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Influence of Statins on Bone Regeneration in Dental Implantology in Hyperlipidemia: A Systematic Review

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Abstract

Statins belong to the class of hypolipidemic drugs, which are the first-line therapy for atherosclerosis, reducing cholesterol and LDL levels in the blood. They are the most studied and safe class of drugs used in the prevention of cardiovascular diseases (CVD), significantly reducing mortality from heart attacks and strokes. It has been found that patients with high lipid levels in the blood have poorer osseointegration of dental implants. Literature data indicate a direct relationship between high lipid levels in the blood and bone resorption due to intermediate products of cholesterol synthesis, slowing bone regeneration. This study examined the influence of statins on implant osseointegration. Articles describing experiments on animals with induced hyperlipidemia using a special diet were analyzed. The results of all the studies we reviewed showed that statins not only reduced hypercholesterolemia levels but also stimulated osteogenesis around the implant by stimulating osteoblasts and inhibiting their apoptosis, as well as inhibiting osteoclasts. Thus, statins can be considered as new, safe, inexpensive, and widely available therapeutic agents to improve implant osseointegration and overall patient quality of life.

Keywords*: hyperlipidemia, statins, bone implant, bone regeneration, simvastatin, osteogenesis*

1. Introduction

Osseointegration is the process of bonding an implant with the jawbone. For successful dental implantation, the process of osteogenesis is crucial, which involves the formation of bone tissue around the implant. Effective osteogenesis plays a key role in implant osseointegration, which depends on several factors: the surgical procedure technique, the patient's health condition, including any existing chronic diseases. According to the World Health Organization (WHO), cardiovascular diseases are the leading cause of death worldwide. Ischemic heart disease (IHD), associated with impaired blood flow through the coronary arteries, can lead to the development of heart attacks or strokes, the causes of which include atherosclerosis.

Atherosclerosis is a chronic vascular disease characterized by the formation of atherosclerotic plaques, the modifiable factor of which is hyperlipidemia.

Hyperlipidemia (HL) is a condition characterized by the deviation of one or more lipid levels in the blood from reference values. Assuming that target lipid values are based on an individual's cardiovascular risk profile, more than half of the population has excessively high levels of LDL cholesterol. Lowering LDL levels reduces the risk of cardiovascular complications (myocardial infarction, stroke, and cardiovascular death). Factors that may contribute to the development of hyperlipidemia include a diet high in saturated or trans fats, lack of physical exercise, nicotine consumption, and obesity (Mozaffarian D et al., 2016; Karr S, 2017). Secondary causes include conditions such as chronic kidney disease, type 2 diabetes mellitus, arterial hypertension, and hypothyroidism. Medications such as glucocorticoids can also lead to increased LDL levels (Stone N et al., 2017). Inherited forms of hypercholesterolemia, which are part of primary hyperlipidemias, also contribute to elevated cholesterol levels. They stem from mono- or polygenetically inherited defects, the severity of which may be exacerbated by exogenous factors such as poor diet or medication intake.

