DR. LUCA LIBERALE (Orcid ID : 0000-0003-1472-7975)

DR. FABRIZIO MONTECUCCO (Orcid ID : 0000-0003-0823-8729)

PROF. AMIRHOSSEIN SAHEBKAR (Orcid ID : 0000-0002-8656-1444)

The role of statins in the differentiation and function of bone cells

Sajad Chamani [1,2], Luca Liberale [3,4], Leila Mobasheri [5], Fabrizio Montecucco [4,6] , Khalid Al-Rasadi [7], Tannaz Jamialahmadi [8,9], Amirhossein Sahebkar [10,11,12,13]

1. Student Research Committee, Birjand University of Medical Sciences, Birjand, Iran
2. Department of Immunology, Faculty of Medicine, Birjand University of Medical Sciences, Birjand, Iran
3. Center for Molecular Cardiology, University of Zürich, Schlieren, Switzerland
4. First Clinic of Internal Medicine, Department of Internal Medicine, University of Genoa, Genoa, Italy.
5. Department of Pharmacology, Faculty of medicine, Mashhad University of Medical Sciences, Mashhad, Iran.
6. IRCCS Ospedale Policlinico San Martino Genoa – Italian Cardiovascular Network, Genoa, Italy.
7. Medical Research Centre, Sultan Qaboos University, Muscat, Oman.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/ECI.13534

8. Department of Food Science and Technology, Quchan Branch, Islamic Azad University, Quchan, Iran.
9. Department of Nutrition, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.
10. Neurogenic Inflammation Research Center, Mashhad University of Medical Sciences, Mashhad, Iran.
11. Biotechnology Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran.
12. Polish Mother's Memorial Hospital Research Institute (PMMHRI), Lodz, Poland.
13. Halal Research Center of IRI, FDA, Tehran, Iran.

Running title: Statins and bone cells.

Correspondence:

- *Prof. Amirhossein Sahebkar*, Biotechnology Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad 9177948564, Iran. E-mail: sahebkara@mums.ac.ir; amir_saheb2000@yahoo.com

Abstract

Statins are 3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors blocking cholesterol biosynthesis in hepatic cells, thereby causing an increase in low-density lipoprotein (LDL) receptors resulting in enhanced uptake and clearance of atherogenic LDL-cholesterol (LDL-C) from the blood. Accordingly, statins decrease the risk of developing atherosclerosis and its acute complications, such as acute myocardial infarction and ischemic stroke. Besides the LDL-C-lowering impact, statins also have other so-called pleiotropic effects. Among them, the ability to modulate differentiation and function of bone cells and exert direct effects on osteosynthesis factors. Specifically, earlier studies have shown that statins cause in vitro and in vivo osteogenic differentiation. Statins increase the expression of many mediators involved in bone metabolism, including bone morphogenetic protein-2 (BMP-2), glucocorticoids, transforming growth factor-beta (TGF-β), alkaline phosphatase (ALP), type I collagen, and collagenase-1. As a result, they enhance bone formation and improve bone mineral density by modulating osteoblast and osteoclast differentiation. This review article summarizes the literature exploring bone-related "pleiotropic" effects of statins and suggesting an anabolic role in the bone tissue for such a drug class. Accordingly, current knowledge encourages further clinical trials to assess their therapeutic potential in the treatment of bone disorders, such as arthritis and osteoporosis.

Keywords: Statins; Osteogenesis; Bone; Osteoblast; Osteoclast

Introduction

Statins are cholesterol-reducing medications that inhibit the function of 3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase and inhibit the synthesis of mevalonate, which is a precursor of cholesterol (1-3). There is evidence that lipid and bone metabolisms are mutually regulated. Common mediators might impact on atherosclerotic plaque calcification, progression and the activity of bone-related disorders, such as osteoporosis and arthritis (4). In addition, lipids and their derivatives can activated osteoblasts via selective lipid receptors and catabolic enzymes for the internalization and utilization of circulating lipids. Dyslipidemia and lipid homeostasis disruption can impair osteoblast function and accelerate osteoclast activity (5, 6). Targeting lipid metabolism with a statin has been shown to improve bone density and quality in metabolic bone diseases (7).

Since their administration causes effective reduction in plasma low-density lipoprotein-cholesterol (LDL-C) concentrations, statins are widely used in the therapy of hypercholesterolemia, which is the leading risk factor for coronary artery disease (CAD) (8-15). Cholesterol is an essential building element of cell membranes and involves regulating many biological functions, including cell integrity, binding receptors to ligands, fluid endocytosis, and cell homeostasis. Besides decreasing the production of cholesterol, statins possess several LDL-independent pleiotropic actions (16-23). Such effects are, at least in part, due to the reduction of other products that originate from the mevalonic acid pathway, including farnesyl pyrophosphate (FPP) and geranylgeranyl pyrophosphate (GGPP), the precursors of isoprenoids (14, 24). Isoprenoids then modulate the effect of several cellular proteins, such as oncoproteins (ras), nuclear proteins (laminins), and small guanosine triphosphate (GTP)-binding proteins (rho, rac, rab) that are essential for cell proliferation, differentiation, and death (25-27).

Given the ubiquitary distribution of statins' pleiotropic downstream targets, these medications likely affect the function of most human cell types, including bone cells (28, 29). Bones are living tissues with architecture to endure maximum weight power. Most bones have a thick, stiff exterior layer made of compact tissue (i.e., cortex) and thin interconnecting bone trabeculas in the core-medullary part, which contains the hemopoietic bone marrow (30). Besides their mineral structure, bones consist of four distinct kinds of cells: osteoblasts forming new bone, osteocytes that are osteoblast trapped in the produced minerals, osteoclasts in charge of bone resorption and remodeling, and the last, bone

lining cells that are thought to be quiescent osteoblast participating into bone remodeling when needed. On bone surfaces, osteoblasts and osteoclasts originate from resident mesenchymal cells known as progenitor cells. In vitro studies indicated an anabolic effect of statins on most bone-related cell lines and cell types, including human immortalized cell lines (31-33), such as human and murine osteoblast-like cells (34, 35) and human bone marrow stromal cells (36). Interestingly, those preliminary *in vitro* effects of statins on bone cells, might be translated in a next future to the clinic. For instance, statins taken for lipid-lowring might also impact on bone metabolism, thus improving both lipid and bone disorders in human beings. Therefore, the clinical relevance of the issues presented in this review might be quite remarkable.

