

Statins, bone biology and revision arthroplasty: review of clinical and experimental evidence

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Abstract: Osteoarthritis is a painful, disabling condition which is increasing in prevalence as a result of an ageing population. With no recognized disease-limiting therapeutics, arthroplasty of the hip and knee is the most common and effective treatment for lower limb osteoarthritis, however lower limb arthroplasty has a finite life-span and a proportion of patients will require revision arthroplasty. With increasing life expectancy and an increasing proportion of younger (<65 years) patients undergoing arthroplasty, the demand for revision arthroplasty after implant failure is also set to increase.

Statins are cholesterol-modulating drugs widely used for cardiovascular risk reduction which have been noted to have pleiotropic effects including potentially influencing arthroplasty survival. *In vitro* studies have demonstrated pleiotropic effects in human bone cells, including enhancement of osteoblastogenesis following simvastatin exposure, and *in vivo* studies have demonstrated that intraperitoneal simvastatin can increase peri-implant bone growth in rats following titanium tibial implant insertion. There is evidence that statins may also influence osseointegration, enhancing bone growth at the bone-implant interface, subsequently improving the functional survival of implants. Data from the Danish Hip Arthroplasty Registry and the Clinical Practice Research Datalink in the UK suggest a reduction in the risk of lower limb revision arthroplasty in statin ever-users versus never-users, and a time-dependent effect of statins in reducing the risk of revision. In this article we review the clinical and experimental evidence linking statins and risk of revision arthroplasty.

Keywords: arthroplasty, hip, knee, loosening, osseointegration, osteolysis, revision, statin

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Introduction

Osteoarthritis (OA) is characterized by articular cartilage degeneration, pain and eventual disability. It is estimated that symptomatic OA affects one in eight men and women in the USA (27–31 million).¹ Disability secondary to OA continues to rise, increasing by 16% between 1990 and 2010,² and the UK National Health Service continues to spend over £900 million annually directly treating the disease.³

Arthroplasty is an effective treatment for end-stage OA which has not responded to conservative measures including analgesia and physiotherapy.⁴

Two of the most common interventions undertaken are primary total hip arthroplasty (THA) and primary total knee arthroplasty (TKA). According to the National Joint Registry (NJR) 91,698 primary THA and 102,177 primary TKA were undertaken in England, Wales and Northern Ireland in 2017, with greater than 90% of these being for the treatment of primary OA.⁵

A proportion of patients require revision of their primary surgery with the main indications for revision being (rate of revision/1000 patient-years) aseptic loosening (1.25 THA, 1.25 TKA), pain (0.84 THA, 0.85 TKA), dislocation (0.87

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THA), adverse reaction to particulate debris (0.86 THA), infection (0.72 THA), instability (0.69 TKA), malalignment (0.38 TKA) and periprosthetic fracture (0.69 THA, 0.16 TKA).⁵ Revision risk increases each year following primary arthroplasty and despite modern surgical advances and improvement in implant materials, the overall revision risk has remained relatively static for the last 5 years.⁵ Comparing 2010 and 2017 NJR data, the 5-year risk of revision was 2.5% and 2.34% for hips, and 2.7% and 2.65% for knees.^{5,6} When compared with primary arthroplasty, revision surgery is recognized to be more complex and is associated with increased risk of dislocation, venous thromboembolism, infection and mortality.⁷ Furthermore, functional improvement after revision surgery may be less than that from the primary procedure.⁸ In addition to being more burdensome at the patient level with a higher risk of failure,⁹ revision surgery impacts on a societal level with greater financial implications arising from increased length of hospital stay, operative time and complexity.^{7,10,11}

With an ageing population, increasing life expectancy and rising obesity rates, the number of people requiring primary arthroplasty of the hip and knee is set to increase substantially.

Efforts to reduce the risk of revision have focused on intra-operative factors including reducing contamination at surgery, optimum placement of the prostheses and development of new implants. There is developing evidence from animal studies however, that 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, commonly known as statins, may influence implant survival following arthroplasty.