The current recommendations of the American Heart Association (AHA) and the American College of Cardiology (ACC) strongly advocate for pharmacological reduction of lipid levels (Alenghat F et al., 2019; Grundy S et al., 2017). The goal of secondary prevention after a cardiovascular event is a relative reduction in LDL cholesterol levels by at least 50% and, depending on the corresponding risk profile, an absolute reduction in LDL cholesterol levels to below 70 mg/dL. For primary prevention, adapted to the risk, relative and absolute reductions in LDL cholesterol are indicated for patients with LDL cholesterol levels ≥190 mg/dL or those with a corresponding cardiovascular risk profile and LDL cholesterol levels ≥70 mg/dL. A healthy lifestyle is strongly recommended for people of all ages. A diet rich in vegetables, fruits, nuts, fish, and dairy products has shown high effectiveness in preventing cardiovascular complications (CC) (Eckel R et al., 2013). Consumption of fish and omega-3 polyunsaturated fatty acids twice a week reduces the risks of CC (Mozaffarian D et al., 2013). Statins are a class of drugs that inhibit a crucial step in cholesterol biosynthesis by competitively inhibiting the enzyme HMG-CoA reductase (3-hydroxy-3-methylglutaryl-coenzyme A reductase), thereby reducing lipid levels (Collins R et al., 2016). Due to their high effectiveness and good tolerability, statins are the first-choice drugs for treating hyperlipidemia. The effectiveness depends on the patient's cardiovascular risk profile and the achieved reduction in LDL cholesterol. Overall, adverse effects with statin therapy occur less frequently than with lipid-lowering drugs from other drug classes. However, it is worth mentioning skeletal muscle-related side effects such as myalgia, myopathy, myositis, and muscle injuries (Stroes E et al., 2015; Rosenson R et al., 2017). However, severe myonecrosis with concomitant rhabdomyolysis is very rare and occurs in approximately 0.1% of patients (Graham D et al., 2004). Severe liver dysfunction is another dangerous side effect, but the risk appears to be very low. Although statin therapy may lead to elevated transaminase levels, the frequency of statin-associated liver failure during drug monitoring was only about 1 in 100,000 patients, although it remains unclear whether there was a specific causal relationship (Björnsson E et al., 2012). Ultimately, the positive impact of statins on preventing cardiovascular events and mortality outweighs both in randomized and observational studies, especially in high-risk patient groups (Ridker P et al., 2012). In recent years, there has been increasing evidence of the influence of statins on osteogenesis.

2. Materials and Methods

Selection of Scientific Publications

Medical research served as the basis for analyzing this topic. Studies were conducted using global web-based databases such as Google Scholar, Scopus, Medline, PubMed, as well as the Russian Scientific Electronic Library Cyberleninka. The literature search process involved the following terms: hyperlipidemia, cardiovascular diseases, statins, bone resorption, alveolar bone, bone implant, experimental studies, implant osseointegration, osteogenesis, animal experiments. Studies describing experiments conducted on humans and animals, published in English, were examined.

Selection Criteria

The inclusion criteria for scientific articles were studies on animals demonstrating the positive influence of local or systemic statins on the osseointegration of dental implants. Articles describing in vitro studies, reviews, and studies on animals with systemic diseases (except hyperlipidemia induced artificially) were not included in this work, as their presence may distort the experimental results. Thus, 5 scientific publications were selected that met all the specified criteria.

3. Results

Mechanism of Action of Statins on Osteogenesis

To understand the influence of statins on osteogenesis, it is necessary to consider the mechanism of cholesterol synthesis, which consists of several stages (Figure 1).

