A Comprehensive Review of the Pharmacology of Statins and its Clinical Implications

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Abstract

Statins are commonly prescribed medications used to lower cholesterol levels and reduce the risk of heart attacks. Recent data suggest that statins also play a role in regulating bone metabolism by stimulating the formation of new bone tissue, both in laboratory studies (in vitro) and in living organisms (in vivo). Among statins, simvastatin has emerged as particularly effective in promoting the activity of bone morphogenetic protein-2 (BMP-2), a key factor in the differentiation of osteoblasts, the cells responsible for bone formation. Furthermore, simvastatin inhibits the production of mevalonate and isoprenoids, compounds crucial for the formation of osteoclasts, the cells involved in bone resorption. This dual action of simvastatin, promoting bone formation while inhibiting bone resorption, suggests its potential as a therapeutic agent for bone regeneration, particularly in the context of dental implants and the treatment of osteoporosis. The aim of this article is to review existing literature on the effects of simvastatin, with a primary focus on its role in promoting BMP-2 activity and its effects on bone formation, especially in patients with diabetes mellitus undergoing dental implantation. An electronic search of the MEDLINE-PubMed database was conducted up to December 2008 to identify relevant in vitro studies investigating the effects of statins on BMP-2 production, as well as in vivo studies evaluating the effects of statins on bone formation and preservation. The majority of reviewed investigations focused on simvastatin as the representative statin agent. These studies generally supported the hypothesis that simvastatin possesses osteoinductive properties mediated through BMP-2 and exerts osteoprotective effects by inhibiting osteoclast activation. Overall, simvastatin shows promise as a potential therapeutic agent for inhibiting and treating bone resorption, offering potential benefits for patients requiring bone regeneration procedures such as dental implantation.

Keywords: Antiresorptive drugs, Bone regeneration, Dental Implants, Diabetes, Osseointegration, Simvastatin

Significance | The study aims to provide a detailed understanding of statins, their pharmacodynamics, and the various types involved as beneficial agents in the treatment of bone resorption and hypercholesterolemia.

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Introduction

The success of implants for replacing missing teeth depends on bone-to-implant contact (BIC), which is influenced by patient-related factors and the degree of osseointegration. Diabetes mellitus (DM) is a systemic disease generally considered a relative contraindication for dental implants. The hyperglycemic effect of diabetes mellitus affects bone-to-implant contact, altering bone remodeling processes and mineralization and leading to altered osseointegration. In dental implant therapy for patients with

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diabetes and counteracting the bone remodeling process, antiresorptive drugs (ARD) play a major role. Simvastatin (SV) is an antiresorptive drug that counteracts bone resorption, and osteoblast function is improved by inhibiting osteoclasts' differentiation and normal function (OCLs), thereby increasing their apoptosis. Simvastatin, with the commercial name Zocor, is made artificially from an Aspergillus terreus fermentation product (Rollini, M. M., M, 2002). It fits the statin class of tablets, which help attain irregular lipid levels and reduce further risk of cardiovascular disease (Duan Y., Gong K, et al., 2022). The hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase is an enzyme associated with lipid, cholesterol metabolism, and low-density lipoprotein (LDL), which is competitively inhibited by statin medications (Sirtori, C. R, 2014). In case of cardiovascular events for persons with a risk of developing cardiovascular disease, like diabetes, statin medications are generally prescribed (Chauvin, B., Drouot, S., et al, 2013). Simvastatin and other statin medications like atorvastatin are other options for treating dyslipidemia (Liao, J. K., & Laufs, U., 2005). More hydrophilic statins like pravastatin and rosuvastatin enter endothelial cells through the OATP1B1 (organic anion transporter protein 1B1).

In contrast, the more lipophilic statins like simvastatin reach the endothelial cells by passive diffusion (Elsby, R., et al 2012, Murphy, C., et al 2020, Ayukawa, Y, et al, 2004). Statins can increase the nature of osseointegration for dental implants (Mundy, G., Garrett, R., Harris, S, et al, 1999). The regenerative ability of the statin group on bone regeneration developed in animal studies with weak bones in a strive to find novel oral biosynthesis medications (Ho, C. K. M., & Walker, S. W, 2011). Therefore, the current review objectives are to assess the pharmacodynamics and the various uses of simvastatin in bone regeneration.