This review was tailored to include all English language, peer-reviewed publications available *via* structured searches of Embase (1974–2019) and Ovid Medline (1946–2019) relating to statins, arthroplasty, revision and the identified mechanisms underlying this phenomenon including osteolysis, loosening, osseointegration and wear debris response. The reference list of each publication identified from searches was also reviewed for relevant articles. Epidemiological, clinical and laboratory studies were included.

What are statins?

Statins are cholesterol-modulating drugs that act upon the mevalonate pathway by inhibition of

HMG-CoA reductase.¹² Reduction of cholesterol by statins has been shown consistently to improve survival in clinical trials by reducing fatal coronary events.^{13,14} The annual number of prescriptions of lipid-lowering drugs in England has increased significantly from 295,000 in 1981 to over 50 million in 2011.¹⁵ Derivatives of mevalonate are required in the post-translational modification of the triphosphate-binding proteins (GTPases) responsible for the regulation of osteoblastogenesis and osteoclastogenesis.¹⁶

Statins and osseointegration of prosthetic implants and bone

Osseointegration is necessary for implant stability and is a result of direct bone-to-implant contact.¹⁷ It is defined as the direct structural and functional connection between bone and implant such that there is no relative movement between the two surfaces as the implant has been incorporated into the living bone.¹⁸ Poor osseointegration of implants may be a risk factor for arthroplasty failure in the short and long term because of micromotion at the bone–implant interface, which can initiate periprosthetic bone resorption and subsequent loosening.¹⁹ This is particularly true in uncemented arthroplasty, which relies on implants integrating with surrounding bone. Optimal osseointegration requires formation of new bone at the bone–implant interface and there is evidence to suggest statins may promote bone growth and osteoblastogenesis *via* bone-morphogenetic protein-2 (BMP-2). Mundy *et al.* demonstrated an increase in *BMP-2* expression, as detected by northern blot, in murine and human bone cells in response to simvastatin exposure,²⁰ and that explanted neonatal murine calvaria demonstrated increased bone growth when exposed to simvastatin, fluvastatin, lovastatin and mevastatin. Furthermore, *in vivo* work demonstrated that lovastatin and simvastatin increased bone formation by nearly 50% in the calvaria of mice when injected subcutaneously, comparable to the effect seen with BMP-2 injection.²⁰ In addition, statins have been shown to induce vascular endothelial growth factor (VEGF) expression. VEGF is a glycoprotein responsible for osteoblast differentiation and an angiogenic factor necessary for vascular invasion prior to bone formation, intercellular communication between endothelial cells and subsequent osteoblast activity necessary for bone growth.²¹

The potential for statins to promote osseointegration *in vivo* has been explored in multiple animal

studies, with systemic administration of simvastatin after implant insertion demonstrating increased bone density around implants and crucially, an increase in the mechanical strength/stability of the bone–implant interface.^{22–25} Du *et al.* demonstrated that administering oral simvastatin to osteoporotic rats (post oophorectomy) could increase implant–bone contact rate in cancellous bone when compared with untreated controls.²⁴ Li *et al.* explored the effect of intraperitoneal simvastatin administration on peri-implant bone growth in rat tibial titanium implants and found an increase in bone formation in the treatment cohort when compared with controls.²⁶

It has been proposed that local application of statins to implants may promote similar potential osteogenic effects, increasing mechanical strength and improving peri-implant bony calcification.^{27–29} Masuzaki *et al.* gave a single injection of fluvastatin-impregnated microspheres to rats with tibial titanium implants. This showed enhanced bone growth and bone contact as demonstrated by staining and microscopy around the implant and was accompanied by an increased bending strength.³⁰ Similar studies have reported encouraging results with simvastatin-coated implants, scaffolds and biomaterials.^{31,32}

Dose-dependency studies have suggested that implants coated with 75 µg of fluvastatin osseointegrate better than control implants, for example a rodent model demonstrated improved implant trabecular bone layer composed of mineral bone and a thicker appearance of the new trabeculae in the medullary canal. Paradoxically at higher doses of fluvastatin (300 µg) the implants perform worse,²⁸ in that there is a delay in calcification of peri-implant bone. Moriyama *et al.* hypothesized that this is due to higher doses of fluvastatin yielding immature osteoblasts, normally developed by osteocalcin expression.²⁸ The maturation of osteoblasts involves the fine balance of RUNX2 suppression (part of the BMP-2 signalling pathway) and Osterix enhancement, however statins have been thought to stimulate RUNX2 expression, potentially suppressing Osterix and the balance required for fully matured osteoblast formation, bone mineralisation and thereby osseointegration.²⁸