Some literature surveys have suggested that statins might have an anabolic effect on stem cells, including murine bone marrow mesenchymal cells (37-39), and human mesenchymal stem cells (40, 41), and murine embryonic stem cells (42) by differentiation and osteogenesis marker expression. In this article, we will review the effects of statins on bone cell differentiation and osteogenesis. We searched in the databases of MEDLINE/PubMed, OVID, EMBASE, Web of Sciences, and SCOPUS from the inception to August 5, 2020. The search strategy was to look for: (“statins” OR "statin therapy" OR "statins therapy" OR “statin” OR "HMG CoA reductase inhibitor" OR “lovastatin” OR “fluvastatin” OR “pravastatin” OR “rosuvastatin” OR “pitavastatin” OR “atorvastatin” OR “simvastatin” OR “cerivastatin” AND “bone” OR “bone cells” OR “osteoblasts” OR “osteoclasts” OR “osteocytes”). The reference lists of articles were checked for other relevant publications.

Statins stimulate bone deposition

The possible effects of statins on bone metabolism were first proven in 1999 when Mundy et al. reported a role of statins in bone formation *in vivo* (43). Specifically, the authors demonstrated that statins (i.e. simvastatin, mevastatin, and fluvastatin) were utmost effective at 5 μM in stimulating generation of neonatal murine calvarial bone organ cultures through the expression of bone morphogenetic protein-2 (BMP-2) gene, which promotes the osteoblast differentiation (43). These results were confirmed by additional studies (44-46). Sugiyama and co-workers reported that compactin (or mevastatin) increased mRNA and protein expression of BMP-2 at 5 μM in a human osteosarcoma (HOS) cell line. Also, compactine and simvastatin were shown to activate the BMP-2

promoter at 25 μM, while pravastatin did not (31). Ruiz-Gaspa and co-workers revealed that different concentrations of simvastatin and atorvastatin (10^{-9} M, 10^{-8} M, 10^{-7} M, 10^{-6} M) are associated with the arrest of proliferation in human osteoblast (hOB) and MG-63 cell line cultures (47). Baek et al. showed that simvastatin decrease the proliferation of human bone marrow stromal cells (BMSCs) in a dose-dependent manner (10^{-6} M and 10^{-8} M of simvastatin) and also, 10^{-6} M of simvastatin enhanced mRNA expression of osteocalcin in an *ex vivo* culture (48). The potential effects of statins in bone formation were investigated in additional experimental models (49, 50). Thylin and co-workers revealed that injection of simvastatin in gel (2.2 mg of simvastatin per 50 μl methylcellulose gel) could stimulate the growth of murine calvarial bone.

Some clinical observation confirmed the anabolic effects of statins on the formation of bone tissue. Chuengsamarn et al. (51) showed an increase of bone mineral density (BMD) and a decrease of bone resorption in 106 hyperlipidemia patients with osteopenia taking statins in comparison n=106 patients without statin. A representative cohort NHANES III study in two-sample Mendelian randomization confirmed the potential protective effects of statins on bone via reducing Low-density lipoprotein cholesterol (LDL-C) and increase in neck BMD (52, 53). Of interest, different statins and different formulations (e.g., transdermal vs. oral administration) might show different efficacy on bone metabolism (54-56).

The molecular mechanisms guiding the anabolic effects of statins on bone tissue will be critically reviewed in the following paragraphs, focusing on the different bone cells. Yet, statins may also indirectly modulate bone deposition through their immunomodulatory effects (24, 57). Indeed, systemic inflammation was previously reported to cause bone loss by inhibiting new bone formation as well as facilitating bone reabsorption (58). The effects of statins on systemic inflammation and immune cells are beyond the scope of the current review and have been previously summarized by eminent articles to which the readers are referred (59, 60).

Statins play roles in osteoblast differentiation and activity

Osteoblasts play a pivotal role in the formation and maintenance of skeletal architecture and are accountable for the deposition of the bone matrix and osteoclast inhibition (61). Osteoblasts originate from bone-marrow stromal cells (BMSCs) or mesenchymal stem cells, or osteoprogenitor cells (62).

Their differentiation is prompted by several mediators, including bone morphogenetic proteins (BMPs), transforming growth factor-β (TGF-β), and glucocorticoids (63). *In vitro,* BMSCs create distinctive cell colonies with fibroblast morphology known as colony-fibroblast units (CFU-Fs) (64). Different bone anabolic agents increase the number of CFU-Fs in *ex vivo* cultures (65, 66), of interest, simvastatin can stimulate CFU-F formation and osteoblastic differentiation (36). Therefore, statins are thought to prompt the mobilization of osteoprogenitor cells from bone marrow and increase their differentiation into bone-deposing cells.

Accordingly, simvastatin-treated embryonal stem cells showed increased osteogenic gene expression, including *Runx2*, *OSX*, and *OCN* (67). Runx2 molecular pathway has been shown to directly stimulate the transcription of other osteoblast-related genes (68, 69). After simvastatin supplementation, Runx2 activation enhances the protein levels of osteocalcin (OCN), osteopontin (OPN), and collagen Type I (68, 69). Again indicating an active role for simvastatin to facilitate embryonic stem cell osteogenic differentiation. As a further mechanism, simvastatin is thought to stimulate the canonical Wnt signaling pathway during the osteogenic differentiation of embryonic stem cells (67). Extracellular Wnt receptors -among the most important regulators of bone biology (70) - induce canonical Wnt/β-catenin signaling to respond to chemical and mechanical stimulation (71-73). Previous studies proved that simvastatin considerably enhances Wnt signaling-related genes during the osteogenic differentiation of BMSCs (74, 75). Also, simvastatin could recover the impaired Wnt/β-catenin signaling caused by the Effect of elevated glucose in mesangial cells and prevent their apoptosis (76). these findings suggest that simvastatin can activate the Wnt/β-catenin signaling pathway, thereby modulating several cell functions, including osteogenic differentiation (77).

Osteoblasts and adipocytes within the bone marrow are derived from common mesenchymal precursors. Pro-adipogenic substances, like rosiglitazone, a peroxisome proliferator-activated receptor (PPAR)-c2 ligand, facilitate mesenchymal cell differentiation adipocytes despite osteoblasts (78). In this context, recent in vitro data have shown that simvastatin and lovastatin can inhibit adipogenic differentiation, facilitating the mesenchymal transition towards osteoblasts (79, 80). This effect is likely mediated by reduced PPAR-c2 expression and increased Runx2/Cbfa1 activation (81). Also, as previously mentioned, statins stimulate the expression of BMP-2 in murine embryonic stem cells (42) and mouse bone marrow stromal cells (79), supporting the hypothesis that the BMP-2/Runx2 axis

