

The effects of statins on osteoarthritis structural progression: another glimpse of the Holy Grail?

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While the last 2 decades have seen major advances and novel treatments for inflammatory arthritides, treatments for osteoarthritis (OA) have not advanced. Meanwhile, OA represents a huge problem for both individuals and health economies, with the OA burden rising quickly in ageing Western societies. Recent evidence-based guidelines provide a range of options for pain relief,^{1,2} often associated with small to moderate effect sizes.³ True structure modification, with its implication for an associated reduction (or at least reduced progression) of symptoms, is often referred to as the Holy Grail of OA research.^{4,5}

In the context of chasing this Grail, the interesting report from Clockaerts and colleagues⁶ adds to a growing strand of research concerning the potential role of statins as structure modifiers in OA. A number of questions arise as a result of this work: Is there a plausible mechanism of action for statins in this context? Is there a real signal of reduced OA structural progression from this and other clinical studies of statins?

HOW MIGHT STATINS WORK IN OA?

Statins are best known as competitive inhibitors of hydroxymethyl-glutaryl-coenzyme A reductase that reduce cholesterol biosynthesis. However, for some years it has been recognised that these agents also have significant anti-inflammatory and immunomodulating effects.⁷⁻⁹ So, it is possible that these agents may benefit the OA joint through a number of non-mutually exclusive mechanisms on different targets.

Inflammation appears universal in symptomatic OA joints, with inflammatory mediators produced by cartilage, bone and synovial cells;^{10,11} this inflammation is thought to be important in subsequent cartilage degradation. A multitude of anti-inflammatory effects of

statins have been reported at the cellular level including inhibition of leucocyte-endothelial adhesion, reduced levels of inducible nitric oxide synthase, inhibition of production and reduced chemoattraction of monocyte chemotactic protein-1, and reduced interleukin-6 (IL 6), IL-8 and IL-1 β production.⁷⁻⁹ Many of these effects are a result of inhibition of inflammation upregulated nuclear factor kappa B.⁷ Statins also decrease T cell activation.⁷

The subchondral bone plays an integral part in OA progression. Statins have been shown to interfere with osteoclast function by a pathway independent of their anti-inflammatory effects, with suppression of bone resorption demonstrated *in vitro*; they have also been shown to promote osteoblast activity, in part through increased production of bone morphogenetic protein-2.⁹ Such effects should beneficially modify the subchondral OA bone, already recognised as a potential target for structure modification.¹²

A recent review has highlighted the growing literature on OA being part of a metabolic syndrome, with links between OA and vascular disease being seen independent of an obesity-biomechanical effect.¹³ All cause mortality has been reported increased in OA knee and hip, with a pronounced effect for cardiovascular mortality, although non-steroidal anti-inflammatory drug treatment effects were among possible confounders.¹⁴ It has long been known that the damaged subchondral bone in OA results in micro-vessel disease with localised vascular hypertension and ischaemia that can worsen progression.¹⁵ We have previously postulated that generalised atheromatous disease may contribute to the progression of OA.¹⁶ It is therefore tempting to speculate that the direct antiatheromatous effect of statins reduces structural deterioration of OA joints by improving blood flow.

Direct effects on chondrocytes have also been demonstrated, with the MMPs suggested as a possible statin target.¹⁷ An *in vitro* study of human chondrocytes

reported dose-dependent reduction in matrix metalloproteinase (MMP)-3 production with simvastatin.¹⁸ Barter et al demonstrated that the lipophilic statins (simvastatin and mevastatin) inhibited IL-1 and oncostatin M-induced collagen breakdown in bovine nasal cartilage and demonstrated reduced MMP-1 and -13 expression as well as reduction of proinflammatory signalling pathways in human cartilage;¹⁹ these latter findings on modification of key signalling molecules were also reported in another experiment on human cartilage.²⁰ Statins may also reduce chondrocyte senescence.²¹

Animal research in this field has largely used anti-inflammatory models, with some models of acute inflammation demonstrating beneficial effects when treated with statins.⁷⁻⁹ There is little work in OA models. However, beneficial effects on morphological and histological chondropathy were demonstrated in a rabbit anterior cruciate ligament (ACL) transection model of OA treated with mevastatin.²² An ACL transection model was also used in Wistar rats where simvastatin reduced MMP-3 expression and improved histological scores.²³

DO STATINS REDUCE OA STRUCTURAL PROGRESSION IN HUMANS?

Many drug effects reported in animal models have not translated to human OA therapeutic benefit. The only clues we have as to the effects of statins on human OA are derived from epidemiological studies. These studies have examined OA progression predominantly through use of radiographs, and they should be cautiously interpreted in light of individual study limitations and also due to modern understanding of the limitations of structure as assessed by radiographs. The Kellgren-Lawrence (KL) summary grading system used in many such studies may be more dependent on osteophytes than joint space narrowing (the surrogate for hyaline cartilage loss), has a ceiling effect at higher grades (3 or 4) and the grading is non-interval; metric measurement of joint space width (JSW) is therefore the preferred radiographic end point for clinical trials of structural progression.²⁴ As well as limitations in the radiographic outcome measures, examining risk factors for progression in joints with existing OA is methodologically highly challenging.²⁵⁻²⁷ This occurs particularly in observational studies of complex, heterogeneous conditions like OA where a range of biases (including uncertainty in the timing of diagnosis and accurately identifying where individuals are in the disease path or trajectory, and risk factors that contribute to

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both initiation and progression) may lead to inaccurate associations of risk factors with progression.^{25–27}

In the population-based study of Clockaerts *et al*, OA patients were followed over 6.5 years, with OA progression estimated by KL grade; progression was defined as any increase in score.⁶ Strengths of this study included the large sample size, good data on statin use by participants and adjustment for known confounders in the multivariate analysis. However, the radiographs were scored by one out of seven readers, and although inter-rater agreement figures were reported, it is not clear what agreement there was on change in scores over time. They found a substantial reduction in OA knee (but not hip) progression.

Why might there be different effects on hip and knee in the recent study? One important issue relates to how the KL scores perform in terms of responsiveness in the two joints (no doubt confounded by the natural history of OA in each joint), and there are limited comparative data on this issue. As stated above, the methodological problems inherent in such observational studies of progression may contribute to the beneficial statin effect reported here. Different risk factors for OA progression at the hip and knee have been reported²⁸ but the biological reasons for this have not been well elucidated. Research to date has highlighted the importance of biomechanical drivers (eg, alignment) in knee progression, and while it seems unlikely that there is a differential direct metabolic effect on different joints, understanding the relative importance of inflammatory or vascular changes in OA progression in both joints is worthy of further investigation.

In the only other study to examine statins and radiographic OA progression, Beattie *et al* reported on a large population-based cohort of older women followed for 8 years, and with hip radiographs evaluated using both a summary grade (a modified Croft score rather than KL) and a minimum JSW method.²⁹ Alternative definitions of incidence and progression used summary grade, JSW changes and osteophytes counts. Statin usage was not as rigorously recorded as in the Clockaerts report, making interpretation more difficult. Statin use was associated with increased risk of incident OA hip (OR 1.92, CI 1.03 to 4.43, $p=0.045$). Progression was assessed in hips with radiographic OA at baseline, and there was a non-significant trend to reduced OA progression in women reportedly taking statins.

Concomitant symptom relief remains an important component of regulatory acceptance of an OA structure modifying therapy. Importantly, neither of these studies

was able to provide data on symptom relief related to statin usage. Such an effect might be possible given the anti-inflammatory properties described above, but data from human studies would be required.

CONCLUSIONS

While there are very plausible mechanisms by which statins may produce beneficial effects on OA joints, the evidence for a beneficial effect of statins in human OA remains very limited. Studies on symptoms may be a feasible step before structure modification trials are considered. However, the growing science supporting this intriguing field together with the parallel growth of research that leads to a ‘systems’ biological approach to the OA joint organ (where cartilage, subchondral bone, inflammation, vascularity and biomechanics are all considered, made feasible with modern imaging) has incredible implications for broadening OA research and tissue targets, and certainly moves us a step closer to finding the Grail.

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