Chapter

Use of Statins in Dental Implantology and Their Impact on Osseointegration: Animal Studies

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Abstract

Statins are one of the most commonly used drugs for the prevention of atherosclerosis and ischemic heart disease. Statins have an antibacterial effect against oral pathogens, especially against *Aggregatibacter actinomycetemcomitans* and *Porphyromonas gingivalis*. Studies on animals that we analyzed in this chapter show that statins promote angiogenesis and osteoblast differentiation. Data on the effect of statins on the process of osseointegration are important in clinical practice and should be an integral part of dental education. PubMed, Cochrane Central, and Web of Science database search was performed for animal studies on statin effects on dental osseointegration. Fifteen studies performed on laboratory animals were identified where statins were applied systemically, locally, orally, subcutaneously, or intraosseously. Titan implants of different diameters were placed in tibia and femur of animals. Statins improved osseointegration and enhanced contact of implant surface with the newly formed bone, as well as significantly increased the volume of newly formed bone in lab animals. The purpose of this chapter is to prove the relationship between local use of statins and better osseointegration, as well as a larger amount of newly formed bone around the implant. Knowledge of the effect of frequently prescribed medications on dental procedures and osseointegration is necessary for both students and physicians.

Keywords: statins, osseointegration, dental implants, bone and implant contact, bone metabolism

1. Introduction

Atherosclerosis and ischemic heart disease are the most common causes of death in the world. Hyperlipidemia is one of the most important risk factors for the development of diseases of the cardiovascular system. