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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 recognised 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 the 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. Epidemiological and experimental research have demonstrated that there may be a biological and population-wide effect of statins in reducing the risk of

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revision arthroplasty. This work summarises the current breadth of evidence for this phenomenon including in vitro, in vivo and epidemiological research.

Introduction

Osteoarthritis (OA) is a condition characterised by articular cartilage degeneration, pain and eventual disability with one third of adults aged over 45 in the United Kingdom (UK) having sought treatment for the condition[1]. Disability secondary to OA continues to rise, increasing by 16% between 1990 and 2010[2] and the National Health Service (NHS) 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/1,000 patient-years): aseptic loosening (1.25 THA, 1.25 TKA), pain (0.84 THA, 0.85 TKA), dislocation (0.87 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 for each year post-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 to primary arthroplasty, revision surgery is recognised to be more technically 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 in the UK, the number of people requiring primary arthroplasty of the hip and knee is set to increase substantially. It is estimated that by 2035, based on the current arthroplasty rates, that the numbers of THA and TKA annually will increase to at least 95,877 and 118,666 respectively, though some estimates are greater[12]. Combining this evidence with a simultaneous increase in the proportion of patients under the age of 65 years requiring arthroplasty[13] it is inevitable that there will be a consequent increase in the demand for revision arthroplasty[14].

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, however, from animal studies that 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase inhibitors, commonly known as statins, may influence implant survival following arthroplasty. This article will review the literature examining the potential impact of statin therapy on implant survival including data from epidemiological, animal and human studies.

What are Statins?

Statins are cholesterol modulating drugs that act upon the mevalonate pathway by inhibition of HMG-CoA reductase[15]. Reduction of cholesterol by statins has been shown consistently to improve survival in clinical trials by reducing fatal coronary event[16,17]. The mounting body of evidence from trials and systematic reviews has led to the widespread

use of statins in primary and secondary prevention of cardiovascular events in adults. The annual number of prescriptions of lipid-lowering drugs in England has increased dramatically from 295,000 in 1981 to over 50 million in 2011[18]. Derivatives of mevalonate are required in the post-translational modification of the triphosphate-binding proteins (GTPases) responsible for the regulation of osteoblastogenesis and osteoclastogenesis[19]. Statin induced mevalonate inhibition has a potentially direct anabolic influence on bone homeostasis by inducing osteoblast differentiation via increased bone morphogenic protetin-2 (BMP-2) expression and osteoblast differentiation whilst inducing osteoclast apoptosis via suppression of nuclear factor kappa B (NFκB)[19].

Statins and Osseointegration of Prosthetic Implants and Bone

Early secure implant stability is important for long-term joint survival. Osseointegration is necessary for implant stability and is a result of direct bone-to-implant contact[20]. 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[21]. Poor osseointegration of implants may be a risk factor for arthroplasty failure in the short and long term because of micro-motion at the bone-implant interface which can initiate periprosthetic bone resorption and subsequent loosening[22]. 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 gene expression as detected by Northern blot, in murine and human bone cells in response to 48 hours of 5μM simvastatin exposure[23]. Mundy also demonstrated that explanted neonatal murine calvarial bones demonstrated

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increased bone growth when exposed to simvastatin, fluvastatin, lovastatin and mevastatin when these compounds where cultured with the bone in tissue culture medium at 1μM for 72 hours. Furthermore, their in vivo work demonstrated that lovastatin and simvastatin increased bone formation by nearly 50% in the calvaria of mice when injected subcutaneously over the calvarial bone, three times a day for five days, comparable to that seen with positive control BMP-2 injection and observed an increase in trabecular bone volume following intraperitoneal simvastatin administration 14 days and 4 days prior to sacrifice[23]. Additionally, 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[24].