Methodology

The current review followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) criteria. (Figure 1)

The literature available between the years 1999 and 2022, was explored by four self-determining investigators from PubMed, Google Scholar, ScienceDirect, LILACS, IndeMED, OVID, EMBASE, and NIH Clinical Trials for reports related to simvastatin. The following keywords were used to develop the search strategy, ((Antiresorptive drugs AND Bone regeneration, Dental Implants, Diabetes, Osseointegration AND Simvastatin)). The academic work types comprised human studies, in vitro, and reviews concerning statins. The eligible criteria for the review were all studies on the outcome of simvastatin on bone-implant contact following dental implantation in diabetic patients. Relevant original and review articles were searched for the pharmacodynamics and various uses of the statin family, simvastatin, and osseointegration.

Results

The statin family reduces high cholesterol and triglyceride levels in the blood. It acts by raising the high-density lipoprotein-cholesterol (HDL-C) concentrations besides lowering the low-density lipoprotein-cholesterol (LDL-C) (Tremblay, A. J., Lamarche, B., Hogue, J.-C., et al, 2009). Plasma concentrations of high triglyceride (TG) and other forms of cholesterol are linked to a bigger hazard of cardiovascular disease and atherosclerosis (de Fost, M., Langeveld, M., Franssen, R., et al, 2009). Calculating the overall fat to HDL-C is a good indicator of ischemic heart disease, and increased percentages remain linked to a developed risk of the condition. Lower cardiovascular risk is related to advanced HDL-C levels (Fernandez, M. L., & Webb, D. 2008). Using the family of statins to reduce the percentage of LDL has been proven by several studies to reduce cardiovascular disease (Adams, S. P., Sekhon, S. S., & Wright, J. M, 2014). The increased LDL levels remain the most common risk factor towards the progress of cardiovascular disease (CVD). Their evidence towards reducing mortality, statins are the choice for CVD (Wang, Y., Lammi-Keefe, C. J., Hou, L., & Hu, G, 2013). Statins have been shown to decrease the complications of cardiovascular disease by 20-22% for every 1 mmol/L reduction in LDL, even in low-risk individuals (Sattar, N., Wannamethee, G., Sarwar, N, et al, 2006). Sometimes, simvastatin causes myopathy, categorized by muscle discomfort and creatine kinase (CK) levels (Stroes, E. S., Thompson, P. D., Corsini, A., et al, 2015). Rhabdomyolysis due to myoglobinuria is one appearance of myopathy, and fatalities are uncommon (Torres, P. A., Helmstetter, J. A., Kaye, A. M., & Kaye, A. D, 2015). Female gender, uncontrolled hypothyroidism, advanced age (65 years), and renal impairment are all risk factors for myopathy. Myopathy may also be more common in Chinese patients. During treatment, when abruptly stopped, muscle signs and CK elevations classically disappeared (Biondi, B., Kahaly, G. J., & Robertson, R. P., 2019). At 20 mg/day and 40 mg/day, the frequency related to muscle illness was almost 0.03% and 0.08%, respectively, in various research records of 41,431 affected populations. However, the risk of muscle disease with simvastatin 80 mg (0.61%) was significantly higher than at the smaller dosages. Hence, individuals having simvastatin of 80 mg frequently without evidence of muscle toxicity should only use this dose of simvastatin. Patients who are previously stable on 80 mg of simvastatin should also be watched for symptoms of muscle toxicity (Hopewell, J. C., Offer, A., Haynes, R., et al, 2020). If a patient is essential to start treatment with a drug that interacts with simvastatin and is contraindicated or has a dose cap, they should change to a dissimilar statin with a lower risk of drug interactions (NEUVONEN, P., NIEMI, M., & BACKMAN, J, 2006). Simvastatin treatment might upsurge the risk of myopathy if cyclosporine, fenofibrate, niacin, gemfibrozil, strong CYP3A4 inhibitors, and

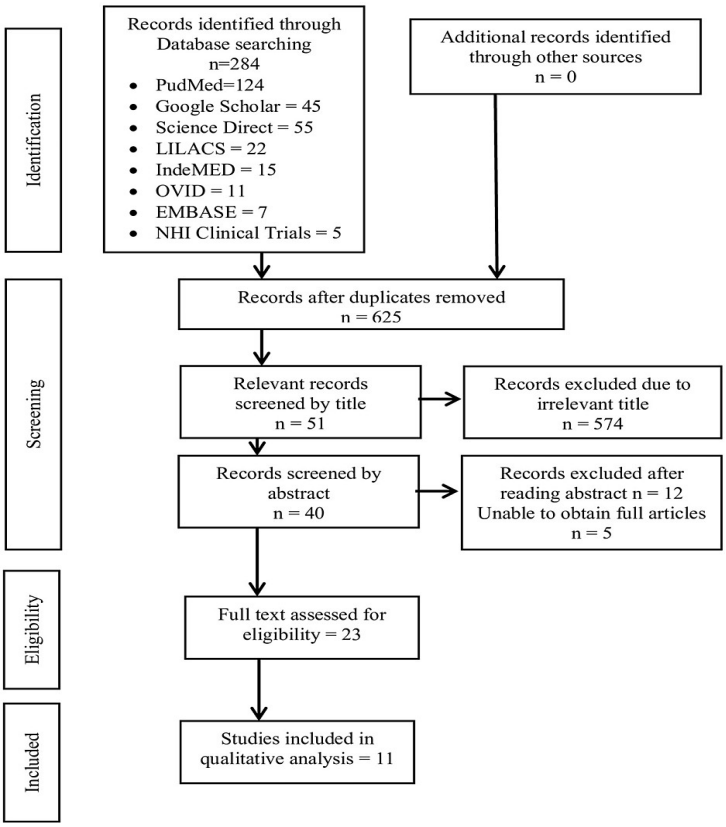

Figure 1. Prisma Flow Chart. The current review adhered to the PRISMA criteria. Literature from 1999 to 2022 was examined by four independent investigators across multiple databases: PubMed, Google Scholar, ScienceDirect, LILACS, IndeMED, OVID, EMBASE, and NIH Clinical Trials. The search strategy used the keywords: ((Antiresorptive drugs AND Bone regeneration, Dental Implants, Diabetes, Osseointegration AND Simvastatin)). The review included human studies, in vitro research, and reviews on statins. Eligibility criteria focused on studies examining the effect of simvastatin on bone-implant contact in diabetic patients post-dental implantation. Relevant articles on the pharmacodynamics and various applications of the statin family, simvastatin, and osseointegration were included.

other interacting medications are taken at the same time (Radcliffe, K. A., & Campbell, W. W. 2008). Patients affected by both muscle disease and rhabdomyolysis are noticed to have HMG-CoA reductase inhibitors co-administered with colchicine (Kapur, N, 2008). In clinical studies, around 1% of patients who received simvastatin experienced increased serum transaminases that surpassed the ULN by over three times (Hyyppä, M. T., Kronholm, E., Virtanen, A, 2003). Transaminase levels typically returned to normal in these patients when simvastatin was withdrawn. There was no connection between the increases or any other clinical features. The statin family, such as simvastatin, has been linked to fasting serum glucose and HbA1c rises. Research has proven that simvastatin has no effect on the process of cholesterol converting to steroid hormones (Wang, H. H., Portincasa, P., de Bari, O., et al 2013). Simvastatin did not raise biliary pathogenicity, so it would not be expected to make gallstones more common (Elavarasu, S., Naveen, D., Nagarathinam, U., et al, 2012). Diabetes mellitus (DM), clinical atherosclerosis (acute coronary syndromes, trans ischemic attack (TIA), stomach aortic aneurysm, kidney infection, and seriously raised LDL-C levels are the common conditions that are suggested for therapy with statins. Simvastatin drugs are synthetic statins with several pleiotropic effects and their slowing of resorption of bone actions. These effects have increased the bone density in diabetes patients who were given statins systemically, improving levels of cholesterol (Maeda, T., Kawane, T., & Horiuchi, N, 2003). These statin family, namely, compactin and pitavastatin improve the differentiation of embryonic stem cells into osteoblasts and upregulate expression for bone morphogenic protein 2 (BMP-2) and osteocalcin by reduction of mevalonate (Pagkalos, J., Cha, J. M., Kang, Y., et al, 2010). The studies on the effect of simvastatin on osteosarcoma cells suggest that they urge bone morphogenic protein 2 (BMP-2), by using reverse transcription polymerase chain reaction (RT-PCR), and alkaline phosphatase assay (ALP) (Sugiyama, M., Kodama, T., Konishi, K, et al, 2000). One study investigated the bone mineral density (BMD) of the femoral bone and quantitative bone histomorphometry (QBH) in simvastatin by placebo surgery and ovariectomized rats, which was related to controls (Maritz, F. J., Conradie, M. M., et al. 2001). The study showed that simvastatin produced a marked percent increase in osteoid volumes, osteoid surfaces, and osteoblast numbers when compared with the control group. Maeda T et al in the year 2003, studied the simvastatin effects on vascular endothelial growth factor (VEGF) expression in MC3T3-E1 cells (a clonal preosteoblastic cell line derived from newborn mouse calvaria). The author concluded that statins stimulate VEGF expression in osteoblasts via reduced protein prenylation and the phosphatidylinositide-3 kinase pathway, promoting osteoblastic differentiation. A study proved the effects of simvastatin on osteogenesis around titanium implants in the tibiae of rats (Moriyama, Y., Yasunori Ayukawa, Ogino, Y., et al, 2008). The result has proven that on histometrical observations, the bone density of the study group was remarkably greater than the control groups, suggesting that simvastatin improved osseointegration around dental implants. Ruiz-Gaspa S et al in the year 2007, assessed the effect of simvastatin and atorvastatin on osteoblast activity by analyzing cell proliferation, as well as collagen, osteocalcin, and bone morphogenetic protein-2 (BMP2) gene expression in primary human osteoblast (hOB) and MG-63 cell line cultures (Ruiz-Gaspa, S., Nogues, X., Enjuanes, A., et al, 2007). The authors concluded that in the simvastatin-treated cells at concentrations of 10(-9) M, 10(-8) M, 10(-7) M, and 10(-6) M), there was elevated levels of osteocalcin and BMP2 gene expression. In another study by Suthanthiran et al in 2012, using osteoblast-like SaOS-2 cells found increased bone mineral density in diabetes mellitus patients who were given statins systemically for the improvement of increased cholesterol levels. In vitro, evaluation of simvastatin on MG63 cell lines proved that they function as a modulator of osteoclastogenesis/osteogenesis (A. Magan-Fernandez, Fernández-Barbero, J. E., et al., 2017). Morse et al. (2018) conducted a meta-analysis review of current literature exploring the mechanisms underlying the putative osteoprotective effects of statins. They reviewed recent clinical studies, ranging from observational cohort studies to randomized clinical trials, testing the effect of statins on bone health in various populations. The article reveals that the remodeling index (ratio of C-telopeptide to osteocalcin) was reduced, suggesting reduced bone resorption compared to formation (Morse, L. R., Coker, J., & Battaglino, R. A., 2018). Various authors proposed that statin drug stimulates bone formation. The review article by Mori et al, explains how statins affect bone regeneration and increase the formation of new bone caused by osteoprotegerin creation with bone morphogenic protein 2 (BMP-2) (Mori, M., Nishikawa, T., Kazuya Masuno, et al, 2010). Further, the utilization of HMG-CoA reductase inhibitors is contraindicated in patients with liver disease or unexplained, constant elevations of serum transaminases. The liver broadly utilizes HMG-CoA reductase inhibitors. Reduced metabolism of the drug might prompt collection and increased toxicity, including biochemical anomalies of the liver and jaundice, hepatitis, cirrhosis, fatty composition change in the liver, and hepatic necrosis. Treatment with HMG-CoA reductase inhibitors ought to be regulated in patients with a medical complication of liver disease or potentially high liquor use. A lower starting dose might be appropriate, and clinical observation of liver transaminase levels in patients. Even though the kidney does not eliminate simvastatin, the plasma concentration of HMG-CoA reductase inhibitors after a single dosage of simvastatin increased in patients with critical renal impairment due to the accumulation of active drug metabolites. An increased level of HMG-CoA reductase inhibitory action might be related to a more serious risk of side effects, including hepatic and

muscular-skeleton toxicity. Treatment with simvastatin ought to be managed carefully at a decreased dosage in patients with extreme renal impairment. Certain HMG-CoA reductase inhibitors raise the HbA1c level when using these agents on diabetic patients. Further, in treatment with simvastatin, some authors have found high levels of osteocalcin and bone alkaline phosphatase, indicating increased bone formation (Ho-Ming Chan, M., Mak, T. W.-L., Chiu, et al, 2001). The use of HMG-CoA reductase inhibitors like simvastatin in patients with severe renal impairment or end-stage renal disease necessitates a lower dosage. Simvastatin also affected the alkaline phosphatase and RT-PCR assay of human osteosarcoma cells in experiments. The results suggested that statins have positive results in managing implant osseointegration. The results indicated that simvastatin can increase and maintain a high level of osteoblastic function.

Conclusion

Among various uses of statins, the process by which they affect bone formation is an important subject. The anti-resorptive nature of statins is attained by inhibiting the mevalonate pathway, which is concerned with cholesterol synthesis and the formation of compounds required for osteoclast activation. Statins, by blocking this important HMG-CoA reductase path, act to lessen bone resorption. Simvastatin drugs are synthetic statins with several pleiotropic effects in addition to their antiresorptive actions. Therefore, the conclusions for this review study are based mainly on research records produced from models utilizing simvastatin. More research is needed on the long-term effectiveness and safety of the widely used statins.

Author contributions

A.I., G.V.V., D.A., A.L.M., J.D., M.S., developed the Study design, and wrote, reviewed, and edited the paper.

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Competing financial interests

The authors have no conflict of interest.

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