might be essential in statin-driven osteoblast differentiation. Furthermore, simvastatin improved protein production in human bone cells through different mechanisms. FPP and GGPP are intermediate metabolites of the mevalonate pathway. FPP can be used to synthesize squalene, but it can also bind to small G-proteins or be transformed into GGPP by GGPP synthase that is used for protein geranylgeranylation (82). By inhibiting HMG-CoA reductase statins reduce intracellular FPP and GGPP availability. Indeed, Weivoda et al. found that during statin-induced differentiation of the osteoblasts, both FPP and GGPP are decreased during statin-induced osteoblast differentiation (83). Accordingly, exogenous induction of FPP by zaragozic acid was shown to suppress osteoblast differentiation (83). Similarly, also GGPP was reported to act as a negative modulator of osteogenesis (84). Ohnaka et al. showed that pitavastatin incubation increases the expression level of primary human osteoblast cells, an effect that was reversed by mevalonate or GGPP addition (85). Similarly, simvastatin can increase osteoblastogenesis by inducing the expression of BMP-2, alkaline phosphatase (ALP), OCN, and vascular endothelium growth factor (VEGF). At the same time, the addition of GGPP into the media prevented simvastatin-induced osteogenic differentiation (35). BMP-2, a low molecular weight glycoprotein, is a member of the TGF-β superfamily, which triggers bone formation and fracture repair by regulating mesenchymal condensation (86-88). As previously mentioned, statins are potent inducers of BMP-2 mainly through the Ras/ PI3K/ Akt pathway (35, 36). Lastly, statins preserve osteoblasts from apoptosis by activating the TGFβ/Smad3 pathway (89) (Figure 1).

Statins and osteoclasts

Osteoclasts have been considered for many years as bone re-absorbing cells. Recent studies have shed light on many other functions for those cells, including modulation of osteoblast activity, facilitating role on bone matrix mineralization, and releasing hematopoietic stem cells from the bone marrow into the blood (90). They are multinucleated giant cells originating from the fusion of different monocytes under the influence of specific cytokines, including macrophage colony-stimulating factor (MCSF) and receptor activator of NF-κB ligand (RANKL) (91, 92). RANKL is essential for osteoclastogenesis and is expressed, in the bone tissue, by osteoblasts, osteocytes, and stromal cells (93-95). The binding of RANKL triggers osteoclasts formation and activation to its receptor (RANK) on the membrane of

osteoclast progenitor cells (96-98). Furthermore, RANKL was shown to inhibit osteoclast apoptosis (99). RANK is a type I integral protein that belongs to the TNFR family and is related to tumor necrosis factor receptor-associated factor (TRAF)1, TRAF2, TRAF3, TRAF5, and TRAF6. It signals through the activation of different transcription factors typically associated with inflammation, such as NF-κB and (c-Jun N-terminal kinase) JNK (100). The pro-osteoclastogenesis RANKL/RANK system is found in osteoprotegerin (OPG) its main physiological inhibitor. OPG works as a decoy receptor for RANKL to reduce osteoclast differentiation, thereby blunting bone reabsorption (101).

Statins regulate osteoclastogenesis by directly acting on OPG/RANKL/RANK signaling pathway. When treated with different statins, murine bone cell cultures increase OPG and RANKL by performing at the transcriptional level (102). Furthermore, statins could prevent RANKL-induced osteoclasts differentiation of the murine monocyte/macrophage RAW 264.7 cell line (103). Specifically, simvastatin could inhibit the activation of NF-κB by RANKL through blocking the phosphorylation and degradation of IκBα (inhibitory κBα), which is essential for the activation of NF-κB (104, 105). As important mediators of NF-κB and JNK activities, reactive oxygen species (ROS) are thought to be deeply involved in osteoclastogenesis, thereby positively influencing catabolism of bone tissue (106). RANK activation by RANKL stimulates the production of intracellular ROS during the osteoclastogenesis (107). Of interest, simvastatin significantly reduced ROS formation during RANKL-mediated differentiation of RAW 264.7 cells (105), suggesting another mechanism for statin inhibition of osteoclast activity (Figure 2).

Cytokines and other circulating mediators play a significant regulatory role in normal and pathologic bone remodeling by osteoclasts and OCPs (108). Estrogens are known to inhibit osteoclastogenesis by reducing levels of RANKL. Of interest, statins can induce the expression of estrogen receptor α (ERα), thereby facilitating the bone protective estrogen signaling [109]. Indeed that statins can improve fracture healing animal menopause experimental models [110], a finding which is confirmed in patients by clinical studies [111].

Osteogenic effects of statins on osteocytes and other bone cells

Osteocytes derive from osteoblasts (112). When compared with osteoblasts and osteoclasts with a shorter life span and are only found on the bone's surface, osteocytes are most abundant and found

within the bone's mineral component. Osteocytes effectively secrete both bone formation stimulating growth factors and sclerostin, which suppresses bone formation (81, 113-115). Osteocytes have several roles, including mineralization control, phosphate and calcium homeostasis, regulation of bone metabolism and vascularization, bone fractures healing via insulin-growth factor (IGF)-1, and modulation myelopoiesis/hematopoiesis via sclerostin and G-CSF (116-119). Among the different molecules involved in osteoclastogenesis, many are known to be regulated by statins in various ways, including matrix metalloproteinases (MMPs), dentin matrix protein 1 (DMP-1), and Klotho (120-122). Yet, our knowledge of the Effect of statins on osteoblast differentiation toward osteocytes remains poor. Tai IC et al. have shown that the RhoA / ROCK mechanism is involved in the osteogenic differentiation of cultured mBMSCs in response to statin. They further demonstrated that this effect was not mediated by prenylation, which is inhibited by simvastatin. Also, simvastatin improved actin cytoskeleton, focal adhesion formation, and cell tension (123).

Conclusions and future perspectives

Statins have a significant effect on bone cell differentiation. Many mediators of osteogenesis, including BMP-2, glucocorticoids, TGF-β, ALP, type I collagen, and MMP-1, are directly influenced by statins. Statins modulate the differentiation of bone cells *via* several cellular pathways such as protein isoprenylation, Wnt/β-catenin, and OPG/RANKL/RANK, eventually impacting on the action of different transcription factors including NF-κβ, JNK, and ERα. Several *in vitro* studies have been performed to clarify the potential influence of statins on bone cell differentiation. Despite the reliable experimental data linking statins with bone deposition, clinical evidence still need further confirmation as it mostly comes from observational studies and post-hoc analysis of RCTs. Therefore, further specific and well-designed RCTs are required to evaluate statins' role in the treatment of bone diseases.

Conflict of interests: none.

Funding: none.

Figure legend

Figure 1. The effects of statins in osteoblastogenesis. Statins block HMG-CoA reductase in the mevalonate pathway and inhibit the production of mevalonate required for the synthesis of cholesterol and isoprenoids like FPP and GGPP. Decreasing cholesterol can increase bone formation. Reducing FPP and GGPP metabolites by decreasing Farnesylated proteins, Geranylgeranylated proteins, and Small G-proteins causes the stimulation of BMP-2, Runx2, VEGF, PI3 Kinase/AKT eventually leading to osteoblast differentiation and bone formation. Also, statins inhibit the apoptosis of osteoblasts by enhancing TGF-β/Smad pathway. BMP2, bone morphogenetic protein 2; Runx2, runt-related transcription factor 2; ALP, alkaline phosphatase; OCN, osteocalcin; BSP, bone sialoprotein; Col-I, collagen type- I; MMP, matrix metalloproteinases; VEGF, vascular endothelial growth factor.

Figure 2. The OPG/RANKL/RANK signaling pathway is regulated by statins. The binding of RANKL to RANK activates the cascade signaling pathways (TRAF6, ROS, JNK, NFK-β, NFACT1) that lead to bone resorption. Statins such as simvastatin can inhibit ROS generation, and NFK-β that block the bone resorption. Statins can upregulate OPG expression by binding to RANKL and avoiding it from contact to RANK, which protects the bone from bone resorption. Also, statins can decrease the osteoclastogenesis through suppressing the RANKL expression in an ER-dependent mechanism. Therefore statins may inhibit osteoclastogenesis by regulating OPG/RANKL/RANK signaling pathway. ER, Estrogen receptor; OPG, Osteoprotegerin; RANK, Receptor activator of nuclear factor-kappa B; RANKL, Receptor activator of nuclear factor-kappa B ligand; ROS, Reactive oxygen species; NFATc1, Nuclear factor of activated T-Cells.

References

1. Pinal-Fernandez I, Casal-Dominguez M, Mammen AL. Statins: pros and cons. Med Clin (Barc). 2018;150(10):398-402.
2. Toth PP, Banach M. Statins: Then and Now. Methodist Debakey Cardiovasc J. 2019;15(1):23-31.
3. Mach F, Ray KK, Wiklund O, Corsini A, Catapano AL, Bruckert E, et al. Adverse effects of statin therapy: perception vs. the evidence - focus on glucose homeostasis, cognitive, renal and hepatic function, haemorrhagic stroke and cataract. Eur Heart J. 2018;39(27):2526-39.
4. Tian L, Yu X. Lipid metabolism disorders and bone dysfunction-interrelated and mutually regulated. Molecular medicine reports. 2015;12(1):783-94.
5. Alekos NS, Moorer MC, Riddle RC. Dual effects of lipid metabolism on osteoblast function. Frontiers in Endocrinology. 2020;11.
6. Suzuki A, Minamide M, Iwaya C, Ogata K, Iwata J. Role of Metabolism in Bone Development and Homeostasis. International journal of molecular sciences. 2020;21(23):8992.
7. Kim H, Oh B, Park-Min K-H. Regulation of Osteoclast Differentiation and Activity by Lipid Metabolism. Cells. 2021;10(1):89.
8. Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. The New England journal of medicine. 1996;335(14):1001-9.
9. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The New England journal of medicine. 1998;339(19):1349-57.
10. Nissen SE, Tuzcu EM, Schoenhagen P, Brown BG, Ganz P, Vogel RA, et al. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. Jama. 2004;291(9):1071-80.

11. LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. The New England journal of medicine. 2005;352(14):1425-35.
12. Ballantyne CM, Bertolami M, Hernandez Garcia HR, Nul D, Stein EA, Theroux P, et al. Achieving LDL cholesterol, non-HDL cholesterol, and apolipoprotein B target levels in high-risk patients: Measuring Effective Reductions in Cholesterol Using Rosuvastatin therapY (MERCURY) II. American heart journal. 2006;151(5):975.e1-9.
13. Rackley CE. Monotherapy with HMG-CoA reductase inhibitors and secondary prevention in coronary artery disease. Clinical cardiology. 1996;19(9):683-9.
14. Reiner Z. Statins in the primary prevention of cardiovascular disease. Nat Rev Cardiol. 2013;10(8):453-64.
15. Reiner Z. Primary prevention of cardiovascular disease with statins in the elderly. Curr Atheroscler Rep. 2014;16(7):420.
16. Afshari AR, Mollazadeh H, Henney NC, Jamialahmad T, Sahebkar A. Effects of statins on brain tumors: a review. Seminars in Cancer Biology. 2020.
17. Bagheri H, Ghasemi F, Barreto GE, Sathyapalan T, Jamialahmadi T, Sahebkar A. The effects of statins on microglial cells to protect against neurodegenerative disorders: A mechanistic review. BioFactors. 2020;46(3):309-25.
18. Bahrami A, Bo S, Jamialahmadi T, Sahebkar A. Effects of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors on ageing: Molecular mechanisms. Ageing Research Reviews. 2020;58.
19. Gorabi AM, Kiaie N, Pirro M, Bianconi V, Jamialahmadi T, Sahebkar A. Effects of statins on the biological features of mesenchymal stem cells and therapeutic implications. Heart Failure Reviews. 2020.
20. Kouhpeikar H, Delbari Z, Sathyapalan T, Simental-Mendía LE, Jamialahmadi T, Sahebkar A. The Effect of Statins through Mast Cells in the Pathophysiology of Atherosclerosis: a Review. Current Atherosclerosis Reports. 2020;22(5).

21. Reiner Ž, Hatamipour M, Banach M, Pirro M, Al-Rasadi K, Jamialahmadi T, et al. Statins and the Covid-19 main protease: In silico evidence on direct interaction. Archives of Medical Science. 2020;16(2):490-6.
22. Sahebkar A, Serban C, Ursoniu S, Mikhailidis DP, Undas A, Lip GYH, et al. The impact of statin therapy on plasma levels of von Willebrand factor antigen: Systematic review and meta-analysis of Randomised placebo-controlled trials. Thrombosis and Haemostasis. 2016;115(3):520-32.
23. Serban C, Sahebkar A, Ursoniu S, Mikhailidis DP, Rizzo M, Lip GYH, et al. A systematic review and meta-analysis of the effect of statins on plasma asymmetric dimethylarginine concentrations. Scientific Reports. 2015;5.
24. Liberale L, Carbone F, Montecucco F, Sahebkar A. Statins reduce vascular inflammation in atherogenesis: A review of underlying molecular mechanisms. Int J Biochem Cell Biol. 2020;122:105735.
25. Liao JK. Isoprenoids as mediators of the biological effects of statins. J Clin Invest. 2002;110(3):285-8.
26. Jeong A, Suazo KF, Wood WG, Distefano MD, Li L. Isoprenoids and protein prenylation: implications in the pathogenesis and therapeutic intervention of Alzheimer's disease. Crit Rev Biochem Mol Biol. 2018;53(3):279-310.
27. Mo H, Jeter R, Bachmann A, Yount ST, Shen CL, Yeganehjoo H. The Potential of Isoprenoids in Adjuvant Cancer Therapy to Reduce Adverse Effects of Statins. Front Pharmacol. 2018;9:1515.
28. Uzzan B, Cohen R, Nicolas P, Cucherat M, Perret GY. Effects of statins on bone mineral density: a meta-analysis of clinical studies. Bone. 2007;40(6):1581-7.
29. Pauly S, Luttosch F, Morawski M, Haas NP, Schmidmaier G, Wildemann B. Simvastatin locally applied from a biodegradable coating of osteosynthetic implants improves fracture healing comparable to BMP-2 application. Bone. 2009;45(3):505-11.
30. Mohamed AM. An overview of bone cells and their regulating factors of differentiation. The Malaysian journal of medical sciences: MJMS. 2008;15(1):4.

31. Sugiyama M, Kodama T, Konishi K, Abe K, Asami S, Oikawa S. Compactin and simvastatin, but not pravastatin, induce bone morphogenetic protein-2 in human osteosarcoma cells. Biochemical and biophysical research communications. 2000;271(3):688-92.
32. Ruiz-Gaspa S, Nogues X, Enjuanes A, Monllau JC, Blanch J, Carreras R, et al. Simvastatin and atorvastatin enhance gene expression of collagen type 1 and osteocalcin in primary human osteoblasts and MG-63 cultures. Journal of cellular biochemistry. 2007;101(6):1430-8.
33. Thunyakitpisal PD, Chaisuparat R. Simvastatin, an HMG-CoA reductase inhibitor, reduced the expression of matrix metalloproteinase-9 (Gelatinase B) in osteoblastic cells and HT1080 fibrosarcoma cells. Journal of pharmacological sciences. 2004;94(4):403-9.
34. Hwang R, Lee EJ, Kim MH, Li SZ, Jin YJ, Rhee Y, et al. Calcyclin, a Ca2+ ion-binding protein, contributes to the anabolic effects of simvastatin on bone. The Journal of biological chemistry. 2004;279(20):21239-47.
35. Maeda T, Matsunuma A, Kurahashi I, Yanagawa T, Yoshida H, Horiuchi N. Induction of osteoblast differentiation indices by statins in MC3T3-E1 cells. Journal of cellular biochemistry. 2004;92(3):458-71.
36. Baek KH, Lee WY, Oh KW, Tae HJ, Lee JM, Lee EJ, et al. The effect of simvastatin on the proliferation and differentiation of human bone marrow stromal cells. J Korean Med Sci. 2005;20(3):438-44.
37. Xu H, Yang YJ, Yang T, Qian HY. Statins and stem cell modulation. Ageing Res Rev. 2013;12(1):1-7.
38. Izadpanah R, Schächtele DJ, Pfnür AB, Lin D, Slakey DP, Kadowitz PJ, et al. The impact of statins on biological characteristics of stem cells provides a novel explanation for their pleiotropic beneficial and adverse clinical effects. Am J Physiol Cell Physiol. 2015;309(8):C522-31.
39. Carson RA, Rudine AC, Tally SJ, Franks AL, Frahm KA, Waldman JK, et al. Statins impact primary embryonic mouse neural stem cell survival, cell death, and fate through distinct mechanisms. PLoS One. 2018;13(5):e0196387.

40. Benoit DS, Nuttelman CR, Collins SD, Anseth KS. Synthesis and characterization of a fluvastatin-releasing hydrogel delivery system to modulate hMSC differentiation and function for bone regeneration. Biomaterials. 2006;27(36):6102-10.
41. Kupcsik L, Meurya T, Flury M, Stoddart M, Alini MJJoc, medicine m. Statin-induced calcification in human mesenchymal stem cells is cell death related. 2009;13(11-12):4465-73.
42. Phillips BW, Belmonte N, Vernochet C, Ailhaud G, Dani CJB, communications br. Compactin enhances osteogenesis in murine embryonic stem cells. 2001;284(2):478-84.
43. Mundy G, Garrett R, Harris S, Chan J, Chen D, Rossini G, et al. Stimulation of bone formation in vitro and in rodents by statins. Science. 1999;286(5446):1946-9.
44. Chen PY, Sun JS, Tsuang YH, Chen MH, Weng PW, Lin FH. Simvastatin promotes osteoblast viability and differentiation via Ras/Smad/Erk/BMP-2 signaling pathway. Nutr Res. 2010;30(3):191-9.
45. Shao PL, Wu SC, Lin ZY, Ho ML, Chen CH, Wang CZ. Alpha-5 Integrin Mediates Simvastatin-Induced Osteogenesis of Bone Marrow Mesenchymal Stem Cells. Int J Mol Sci. 2019;20(3).
46. Monjo M, Rubert M, Ellingsen JE, Lyngstadaas SP. Rosuvastatin promotes osteoblast differentiation and regulates SLCO1A1 transporter gene expression in MC3T3-E1 cells. Cell Physiol Biochem. 2010;26(4-5):647-56.
47. Ruiz-Gaspa S, Nogues X, Enjuanes A, Monllau JC, Blanch J, Carreras R, et al. Simvastatin and atorvastatin enhance gene expression of collagen type 1 and osteocalcin in primary human osteoblasts and MG-63 cultures. Journal of cellular biochemistry. 2007;101(6):1430-8.
48. Baek KH, Lee WY, Oh KW, Tae HJ, Lee JM, Lee EJ, et al. The effect of simvastatin on the proliferation and differentiation of human bone marrow stromal cells. Journal of Korean medical science. 2005;20(3):438.
49. Masuzaki T, Ayukawa Y, Moriyama Y, Jinno Y, Atsuta I, Ogino Y, et al. The effect of a single remote injection of statin-impregnated poly (lactic-co-glycolic acid) microspheres on osteogenesis around titanium implants in rat tibia. Biomaterials. 2010;31(12):3327-34.
50. Wong RW, Rabie AB. Statin collagen grafts used to repair defects in the parietal bone of rabbits. The British journal of oral & maxillofacial surgery. 2003;41(4):244-8.

51. Chuengsamarn S, Rattanamongkoulgul S, Suwanwalaikorn S, Wattanasirichaigoon S, Kaufman L. Effects of statins vs. non-statin lipid-lowering therapy on bone formation and bone mineral density biomarkers in patients with hyperlipidemia. Bone. 2010;46(4):1011-5.
52. Al-Khazaali A, Situala S, Dhindsa S. Letter to the Editor:"Association Between Cortical Bone Microstructure and Statin Use in Older Women". The Journal of Clinical Endocrinology & Metabolism. 2019;104(8):3367-.
53. Li GH, Cheung CL, Au PC, Tan KC, Wong IC, Sham PC. Positive effects of low LDL-C and statins on bone mineral density: an integrated epidemiological observation analysis and Mendelian randomization study. Int J Epidemiol. 2020;49(4):1221-35.
54. Mundy GR. Statins and their potential for osteoporosis. Bone. 2001;29(6):495-7.
55. Wang Z, Li Y, Zhou F, Piao Z, Hao J. Effects of Statins on Bone Mineral Density and Fracture Risk: A PRISMA-compliant Systematic Review and Meta-Analysis. Medicine (Baltimore). 2016;95(22):e3042.
56. Gutierrez G, Garrett I, Rossini G, Escobedo A, Horn D, Qiao M, et al., editors. Dermal application of lovastatin for 5 days stimulates bone formation in ovariectomized rats by 160%. JOURNAL OF BONE AND MINERAL RESEARCH; 2001: AMER SOC BONE & MINERAL RES 2025 M ST, NW, STE 800, WASHINGTON, DC 20036 ….
57. Kwak B, Mulhaupt F, Myit S, Mach F. Statins as a newly recognized type of immunomodulator. Nature medicine. 2000;6(12):1399-402.
58. Redlich K, Smolen JS. Inflammatory bone loss: pathogenesis and therapeutic intervention. Nat Rev Drug Discov. 2012;11(3):234-50.
59. Zeiser R. Immune modulatory effects of statins. Immunology. 2018;154(1):69-75.
60. Tunon J, Badimon L, Bochaton-Piallat ML, Cariou B, Daemen MJ, Egido J, et al. Identifying the anti-inflammatory response to lipid lowering therapy: a position paper from the working group on atherosclerosis and vascular biology of the European Society of Cardiology. Cardiovasc Res. 2019;115(1):10-9.
61. Curate F, Albuquerque A, Correia J, Ferreira I, de Lima JP, Cunha EM. A glimpse from the past: osteoporosis and osteoporotic fractures in a Portuguese identified skeletal sample. Acta reumatologica portuguesa. 2013;38(1):20-7.

62. Florencio-Silva R, Sasso GR, Sasso-Cerri E, Simões MJ, Cerri PS. Biology of Bone Tissue: Structure, Function, and Factors That Influence Bone Cells. Biomed Res Int. 2015;2015:421746.
63. Behera J, Tyagi N. Exosomes: mediators of bone diseases, protection, and therapeutics potential. Oncoscience. 2018;5(5-6):181-95.
64. Robey PG, Kuznetsov SA, Riminucci M, Bianco P. Bone marrow stromal cell assays: in vitro and in vivo. Methods Mol Biol. 2014;1130:279-93.
65. Wein MN, Kronenberg HM. Regulation of Bone Remodeling by Parathyroid Hormone. Cold Spring Harb Perspect Med. 2018;8(8).
66. Balani DH, Kronenberg HM. Withdrawal of parathyroid hormone after prolonged administration leads to adipogenic differentiation of mesenchymal precursors in vivo. Bone. 2019;118:16-9.
67. Qiao LJ, Kang KL, Heo JS. Simvastatin promotes osteogenic differentiation of mouse embryonic stem cells via canonical Wnt/β-catenin signaling. Molecules and cells. 2011;32(5):437-44.
68. Harada H, Tagashira S, Fujiwara M, Ogawa S, Katsumata T, Yamaguchi A, et al. Cbfa1 isoforms exert functional differences in osteoblast differentiation. Journal of Biological Chemistry. 1999;274(11):6972-8.
69. Kern B, Shen J, Starbuck M, Karsenty G. Cbfa1 contributes to the osteoblast-specific expression of type I collagen genes. Journal of Biological Chemistry. 2001;276(10):7101-7.
70. Rawadi G, Vayssiere B, Dunn F, Baron R, Roman-Roman S. BMP-2 controls alkaline phosphatase expression and osteoblast mineralization by a Wnt autocrine loop. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. 2003;18(10):1842-53.
71. Grebenova D, Kuzelova K, Smetana K, Pluskalova M, Cajthamlova H, Marinov I, et al. Mitochondrial and endoplasmic reticulum stress-induced apoptotic pathways are activated by 5-aminolevulinic acid-based photodynamic therapy in HL60 leukemia cells. Journal of photochemistry and photobiology B, Biology. 2003;69(2):71-85.

72. Heo JS, Lee JC. beta-Catenin mediates cyclic strain-stimulated cardiomyogenesis in mouse embryonic stem cells through ROS-dependent and integrin-mediated PI3K/Akt pathways. Journal of cellular biochemistry. 2011;112(7):1880-9.
73. Guo AJ, Choi RC, Cheung AW, Chen VP, Xu SL, Dong TT, et al. Baicalin, a flavone, induces the differentiation of cultured osteoblasts: an action via the Wnt/beta-catenin signaling pathway. The Journal of biological chemistry. 2011;286(32):27882-93.
74. Shao P-L, Wu S-C, Lin Z-Y, Ho M-L, Chen C-H, Wang C-Z. Alpha-5 Integrin Mediates Simvastatin-Induced Osteogenesis of Bone Marrow Mesenchymal Stem Cells. International journal of molecular sciences. 2019;20(3):506.
75. Zhang L, Zhang L, Tian F, Han D, Niu J, Liu X. [Effect of simvastatin on mRNA expressions of some components of Wnt signaling pathway in differentiation process of osteoblasts derived from BMSCs of rats]. Zhongguo xiu fu chong jian wai ke za zhi = Zhongguo xiufu chongjian waike zazhi = Chinese journal of reparative and reconstructive surgery. 2009;23(11):1371-5.
76. Lin CL, Cheng H, Tung CW, Huang WJ, Chang PJ, Yang JT, et al. Simvastatin reverses high glucose-induced apoptosis of mesangial cells via modulation of Wnt signaling pathway. American journal of nephrology. 2008;28(2):290-7.
77. Liu J, Chanumolu S, Krei Z, Albahrani M, Akhtam A, Jia Z, et al. Identification of Genes Differentially Expressed in Simvastatin-Induced Alveolar Bone Formation. JBMR plus. 2019;3(5):e10122.
78. Lecka-Czernik B, Moerman EJ, Grant DF, Lehmann JrM, Manolagas SC, Jilka RLJE. Divergent effects of selective peroxisome proliferator-activated receptor-γ2 ligands on adipocyte versus osteoblast differentiation. 2002;143(6):2376-84.
79. Song C, Guo Z, Ma Q, Chen Z, Liu Z, Jia H, et al. Simvastatin induces osteoblastic differentiation and inhibits adipocytic differentiation in mouse bone marrow stromal cells. Biochemical and biophysical research communications. 2003;308(3):458-62.
80. Li X, Cui Q, Kao C, Wang GJ, Balian G. Lovastatin inhibits adipogenic and stimulates osteogenic differentiation by suppressing PPARgamma2 and increasing Cbfa1/Runx2 expression in bone marrow mesenchymal cell cultures. Bone. 2003;33(4):652-9.