In multiple animal studies, systemic administration of simvastatin after implant insertion has been demonstrated to promote osseointegration, increase bone density around implants and crucially, to increase the mechanical strength/stability of the bone-implant interface[25-28]. Du et al demonstrated administering oral simvastatin for either 24 or 48 days to osteoporotic rats (post oophorectomy) could increase implant-bone contact rate in cancellous bone when compared to untreated controls. This was measured by percentage bone to implant contact on histomorphometric analysis with haemotoxylin and eosin staining and light microscopy and demonstrates an increase in secondary stability and improving osseointegration[27]. Li et al explored the effect of a seven-day course of intraperitoneal simvastatin administration on peri-implant bone growth in rat tibial titanium implants by micro-CT and histomorphometric analysis and found an increase in bone formation in the treatment cohort when compared to controls[29].

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In addition to systemic statin administration it has been proposed that local application of statins (particularly fluvastatin) to implants may promote similar osteogenic effects, increasing mechanical strength and improving peri-implant bony calcification[30-32]. Masuzaki et al gave a single injection of fluvastatin impregnated microspheres to rats with tibial titanium implants, this demonstrated enhanced bone growth and bone contact at 14 days as demonstrated by staining and microscopy around the implant and was accompanied by an increased bending strength, as measured by extraction of the femur following implantation at 2 or 4 weeks after surgery followed by three point bending with a universal testing machine[33]. Similar studies have reported encouraging results with simvastatin coated implants, scaffolds and biomaterials[34,35]. Topical application of statins may therefore confer the potential beneficial osteogenic effects outlined previously but ameliorate concomitant clinical side effects such as headache, gastrointestinal disturbance and myopathy.

There are conflicts in the experimental literature however. Dose dependency studies have suggested that implants coated with 75µg of fluvastatin osseointegrate better than control implants, for example a rodent model demonstrated improved implant trabecular bone layer comprised of mineral bone and thicker appearance of the new trabeculae in the medullary canal. Paradoxically at higher doses of fluvastatin (300µg) the implants perform worse[31], in that there is a delay in calcification of peri-implant bone. Moriyama et al hypothesise this is due to higher doses of fluvastatin yielding immature osteoblasts, normally developed by osteocalcin expression[31]. The maturation of osteoblasts involves the fine balance of RUNX2 suppression (part of the BMP-2 signaling 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[31].

Osseointegration generally occurs within 3 months of primary arthroplasty[36,37]. Therefore pre-loading with statins prior to primary arthroplasty and early statin use in the initial weeks and month's post-implant insertion theoretically could be associated with a reduction in complications as a result of sub-optimal osseointegration such as implant stem migration, periprosthetic fracture and loosening as a result of failure of trabecular bone ingrowth[38].

This is supported by animal study data from Li et al who demonstrated 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[29]

There have also been reports of adverse effects to osseointegration with topical statin administration[29], Pauly et al investigated the effect of locally applied simvastatin to intramedullary nails in rat femurs and found impaired implant integration compared to controls in the form of reduced implant-bone contact and reduced new bone formation[35].

Statins and Periprosthetic Osteolysis (PPOL)

PPOL is the gradual, progressive resorption of bone and subsequent reduction in bone density around the bone-implant interface in THA and TKA[39]. It has been established that 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[38,39]. 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

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derivatives (e.g. foreign body giant cells and osteoclasts) have been implicated in the resorption of bone and PPOL in arthroplasty since early 1990[42].

There is an established research base for a class of drug known as bisphosphonates (BP) in inhibiting osteoclast formation and function, this 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[43,44] and animal[45,46] 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[44]. More recent research identified an associated risk reduction of up to 59% in those starting BP after arthroplasty surgery[43].

As outlined earlier statins also inhibit the mevalonate pathway up-stream of FPP and therefore have the potential to exert a similar molecular response as BP, inhibiting the osteolytic cascade and reducing PPOL. This hypothesis has been explored in experimental models. A murine calvarial study noted that introduction of UHMWPE particles induced a pronounced bone resorption response when compared to controls. In the group treated with one of the most commonly prescribed statins, simvastatin, this effect was significantly abrogated. Osteoclast numbers were 48.7 ± 7.1 in the UHMWPE group and 6.2 ± 3.1 in the UHWMPE-simvastatin treated group (p = 0:00002)[47].