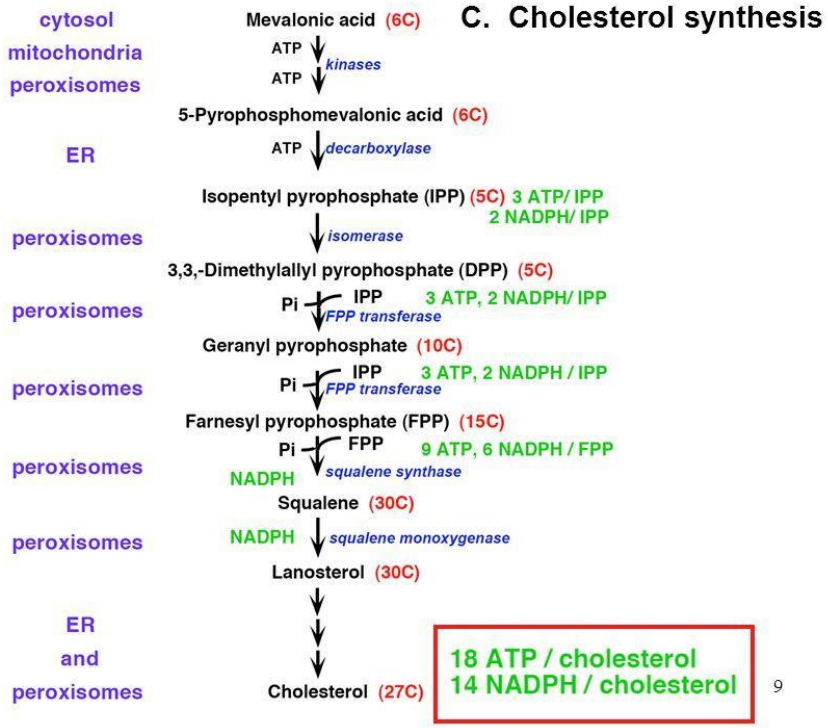

Figure 1: *Cholesterol Synthesis*

It has been established that bone and vascular tissues share a number of common morphological and molecular properties. Activation of osteoclasts occurs with the involvement of intermediate products of cholesterol synthesis - farnesyl pyrophosphate and geranyl pyrophosphate, which leads to bone tissue destruction. The formation of osteoclast-activating products can be effectively limited in vitro by statins, which inhibit the production of mevalonic acid. Statins induce osteoclast apoptosis, thereby slowing down the bone resorption process (Oryan A et al., 2015).

Another mechanism through which statins can influence the mineral composition of the skeleton is the activation of bone morphogenetic protein-2 (BMP-2) promoter - a growth factor

that promotes the proliferation and maturation of osteoblasts. However, this mechanism is characteristic only of lipophilic statins such as simvastatin, fluvastatin, and lovastatin, while the hydrophilic pravastatin did not show activation of BMP-2.

In addition, statins inhibit osteoblast apoptosis through the TGFβ/Smad3 signaling pathway. Osteoblasts are cells that contribute to bone tissue formation. Apoptosis of osteoblastic cells leads to an imbalance between bone formation and resorption processes. Transforming growth factor beta (TGFβ) activates the Smad3 protein, which stimulates the synthesis of protein and alkaline phosphatase activity, thereby promoting osteogenesis (Krstic, J et al., 2014). Simvastatin, pitavastatin, and mevastatin induce the expression of Smad3 protein, inhibiting the process of osteoblast apoptosis.

Thus, statins stimulate osteogenesis through the following pathways (Figure 2):

1. Stimulate osteoblast differentiation;
2. Inhibit osteoblast apoptosis;
3. Inhibit osteoclast activation (Oryan A et al., 2015).

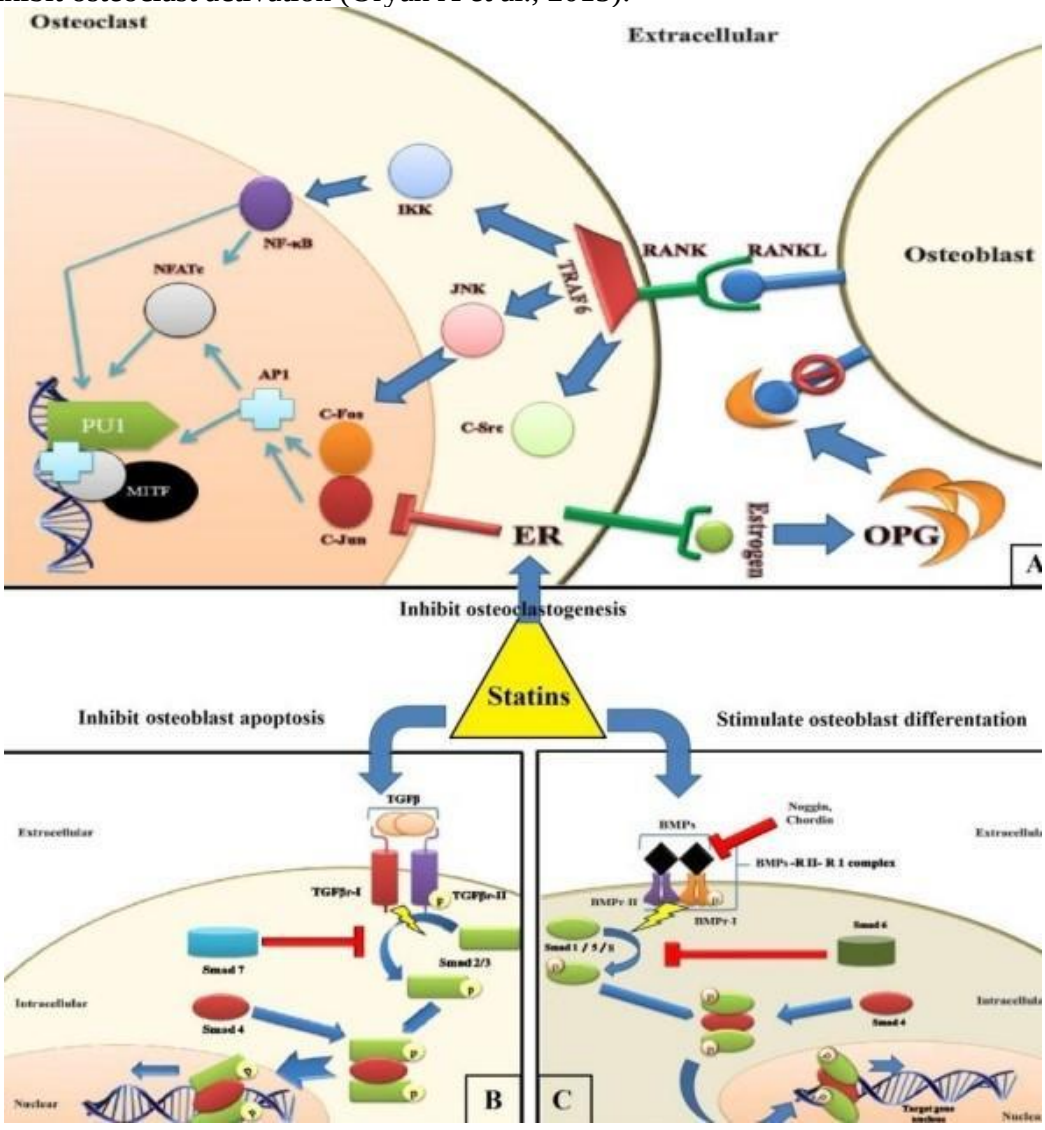

Figure 2: *Mechanism of Action of Statins on Osteogenesis*

The Influence of Statin Intake on Implant Osseointegration

Studies evaluating the effect of statin drugs on implant osseointegration in experimental animals were analyzed (Table 1). The results of the studies were obtained through

immunohistochemical and histomorphometric analyses, comparing the control group with the experimental groups. All studies demonstrated a positive effect of statins on the integration of dental implants with bone tissue both with local and oral administration. Additionally, the formation of bone tissue around the implant was observed due to the mechanisms described earlier.

Table 1: Influence of Statins on Implant Osseointegration (Review of Articles)

Author, Year	Study Type	Sample	Statins	Daily Dose	Duration of Experiment	Method of Administration	Results
Moriyama et al., 2008	Animal Testing: Rats	60	Fluvastatin	3, 15, 75 mcg (depending on the group)	2 weeks	Local	Enhancement of osteogenesis and implant integration
Moriyama et al., 2010	Animal Testing: Rats	60	Fluvastatin	3, 15, 75, 300 mcg (depending on the group)	4 weeks	Local	Enhancement of osteogenesis and implant integration
Tan et al., 2015	Animal Testing: Rats	48	Simvastatin	5, 10 mg (depending on the group)	4 weeks	Local	A single local injection of simvastatin improved osseointegration and implant fixation
Gao et al., 2021	Animal Testing: Rats	30	Simvastatin	5 mg/kg	8 weeks	Oral	Stimulation of osteogenesis and activation of BMP-2
Öztürk et al., 2023	Animal Testing: Rabbits	16	Atorvastatin	10 mg/kg	8 weeks	Oral	The use of atorvastatin showed positive results in bone healing compared to the control group