81. Balaz M, Becker AS, Balazova L, Straub L, Müller J, Gashi G, et al. Inhibition of mevalonate pathway prevents adipocyte browning in mice and men by affecting protein prenylation. Cell metabolism. 2019;29(4):901-16. e8.
82. Goldstein JL, Brown MS. Regulation of the mevalonate pathway. Nature. 1990;343(6257):425.
83. Weivoda MM, Hohl RJ. Effects of farnesyl pyrophosphate accumulation on calvarial osteoblast differentiation. Endocrinology. 2011;152(8):3113-22.
84. Yoshida T, Asanuma M, Grossmann L, Fuse M, Shibata T, Yonekawa T, et al. Geranylgeranyl-pyrophosphate (GGPP) synthase is down-regulated during differentiation of osteoblastic cell line MC3T3-E1. FEBS letters. 2006;580(22):5203-7.
85. Ohnaka K, Shimoda S, Nawata H, Shimokawa H, Kaibuchi K, Iwamoto Y, et al. Pitavastatin enhanced BMP-2 and osteocalcin expression by inhibition of Rho-associated kinase in human osteoblasts. Biochemical and biophysical research communications. 2001;287(2):337-42.
86. Tsuji K, Bandyopadhyay A, Harfe BD, Cox K, Kakar S, Gerstenfeld L, et al. BMP2 activity, although dispensable for bone formation, is required for the initiation of fracture healing. Nature genetics. 2006;38(12):1424.
87. Lissenberg-Thunnissen SN, de Gorter DJ, Sier CF, Schipper IB. Use and efficacy of bone morphogenetic proteins in fracture healing. International orthopaedics. 2011;35(9):1271.
88. Smith DM, Cooper GM, Mooney MP, Marra KG, Losee JE. Bone morphogenetic protein 2 therapy for craniofacial surgery. Journal of Craniofacial Surgery. 2008;19(5):1244-59.
89. Shapira KE, Ehrlich M, Henis YI. Cholesterol depletion enhances TGF-β Smad signaling by increasing c-Jun expression through a PKR-dependent mechanism. Mol Biol Cell. 2018;29(20):2494-507.
90. Madel MB, Ibanez L, Wakkach A, de Vries TJ, Teti A, Apparailly F, et al. Immune Function and Diversity of Osteoclasts in Normal and Pathological Conditions. Front Immunol. 2019;10:1408.
91. Park JH, Lee NK, Lee SY. Current Understanding of RANK Signaling in Osteoclast Differentiation and Maturation. Mol Cells. 2017;40(10):706-13.

92. Harre U, Georgess D, Bang H, Bozec A, Axmann R, Ossipova E, et al. Induction of osteoclastogenesis and bone loss by human autoantibodies against citrullinated vimentin. J Clin Invest. 2012;122(5):1791-802.
93. Bellido T, Plotkin LI, Bruzzaniti A. Bone cells. Basic and applied bone biology: Elsevier; 2019. p. 37-55.
94. Lacey DL, Timms E, Tan HL, Kelley MJ, Dunstan CR, Burgess T, et al. Osteoprotegerin ligand is a cytokine that regulates osteoclast differentiation and activation. Cell. 1998;93(2):165-76.
95. Huang T-b, Li Y-z, Yu K, Yu Z, Wang Y, Jiang Z-w, et al. Effect of the Wnt signal-RANKL/OPG axis on the enhanced osteogenic integration of a lithium incorporated surface. Biomaterials science. 2019;7(3):1101-16.
96. Sodek J, Mckee MD. Molecular and cellular biology of alveolar bone. Periodontology 2000. 2000;24(1):99-126.
97. Boyce BF, Hughes DE, Wright KR, Xing L, Dai A. Recent advances in bone biology provide insight into the pathogenesis of bone diseases. Laboratory investigation; a journal of technical methods and pathology. 1999;79(2):83-94.
98. Yavropoulou MP, Yovos JG. Osteoclastogenesis--current knowledge and future perspectives. Journal of musculoskeletal & neuronal interactions. 2008;8(3):204-16.
99. Ruan F, Zheng Q, Wang J. Mechanisms of bone anabolism regulated by statins. Bioscience reports. 2012;32(6):511-9.
100. Boyce BF, Xiu Y, Li J, Xing L, Yao Z. NF-κB-Mediated Regulation of Osteoclastogenesis. Endocrinol Metab (Seoul). 2015;30(1):35-44.
101. Kang JH, Ko HM, Moon JS, Yoo HI, Jung JY, Kim MS, et al. Osteoprotegerin expressed by osteoclasts: an autoregulator of osteoclastogenesis. J Dent Res. 2014;93(11):1116-23.
102. Kaji H, Kanatani M, Sugimoto T, Chihara K. Statins modulate the levels of osteoprotegerin/receptor activator of NFkappaB ligand mRNA in mouse bone-cell cultures. Hormone and metabolic research = Hormon- und Stoffwechselforschung = Hormones et metabolisme. 2005;37(10):589-92.

103. Ahn KS, Sethi G, Chaturvedi MM, Aggarwal BB. Simvastatin, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, suppresses osteoclastogenesis induced by receptor activator of nuclear factor-kappaB ligand through modulation of NF-kappaB pathway. International journal of cancer. 2008;123(8):1733-40.

104. Franzoso G, Carlson L, Xing L, Poljak L, Shores EW, Brown KD, et al. Requirement for NF-kappaB in osteoclast and B-cell development. Genes & development. 1997;11(24):3482-96.

105. Moon HJ, Kim SE, Yun YP, Hwang YS, Bang JB, Park JH, et al. Simvastatin inhibits osteoclast differentiation by scavenging reactive oxygen species. Experimental & molecular medicine. 2011;43(11):605-12.

106. Agidigbi TS, Kim C. Reactive Oxygen Species in Osteoclast Differentiation and Possible Pharmaceutical Targets of ROS-Mediated Osteoclast Diseases. Int J Mol Sci. 2019;20(14).

107. Fujita H, Ochi M, Ono M, Aoyama E, Ogino T, Kondo Y, et al. Glutathione accelerates osteoclast differentiation and inflammatory bone destruction. Free radical research. 2019;53(2):226-36.

108. Boyce BF, Yao Z, Xing L. Osteoclasts have multiple roles in bone in addition to bone resorption. Critical reviews in eukaryotic gene expression. 2009;19(3):171-80.

109. Li X, Song QS, Wang JY, Leng HJ, Chen ZQ, Liu ZJ, Dang GT, Song CL. Simvastatin induces estrogen receptor-alpha expression in bone, restores bone loss, and decreases ERα expression and uterine wet weight in ovariectomized rats. J Bone Miner Metab. 2011 Jul;29(4):396-403.