Polymethylmethacrylate (PMMA) particles, released in cemented arthroplasty, have also been implicated as a potential trigger for PPOL via production of pro-inflammatory cytokine Tumour Necrosis Factor-alpha (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[48]. In a case control study of patients with radiologically detectable femoral osteolysis in THA, the authors compared

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statin “ever-users” and “never-users” at five years post-THA. Crude risk ratio of femoral osteolysis in the ever-use cohort was 0.36 (95% CI 0.14; 0.92) when compared to never-users. The relative risk ratio after adjustment for confounders (age, sex, activity level, BMI, 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[49].

Pro-inflammatory cytokines are considered to be major mediators of osteolysis and ultimately aseptic loosening; three of the most widely implicated are Interleukin-1 (IL-1), Interleukin-6 (IL-6), and TNFα[50]. Experimentally it has been demonstrated that TNFα up-regulates 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 THR[51]. TNFα production is up-regulated in experimental and clinical models of osteolysis, this upregulation is further associated with particulate wear debris in vitro and in vivo[50,52,53]. Similar molecular up-regulation of both IL-1[50,54,55] and IL-6[50,56] 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[57]. As outlined previously there is evidence to suggest that Cerivastatin inhibits PMMA induced inflammation in vitro via abrogation of the production of TNFα[48].Cerivastatin also reduces production of the chemokine monocyte chemotactic protein-1 (MCP-1), which facilitates migration and infiltration of leukocytes into tissues[48,58]. Simvastatin has been demonstrated experimentally to inhibit particle-mediated induction of IL-6 gene expression in human osteoblasts treated with titanium[59]. Aseptic loosening and PPOL resulting from inflammatory processes occurring over a longer period of time may theoretically be reduced by long term statin exposure, with statin administration potentially reducing late

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onset complications. These data are summarised in Table 1 and a mechanistic model of statin effects is presented in Figure 1.

Pharmacoepidemiologic Evidence of a Role for Statins in Arthroplasty Survival

There is growing observational evidence which suggests that statins may impact on arthroplasty survival. Using data from the DHAR, 2,349 patients who had THA between 1996 and 2005 and also had revision arthroplasty during this period were identified[60]. In a multivariable, propensity-score matched conditional logistic regression model, the relative risk (95% CI) of revision in those exposed to statins, compared to 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 vs never' statin exposure.

Of note in their work the adjusted relative risk of revision was lowest in periprosthetic fracture; (0.12, 0.04-0.33) and dislocation (0.28, 0.20-0.40), these are generally early complications and it could be hypothesised that improved bone-implant osseointegration as a result of early statin administration may reduce the risk of both complications. It is however important to highlight that the literature regarding statins and implant osseointegration has not generated a consensus view.

Using data from Clinical Practice Research Datalink (CPRD) in the UK and the Danish National Health System (DNHS), Lalmohamed et al analysed the association between statin exposure and revision of primary THA and TKA during the period 1987 to 2007[61]. In total, data from 189,286 participants were analysed. In the primary analysis, statin exposure was modelled in a time-dependent manner from the date of the primary THA/TKA. In a time-dependent multivariable Cox regression model including 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). Lalmohamed et al demonstrated that depending on the epidemiological study design used there can be