Osseointegration generally occurs within 3 months of primary arthroplasty.^{33,34} Therefore preloading with statins prior to primary arthroplasty and early statin use in the initial weeks and months postimplant insertion could theoretically be

associated with a reduction in complications as a result of suboptimal osseointegration, such as implant stem migration, periprosthetic fracture and loosening as a result of failure of trabecular bone ingrowth.³⁵ This is supported by animal data from Li *et al.* who demonstrated that early use of statins after implant insertion promotes peri-implant bone growth, and discontinuation of statins in this early period leads to rebound bone resorption.²⁶ Animal models should, however, be interpreted with caution. Many of the animal studies referenced administered statins for 30 days or less, osseointegration in humans is thought to occur within a more prolonged period (3 months). Furthermore, the dynamic forces on the human hip joint in gait are not directly comparable with those of animals used in the referenced studies. In addition, load bearing is an important aspect of lower limb arthroplasty osseointegration and some of the studies are not designed for load bearing of the implant.

Statins and periprosthetic osteolysis

Periprosthetic osteolysis (PPOL) is the gradual, progressive resorption of bone and subsequent reduction in bone density around the bone–implant interface in THA and TKA.^{36–38} The initial trigger for this process is activation of phagocytic cells in response to wear-related debris particles released from the bone–implant interface following arthroplasty.^{35,36} Specific articulation surface debris such as ultra-high molecular weight polyethylene (UHMWPE) have been implicated in phagocyte activation and the subsequent osteolytic cascade weakens the bone–implant interface. This process is generally asymptomatic and can go clinically undetected until there is decompensation and biomechanical instability. Symptomatic PPOL with aseptic loosening presents late and commonly revision arthroplasty is required to salvage joint function. Monocyte/macrophages and their derivatives have been implicated in the resorption of bone and PPOL in arthroplasty since early 1990.³⁹

There is an established research base for a class of drug known as bisphosphonates (BP) in inhibiting osteoclast formation and function that is facilitated by their interaction with the mevalonate pathway by inhibition farnesyl pyrophosphate (FPP), downstream of the influence of statins. Some authors have highlighted the potential benefit of BP in arthroplasty survival in human^{40,41} and animal^{42,43} models. In a study using data

from the Danish Hip Arthroplasty Register (DHAR), BP use for more than 240 days was associated with a reduction in the relative risk of revision of 0.58 (95% CI; 0.32–1.05) for all indications.⁴¹ More recent research identified an associated risk reduction of up to 59% in those starting BP after arthroplasty surgery.⁴⁰

Statins inhibit the mevalonate pathway upstream of FPP and have the potential to exert a similar molecular response as BP, inhibiting the osteolytic cascade and reducing PPOL. A murine calvarial study noted that introduction of UHMWPE particles induced a pronounced bone resorption response when compared with controls; this effect was significantly abrogated in the group treated with simvastatin.⁴⁴ Polymethylmethacrylate (PMMA) particles, released in cemented arthroplasty, have also been implicated as a potential trigger for PPOL *via* production of the pro-inflammatory cytokine tumour necrosis factor- α (TNF α) by human monocytes. An *in vitro* experimental model of PMMA-induced inflammation using human peripheral blood monocytes has suggested that the potent HMG-CoA reductase inhibitor cerivastatin significantly inhibited this response *via* the intracellular Raf-MEK-ERK pathway.⁴⁴ In a case-control study of patients with radiologically detectable femoral osteolysis in THA, the authors compared statin ‘ever-users’ and ‘never-users’ at 5 years post-THA. The relative risk ratio after adjustment for confounders (age, sex, activity level, body mass index, diagnosis, bearing surface, type of stem) was 0.38 (95% CI 0.15, 0.99). This analysis did not have sufficient follow-up length to determine whether the risk of revision was lower in the statin ever-use group.⁴⁵