110. Wang JW, Xu SW, Yang DS, Lv RK. Locally applied simvastatin promotes fracture healing in ovariectomized rat. Osteoporos Int. 2007 Dec;18(12):1641-50.

111. De Leo V, Morgante G, la Marca A, Lanzetta D, Cobellis L, Petraglia F. Combination of statins and hormone replacement therapy in postmenopausal women is associated with increased bone mineral density. Gynecol Endocrinol. 2003 Aug;17(4):329-32.

112. Mullen CA, Haugh MG, Schaffler MB, Majeska RJ, McNamara LM. Osteocyte differentiation is regulated by extracellular matrix stiffness and intercellular separation. Journal of the mechanical behavior of biomedical materials. 2013;28:183-94.

113. Neve A, Corrado A, Cantatore FP. Osteocytes: central conductors of bone biology in normal and pathological conditions. Acta Physiologica. 2012;204(3):317-30.

114. Kular J, Tickner J, Chim SM, Xu J. An overview of the regulation of bone remodelling at the cellular level. Clinical biochemistry. 2012;45(12):863-73.

115. Heino TJ, Kurata K, Higaki H, Vaananen HK. Evidence for the role of osteocytes in the initiation of targeted remodeling. Technology and health care : official journal of the European Society for Engineering and Medicine. 2009;17(1):49-56.

116. Bonewald LF. The amazing osteocyte. Journal of Bone and Mineral Research. 2011;26(2):229-38.

117. Plotkin LI, Bellido T. Osteocytic signalling pathways as therapeutic targets for bone fragility. Nature Reviews Endocrinology. 2016;12(10):593.

118. Fulzele K, Krause DS, Panaroni C, Saini V, Barry KJ, Liu X, et al. Myelopoiesis is regulated by osteocytes through Gsalpha-dependent signaling. Blood. 2013;121(6):930-9.

119. Pajevic PD, Krause DS. Osteocyte regulation of bone and blood. Bone. 2019;119:13-8.

120. Luan Z, Chase AJ, Newby AC. Statins inhibit secretion of metalloproteinases-1, -2, -3, and -9 from vascular smooth muscle cells and macrophages. Arterioscler Thromb Vasc Biol. 2003;23(5):769-75.

121. Tahamtan S, Shirban F, Bagherniya M, Johnston TP, Sahebkar A. The effects of statins on dental and oral health: a review of preclinical and clinical studies. J Transl Med. 2020;18(1):155.

122. Yoon HE, Lim SW, Piao SG, Song JH, Kim J, Yang CW. Statin upregulates the expression of klotho, an anti-aging gene, in experimental cyclosporine nephropathy. Nephron Exp Nephrol. 2012;120(4):e123-33.

123. Tai IC, Wang YH, Chen CH, Chuang SC, Chang JK, Ho ML. Simvastatin enhances Rho/actin/cell rigidity pathway contributing to mesenchymal stem cells' osteogenic differentiation. International journal of nanomedicine. 2015;10:5881-94.

Figure 1

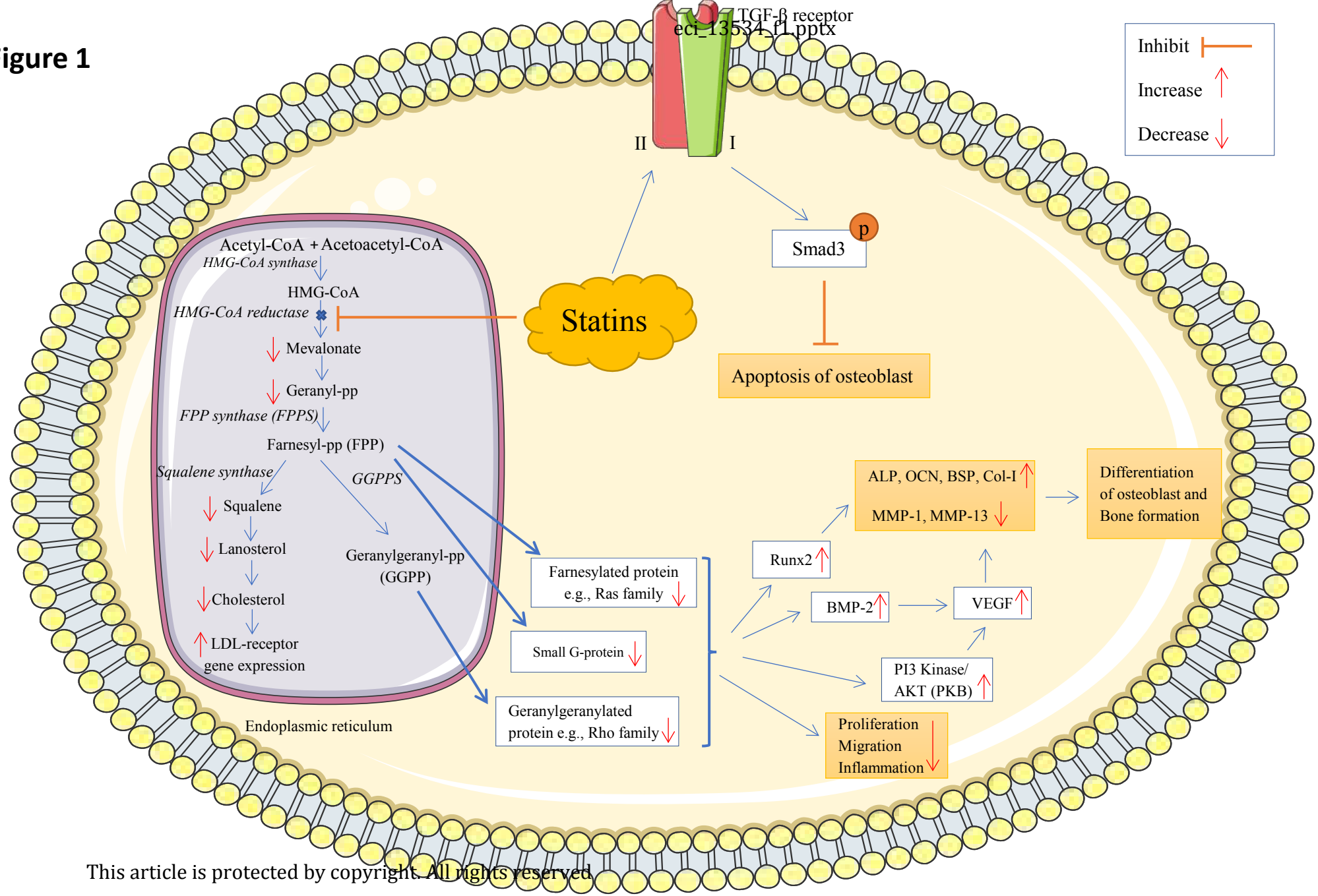

Figure 2