significant differences calculated in incidence ratio of revision surgery. A more recent analysis using CPRD data sought to further investigate association between statins exposure and risk of revision following THA/TKA and also the impact of duration and timing of statin exposure on revision risk, using propensity score adjusted Cox models [62]. Postoperative statin exposure was modelled as a time-varying variable and a total of 164,224 participants, who had a THA or TKA between 1988 and 2016 were included. Of those exposed to statins following THA/TKA, 852 (1.3%) had revision arthroplasty, compared to 2,648 (3.1%) of those unexposed; adjusted hazard ratio for revision in those exposed vs those unexposed, 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). Considering the timing of the first postoperative statin exposure, exposure in the first 5 years following surgery appeared protective; compared to those who were not exposed to statins, the hazard ratio (95%CI) of revision in those first exposed to statins in the periods 0-1 and 1-5 years after the primary surgery was 0.82 (0.74, 0.91) and 0.76 (0.65, 0.90) respectively. There was a small protective effect of exposure to statins > 5 years following primary surgery, though the confidence intervals included unity. Compared to participants exposed to statins for a total duration of less than one 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 for revision, 0.74 (0.62, 0.88)[62].

Conclusion

In this article we present a broad review of the evidence of the effect of statin therapy on bone biology and risk of revision arthroplasty. There is some evidence from animal and in vitro models to suggest that statin therapy may promote osseointegration and reduce periprosthetic osteolysis. Data from observational clinical studies support a weak effect of statins on bone 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. Currently there is inadequate evidence to support use of prophylactic statins in revision surgery.

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 clinical prescribing of statin therapy in patients undergoing arthroplasty of the hip or knee. Given the modest but statistically significant effect of statins on reducing the risk of revision arthroplasty and the large body of in vitro and in vivo evidence which may support these observations, further research is needed to study this effect prior to advocating statin use.

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Conflicting Interests

All named authors declare no conflicting interests.

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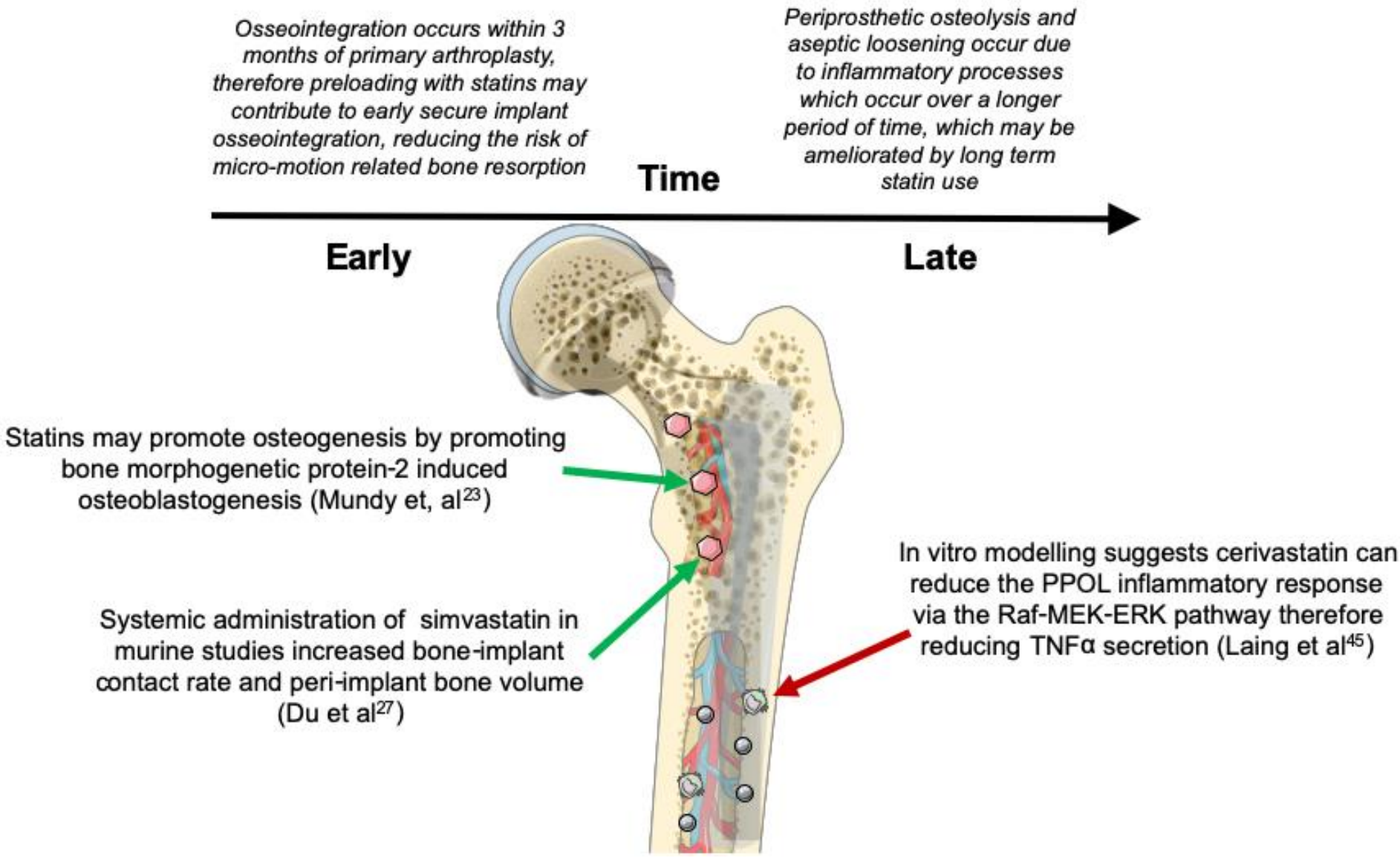