Pro-inflammatory cytokines are considered to be major mediators of osteolysis and ultimately aseptic loosening; three of the most well characterized are interleukin-1 (IL-1), interleukin-6 (IL-6), and TNF α .⁴⁶ Experimentally it has been demonstrated that TNF α upregulates IL-1 and IL-6 and plays a pivotal role, both directly and indirectly, in the activation and recruitment of osteoclasts with subsequent induction of PPOL in total hip replacement.⁴⁷ TNF α production is upregulated in experimental and clinical models of osteolysis, and this upregulation is further associated with particulate wear debris *in vitro* and *in vivo*.^{46,48,49} Similar molecular upregulation of both IL-1^{46,50,51} and IL-6^{46–52} has been reported in aseptic loosening models.

The presence of cells releasing IL-1, IL-6 and TNF has been directly correlated with the severity of osteolysis in THA and the authors suggest pharmacological modulation of these pathways may be a potential target for inhibition of prosthesis loosening.⁵³ There is evidence to suggest that cerivastatin inhibits PMMA-induced inflammation *in vitro* *via* abrogation of TNF α .⁵⁴ Cerivastatin also reduces production of the chemokine monocyte chemoattractant protein-1, which facilitates migration and infiltration of leukocytes into tissues.^{54,55} Simvastatin has been demonstrated experimentally to inhibit particle-mediated induction of IL-6 in human osteoblasts treated with titanium.⁵⁶ Aseptic loosening and PPOL resulting from inflammatory processes occurring over a longer period of time may theoretically be reduced by long-term statin exposure. These data are summarized in Table 1 and a mechanistic model of statin effects is presented in Figure 1.

Pharmacoepidemiological evidence of a role for statins in arthroplasty survival

There is observational evidence which suggests that statins may impact on arthroplasty survival. Using data from the UK Clinical Practice Research Datalink (CPRD), Sarmanova *et al.* conducted a propensity score-matched cohort study, matching 178,467 statin users to the same number of nonstatin users to assess the impact of statins on risk of requiring joint arthroplasty for the treatment of OA and rheumatoid arthritis (RA).⁵⁷ The results of the analysis suggested that statin prescriptions were associated with a reduced risk of joint arthroplasty due to RA but not OA.

Data from the DHAR identified 2349 patients who underwent THA between 1996 and 2005 and also had revision arthroplasty during this period.⁵⁸ In a multivariable, propensity-score matched conditional logistic regression model, the relative risk (95% CI) of revision in those exposed to statins compared with those unexposed was 0.34 (0.28–0.41). Statin exposure was not modelled in a time-dependent manner but was more crudely assigned as ‘ever *versus* never’ statin exposure.

In a study which used data from both the CPRD in the UK and the Danish National Health System, Lalmohamed *et al.* analysed the association between statin exposure and revision of primary THA and TKA.⁵⁹ In the primary analysis,

Table 1. Summary of studies investigating links between statins and bone biology.

Study	Model	Statin	Mode of administration	Observed effect	Conclusions
Mundy <i>et al.</i> ²⁰	Cultured human (MG-63) and murine (2T3) cell lines with statin to assess BMP-2 expression by northern blot	Simvastatin	5 μM of statin cultured with cell lines for 48 h	Increased BMP-2 expression by northern blot in cell lines exposed to simvastatin for 48 h	As BMP-2 increases osteoblast differentiation and proliferation, statins may promote bone growth
Mundy <i>et al.</i> ²⁰	Explanted neonatal murine calvarial bones were placed in tissue culture medium with test compound to assess bone growth	Simvastatin, fluvastatin, lovastatin and mevastatin	1 μM of test statin was incubated with the calvarial bone for 72 h	Increased bone growth on histomorphometric analysis	Simvastatin, fluvastatin, lovastatin and mevastatin all increased bone formation by approximately two- to threefold, comparable with BMP-2 and fibroblast growth factor-1
Mundy <i>et al.</i> ²⁰	Statin injected into the subcutaneous tissue over the calvaria of mice to assess growth in calvarial bone	Lovastatin and simvastatin	5 mg/kg/day or 10 mg/kg/day of statin injected subcutaneously over calvaria three times a day for 5 days	On histomorphometric analysis at day 21, a near 50% increase in bone formation demonstrated with statin administration	Local subcutaneous injection of statins may increase bone formation
Mundy <i>et al.</i> ²⁰	Statins administered systemically to assess effect on bone formation	Simvastatin	Intraperitoneal injection at 14 days and 4 days prior to sacrifice	Tibia, femur and lumbar vertebrae were analyzed by histomorphometric analysis	Simvastatin increased trabecular bone formation
Du <i>et al.</i> ²⁴	Titanium implants inserted into the tibia of oophorectomized <i>versus</i> sham surgery to assess osseointegration in rats	Simvastatin	Oral administration 5 mg/kg for either 28 days or 84 days before sacrifice	Increase in the percentage of cancellous bone to implant contact as measured by histomorphometric analysis from both sides of the implant; no significant difference observed in cortical bone contact	Simvastatin may improve osseointegration
Li <i>et al.</i> ²⁶	Titanium tibial implant inserted into mice and bone growth assessed by micro-CT scanning and histomorphometric analysis	Simvastatin	Daily intraperitoneal injections of 10 mg/kg of simvastatin for 7 days	Following 7 days of simvastatin administration, there was an increase in peri-implant bone growth compared with control. There was a decrease in bone growth following simvastatin discontinuation as confirmed by histology	Short-term statin administration is associated with peri-implant bone growth and there is rebound loss of bone on discontinuation
Masuzaki <i>et al.</i> ³⁰	Single injection of fluvastatin-impregnated microspheres to rats with tibial titanium implants	Fluvastatin	Fluvastatin-impregnated microspheres were injected beneath the skin at the implant site following surgery	Peri-implant bone growth measured by staining and light microscopy demonstrated an increase in bone growth and bone strength was increased when assessed by three-point bending	A single injection of fluvastatin-impregnated microspheres increased implant osseointegration and the mechanical strength of the bone
Laing <i>et al.</i> ⁵⁴	<i>In vitro</i> model of monocyte/macrophage inflammatory response to PMMA particles, compared with pretreatment with statin	Cerivastatin	Cerivastatin dissolved in media to 150 μM or 300 μM for 1 h followed by PMMA exposure for 23 h	Inflammatory cytokine TNFα production is significantly abrogated with cerivastatin pretreatment	Cerivastatin reduces production of a pro-inflammatory cytokine implicated in osteolysis

BMP-2, bone-morphogenetic protein-2; CT, computed tomography; PMMA, polymethylmethacrylate; TNFα, tumour necrosis factor-alpha.