Despite the positive results, further preclinical studies are needed to investigate the influence of statins on the process of implant osseointegration with jawbone in hyperlipidemia, as several studies have shown a small sample size (for example, Kübra et al., 2023), which may not provide statistically significant results in clinical trials. Additionally, for conducting clinical trials in humans, it is necessary to choose the optimal route of statin administration, determine the required dosage (depending on local or systemic action), and take into account the health condition of the subjects, as the presence of chronic diseases may affect the research outcomes, thus defining selection criteria is essential.

4. Conclusion

Literature data indicate a direct correlation between high lipid levels in the blood and bone resorption. This is associated with intermediate products of cholesterol synthesis - geranyl pyrophosphate and farnesyl pyrophosphate, which stimulate osteoclasts, leading to bone resorption. Analysis of experimental animal studies has shown a positive correlation between statin intake and stimulation of alveolar bone osteogenesis. Mice, rabbits, and rats were used as experimental models, in which hypercholesterolemia was artificially induced by feeding them high-cholesterol diets. The result of feeding was not only induced hypercholesterolemia but also the loss of alveolar bone mass, demonstrating the influence of high cholesterol and lipid levels in the blood on bone destruction. After several weeks on such a diet, animals received statin doses, and at the end of the study, they were compared with a control group that did not receive the drug using histomorphometric and immunohistochemical analyses. The results of all studies reviewed by us have shown that statins not only reduced hypercholesterolemia levels but also stimulated osteogenesis around the implant through mechanisms previously studied by us. However, many studies have limitations due to small sample sizes for clinical trials. Therefore, further research on the influence of statins on implant osseointegration and a detailed examination of their mechanisms of action are necessary. This includes selecting the most effective dosage, determining the ideal duration of action, and selecting specific drugs with a larger sample size. Additionally, it's essential to use not only a negative control group (animals not receiving statins) but also a positive control group (animals receiving a drug with proven efficacy in stimulating osteogenesis) to increase the reliability of research results. Thus, statins can be considered as new, safe, inexpensive, and widely available therapeutic agents for improving implant survival and overall quality of life for patients.

5. References

Alenghat, F.J., Davis, A.M. (2019). Management of Blood Cholesterol. *JAMA*. 321(8), 800-801.

Björnsson, E., Jacobsen and E.I., Kalaitzakis, E. (2019). Hepatotoxicity associated with statins: reports of idiosyncratic liver injury post-marketing. *J Hepatol.* 56(2), 374-380.

Collins, R., Reith, C., Emberson, J., Armitage, J., Baigent, C., Blackwell, L., Blumenthal, R., Danesh, J., Smith, G.D. and DeMets, D. (2016). Interpretation of the evidence for the efficacy and safety of statin therapy. *Lancet (London, England)*. 388(10059), 2532-2561.

Eckel, R.H., Jakicic, J.M. and Ard, J.D. (2013). AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk. *Circulation.* 129(25 suppl 2): S76–S99. https://doi.org/10.1161/01.cir.0000437740.48606.d1

Gao, X., Zhou, J., Bian, Y., Huang, S. and Zhang, D. (2021). Simvastatin intervention mitigates hypercholesterolemia-induced alveolar bone resorption in rats. *Exp Ther Med.*, 628. https://doi.org/10.3892/etm.2021.10060

Graham, D.J., Staffa, J.A., Shatin, D., Andrade, S.E., Schech, S.D., La Grenade, L., Gurwitz, J.H., Chan, K.A., Goodman, M.J. and Platt, R. (2004). Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. *JAMA*. 292(21), 2585-2590.

Grundy, S.M., Stone, N.J., Bailey, A.L., Beam, C., Birtcher, K.K., Blumenthal, R.S., Braun, L.T., de Ferranti, S., Faiella-Tommasino, J. and Forman, D.E. (2019) AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: Executive Summary. *A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines.* 73(24), 3168-3209.

Karr, S. (2017). Epidemiology and management of hyperlipidemia. *Am J Manag Care.* 23(9 Suppl), 139-148.

Krstic, J.F. (2014). Transforming Growth Factor-Beta and Matrix Metalloproteinases: Functional Interactions in Tumor Stroma-Infiltrating Myeloid Cells. *ScientificWorldJournal, Volume 2014*.

Moriyama, Y., Ayukawa, Y., Ogino, Y., Atsuta, I. and Koyano, K. (2008). Topical application of statin affects bone healing around implants. *Clin Oral Implants Res.* 19, 600–605.

Moriyama, Y., Ayukawa, Y., Ogino, Y., Atsuta, I., Todo, M., Takao, Y. and Koyano, K. (2010). Local application of fluvastatin improves peri-implant bone quantity and mechanical properties: a rodent study. *Acta Biomater*.6, 1610–1618.

Mozaffarian, D., Benjamin, E.J., Go, A.S., Arnett, D.K., Blaha, M.J., Cushman, M., Das, S.R., de Ferranti, S., Després, J.P. and Fullerton, H.J. (2016). Heart Disease and Stroke Statistics-2016 Update: A Report from the American Heart Association. *Circulation.* 133(4), 338-360.

Mozaffarian, D., Lemaitre, R.N. and King, I.B. (2013). Plasma Phospholipid Long-Chain ω-3 Fatty Acids and Total and Cause-Specific Mortality in Older Adults. *Ann Intern Med.* 158(7), 515–525. https://doi.org/10.7326/0003-4819-158-7-201304020-00003

Oryan, A., Kamali, A. and Moshiri, A. (2015). Potential mechanisms and applications of statins on osteogenesis: Current modalities, conflicts and future directions. *Journal of Controlled Release*, doi: 10.1016/j.jconrel.2015.07.02

Öztürk, K., Kuzu, T.E. and Ayrıkçil, S. (2023). Effect of systemic atorvastatin on bone regeneration in critical-sized defects in hyperlipidemia: an experimental study. *Int J Implant Dent 9*. 50. https://doi.org/10.1186/s40729-023-00508-9

Ridker, P.M., Pradhan, A., MacFadyen, J.G., Libby, P. and Glynn, R.J. (2012). Cardiovascular benefits and diabetes risks of statin therapy in primary prevention: an analysis from the JUPITER trial. *Lancet (London, England)*. 380(9841), 565-571.

Rosenson, R.S., Baker, S., Banach, M., Borow, K.M., Braun, L.T., Bruckert, E., Brunham, L.R., Catapano, A.L., Elam, M.B. and Mancini, G.B.J. (2017). Optimizing Cholesterol Treatment in Patients with Muscle Complaints. *J Am Coll Cardiol*. 70(10), 1290-1301.

Stone N.J., Robinson J.G., Lichtenstein A.H., Bairey Merz C.N., Blum C.B., Eckel R.H., Goldberg A.C., Gordon D., Levy D. and Lloyd-Jones D.M. (2013). ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 63(25 Pt B), 2889-2934.

Stroes, E.S., Thompson, P.D., Corsini, A., Vladutiu, G.D., Raal, F.J., Ray, K.K., Roden, M., Stein, E., Tokgözoğlu, L. and Nordestgaard, B.G. (2015). Statin-associated muscle symptoms: impact on statin therapy. European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management. *Eur Heart J.* 36(17), 1012-1022.

Tan, J., Yang, N., Fu, X., Cui, Y., Guo, Q., Ma, T., Yin, X., Leng, H. and Song, C. (2015). Single-dose local simvastatin injection improves implant fixation via increased angiogenesis and bone formation in an ovariectomized rat model. *Med Sci Monit.* 18;21, 1428-39. https://doi.org/10.12659/MSM.892247