link may be with widespread OA or severe joint damage rather than with all degrees of structural OA. Epidemiological data suggest that the risk factors for progression are not the same as those for initiation of OA,^{1, 30} in which case the processes may be different. Our hypothesis is that atheromatous vascular disease is more

important in the progression of OA to severe joint damage than in its initiation, and the subchondral bone ischaemia theory would appear to be the most likely one to explain that link.

Scintigraphy has been reported to predict structural joint progression.³¹ The uptake of radiolabelled bisphosphonates in joints depends on two factors—the vascularity of the joint and the turnover of subchondral bone—so the fact that OA progression is very unlikely in the absence of increased scintigraphic activity in the joint is consistent with the theory that abnormalities of subchondral bone, possibly driven by atheromatous disease, are the drivers of progressive joint damage. Areas of bone marrow oedema on MRI also predict compartment-specific progression in knee OA.¹⁵

Of course, a vascular model cannot directly explain all the pathological findings in OA, such as osteophyte formation, although this and some other features are likely to be a secondary response to mechanical changes in the joint.

IS A VASCULAR MODEL FOR OA IMPORTANT?

Current OA treatments aim only at reducing pain and improving function, as disease prevention or modification are not yet realities. Clearly, despite public health messages obesity continues to increase, and similarly, as more people take part in leisure activities such as running and skiing, the prevalence of joint injury is increasing. We believe that there is a need to examine alternative concepts of OA, such as this hypothesis, not only because of their obvious potential importance to our understanding of the disease process and subsequent treatments but also because they may lead to alternative strategies for the prevention of OA. Our vascular hypothesis suggests that the future treatments being developed for OA, most of which concentrate on altering cartilage degradation or repair, may fail because they are aimed at the wrong target.

“Atheromatous vascular disease is more important in the progression than initiation of OA”

It will be difficult to demonstrate the importance of atheromatous changes in OA directly, as conventional angiographic studies in people with a relatively benign condition will be hard to justify. However, arterial calcification may prove a valuable marker for the process, and it can be detected with imaging studies. In the spine, an association has been demonstrated between arterial calcification detected by computed tomography and the degree of disc degeneration³²; a correlation between such disc degeneration and adjacent bony end plate damage has also been found.³³ Recently, an association has been demonstrated between OA changes in the hand and aortic calcification.³⁴

Clearly, there are some epidemiological data supporting a link between OA and vascular disease and there are plausible mechanisms whereby vascular pathology might cause the pathology of the disease. The associations may not be causal. We can only find that out through clinical trials. Given the data summarised above, including the suggestion that raised cholesterol levels and atheromatous vascular disease may be associated with OA, examination of the effects of treatments such as statins on the prevention and treatment of OA would seem to be essential. A recent report from Beattie *et al.*, reported that statin use was associated with increased risk of developing moderate grade radiographic hip OA in elderly women.³⁵ One interpretation of this would support the notion that hypercholesterolaemia is a risk factor for OA development. In addition, a small sample in this study suggested non-significant trend towards decreased progression of hip OA in the statin users, supporting our hypothesis. Statins

may also have a potentially beneficial effect on subchondral bone.³⁶ It may be that some indication of their possible efficacy can be obtained from reanalysis of existing trial data on statin use, but it seems likely that large randomised controlled trials, including progression of joint disease as a primary end point, will need to be undertaken.

In conclusion we believe that OA, or at least OA structural progression, may be primarily an atheromatous vascular disease of subchondral bone, and that epidemiological studies, imaging investigations to detect arterial calcification, and trials of the effects of statins on the prevention and treatment of OA should be undertaken to examine this hypothesis.

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