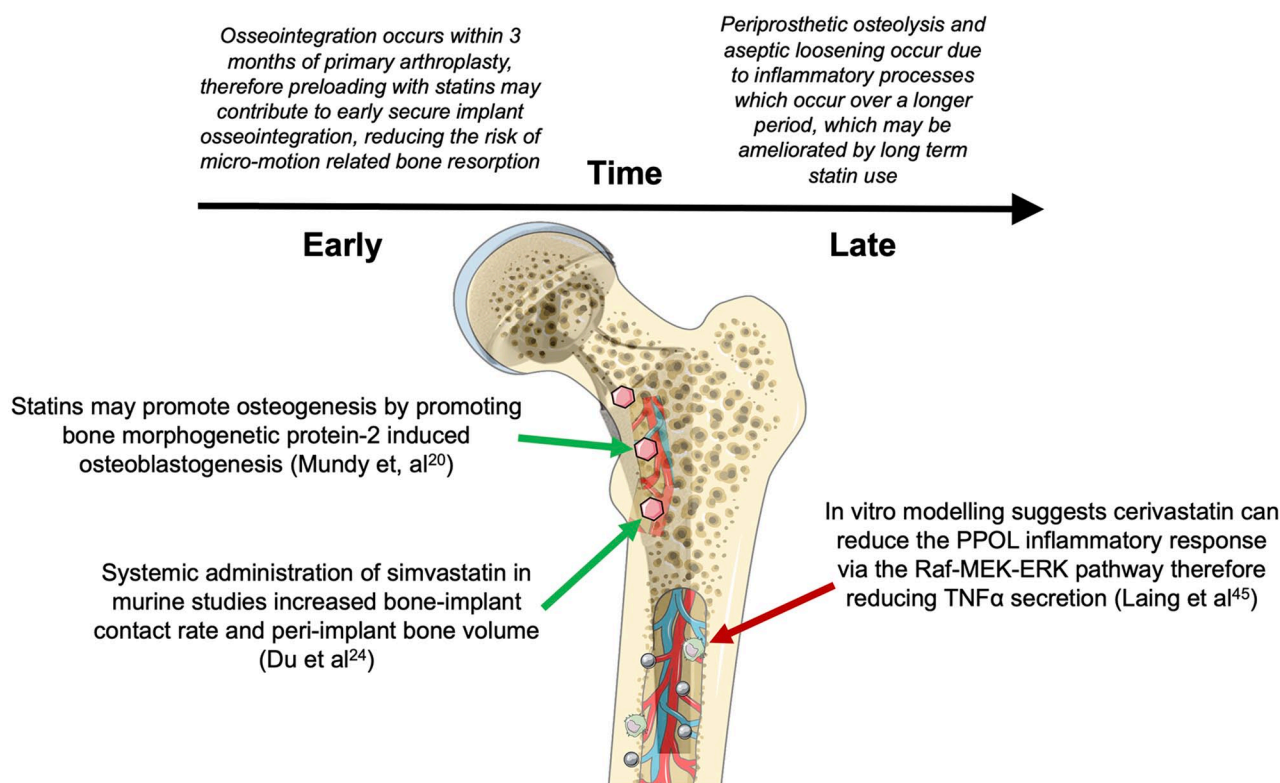


Figure 1. Mechanistic model of interaction between statins and bone-implant interface biology. PPOL, periprosthetic osteolysis; TNF α , tumour necrosis factor-alpha.

statin exposure was modelled in a time-dependent manner from the date of the primary THA/TKA. Using data from both cohorts, statin exposure was associated with a small though significant reduction in risk of revision (incident rate ratio = 0.9; 95% CI, 0.89, 0.96). A more recent analysis using CPRD data looked at impact of duration and timing of statin exposure on revision risk.⁶⁰ Of those exposed to statins following THA/TKA, 852 (1.3%) had revision arthroplasty, compared with 2648 (3.1%) of those unexposed, with an adjusted hazard ratio for revision in those exposed *versus* those unexposed of 0.82 (0.75, 0.90). Similar results were seen in participants who had a THA 0.86 (0.76, 0.98) and TKA 0.76 (0.66, 0.88). Exposure in the first 5 years following surgery appeared protective: compared with those who were not exposed to statins, the hazard ratio of revision in those first exposed to statins in the periods 0–1 years and 1–5 years after the primary surgery was 0.82 (0.74, 0.91) and 0.76 (0.65, 0.90), respectively. No statistically significant effect of statin exposure on revision risk >5 years following primary surgery was observed. Compared with participants exposed to statins for a total duration of

less than 1 year, exposure for 1–2, 2–3, 3–4 and 4–5 years did not appear to be associated with THA/TKA revision risk, though exposure for a total duration of >5 years was associated with a reduced hazard ratio of 0.74 (0.62, 0.88) for revision surgery.⁶⁰ The data from these studies demonstrate a small but significant effect of statins on reducing the risk of revision arthroplasty. There are however important limitations in interpreting the data and in particular the potential for unmeasured confounding factors which may have influenced the observed associations, and also changes in surgical technique and implants which have occurred during the course of the observation period. The findings are less convincing than those observed in animal/*in vitro* studies, highlighting the importance of human studies in investigating the association.

Conclusion

There is some evidence from animal and *in vitro* models to suggest that statin therapy may promote osseointegration and reduce PPOL. Data from observational clinical studies support a weak effect of statins on arthroplasty revision.

However there are significant limitations to the interpretation of these data, such as the potential for unmeasured confounding factors to influence results and improvements in surgical technique and implants during the study period.

Taken together the published literature suggests that although there is likely an association between statin therapy and reduced revision risk in lower limb arthroplasty and a body of mechanistic evidence from animal models, the causal relationship is far from clear and there is currently inadequate evidence to recommend routine clinical prescribing of statin therapy in patients undergoing arthroplasty of the hip or knee.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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