Figure 1. Mechanistic model of statin interactions with the bone-implant environment

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Study	Model	Statin	Mode of administration	Observed effect	Conclusions
Mundy et al, 1999 [23]	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 hours	Increased BMP-2 expression by Northern blot in cell lines exposed to simvastatin for 48 hours	As BMP-2 increases osteoblast differentiation and proliferation, statins may promote bone growth
Mundy et al, 1999 [23]	Explanted neonatal murine calvarial bones were placed in tissue culture medium with test compound to assess bone growth	Simvastatin, fluvastatin, lovastatin and mevastatin	1µM of test statin was incubated with the calvarial bone for 72 hours	Increased bone growth on histomorphometric analysis	Simvastatin, fluvastatin, lovastatin and mevastatin all increased bone formation by approximately two- to threefold, comparable to BMP-2 and fibroblast growth factor–1, the positive controls
Mundy et al, 1999 [23]	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 et al, 1999 [23]	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 analysed by histomorphometric analysis	Simvastatin increased trabecular bone formation
Du et al, 2008 [27]	Titanium implants inserted into the tibia of oophorectomized vs sham surgery to assess osseointegration in rats	Simvastatin	Oral administration 5 mg/kg for either 28 or 84 days before sacrifice	Increase in the percentage of cancellous bone to implant contact as measured by histometric analysis from both sides of the implant. No significant difference observed in cortical bone contact	Simvastatin may improve osseointegration
Li et al, 2016 [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 seven days of simvastatin administration, there was an increase in peri-implant bone growth compared to control, however there is a decrease in bone growth following simvastatin discontinuation which is confirmed by histology	Short term statin administration is associated with peri-implant bone growth, however there is rebound loss of bone on discontinuation
Masuzaki et al, 2010 [33]	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 increase bone growth. Bone strength was increased by testing with three point bending.	A single injection of fluvastatin microspheres increased implant osseointegration and the mechanical strength of the bone
Laing et al, 2009 [48]	In vitro model of monocyte/macrophage inflammatory response to poly-methylmethacrylate (PMMA) particles, compared to pre-treatment with statin	Cerivastatin	Cerivastatin dissolved in media to 150 or 300µM for 1 hour followed by PMMA exposure for 23 hours	Inflammatory cytokine TNF alpha production is significantly abrogated with cerivastatin pre-treatment	Cerivastatin may reduce pro-inflammatory cytokine release responsible for osteolysis

Table 1. Summary table of biological studies investigating statins and arthroplasty biology