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 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 also 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 Clinical Practice Research Datalink in the UK suggest a reduction in the risk of lower limb revision arthroplasty in statin ever-users vs never users, and a time dependent effect of statin administration on reduction in risk of revision. In this article we review the clinical and scientific evidence linking statins and risk of revision arthroplasty.

Keywords: statin; arthroplasty; revision; failure; osseointegration; osteolysis; loosening

Introduction

Osteoarthritis (OA) is characterised 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 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 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 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, 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 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 micro-motion 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]. 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[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 administering oral simvastatin to osteoporotic rats (post oophorectomy) could increase implant-bone contact rate in cancellous bone when compared to 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 to 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 demonstrated 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 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[28], 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[28]. 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[28]. Osseointegration generally occurs within 3 months of primary arthroplasty[33,34]. 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[35]. 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[24]. Animal models should, however, be interpreted with caution. Many of the animal studies referenced administered statins for 30 days or less, in humans osseointegration is thought to occur within a more prolonged period (3 months). Furthermore, the dynamic forces on the human hip joint in gait is not directly comparable to that 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 (PPOL)

PPOL is the gradual, progressive resorption of bone and subsequent reduction in bone density around the bone-implant interface in THA and TKA[36]. 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, 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[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 up-stream 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 to controls. In the group treated with simvastatin, this effect was significantly abrogated[44]. 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[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 five years post-THA. 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[46].

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[47]. 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[48]. 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[47,49,50]. Similar molecular up-regulation of both IL-1[47,51,52] and IL-6[47-53] 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[54]. There is evidence to suggest that Cerivastatin inhibits PMMA induced inflammation in vitro via abrogation of the production of TNFα[45]. Cerivastatin also reduces production of the chemokine monocyte chemotactic protein-1 (MCP-1), which facilitates migration and infiltration of leukocytes into tissues[45,55]. Simvastatin has been demonstrated experimentally to inhibit particle-mediated induction of IL-6 gene expression 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 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 observational evidence which suggests that statins may impact on arthroplasty survival. Using data from the UK Clinical Practice Research Datalink, Sarmanova et al conducted a propensity score-matched cohort study, matching 178,467 statin users to the same number of non-statin 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 2,349 patients who had 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 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.

In a study which used data from both the 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[59]. In the primary analysis, 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 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). 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. No statistically significant effect of statin exposure on revision risk >5 years following primary surgery was observed. 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 surgery, (HR (95%CI) 0.74 (0.62, 0.88)[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 suggested by the 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 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.

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.

Acknowledgements and Funding

This research was supported by the NIHR Manchester Biomedical Research Centre. Antony K Sorial and Sami A Anjum were funded through the NIHR integrated academic training programme. Funding for Michael J Cook was provided by the John Charnley Trust and Wrightington Three Wishes Foundation.

Conflicting Interests

All named authors declare no conflicting interests.

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Study	Model	Statin	Mode of Administration	Observed Effect	Conclusions
Mundy et al, 1999 [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 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 [20]	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
Mundy et al, 1999 [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 et al, 1999 [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 analysed by histomorphometric analysis	Simvastatin increased trabecular bone formation
Du et al, 2008 [24]	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 and there is rebound loss of bone on discontinuation
Masuzaki et al, 2010 [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 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 [45]	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 of studies investigating links between statins and bone biology
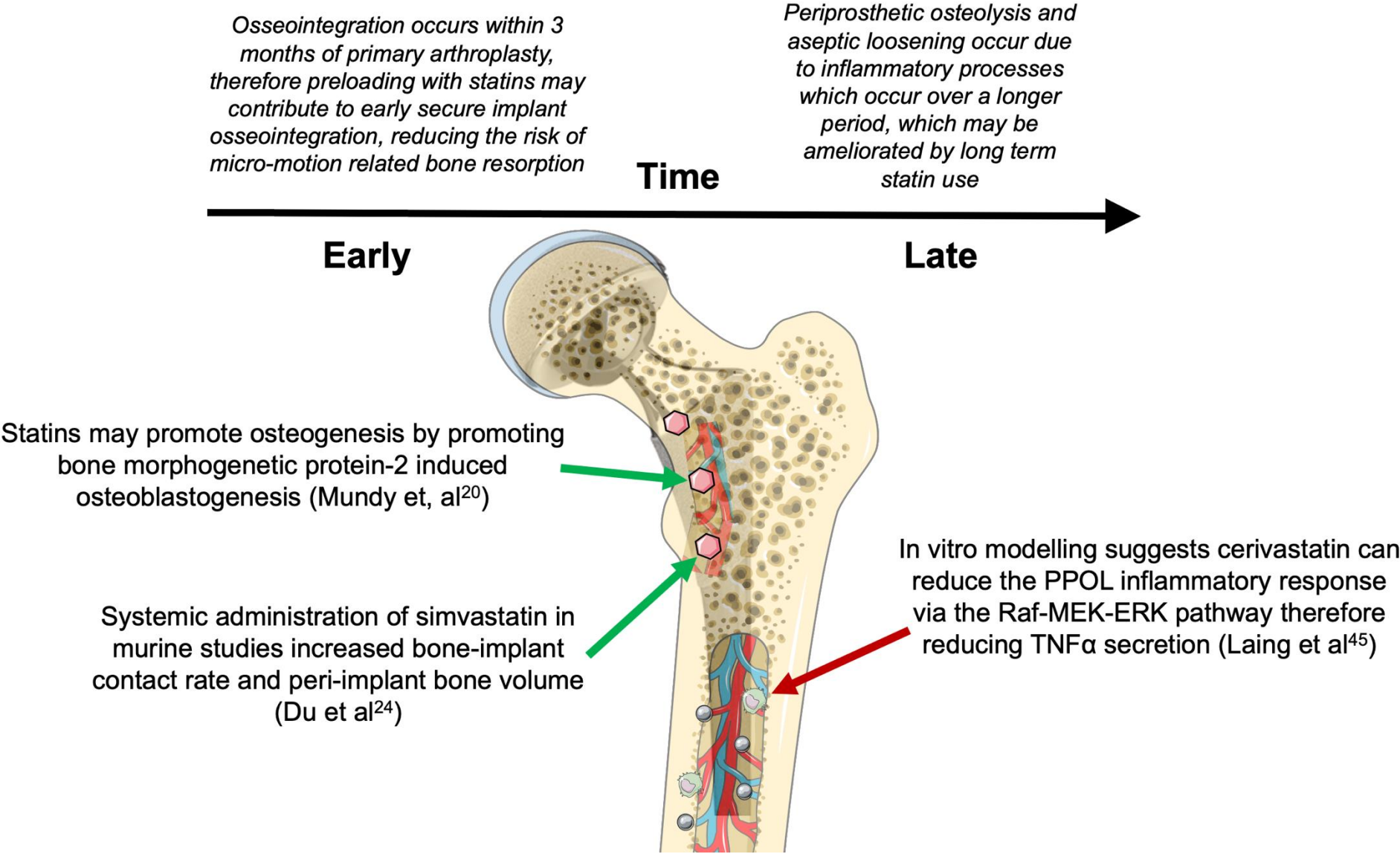
Figure 1: Mechanistic model of interaction between statins and bone implant interface biology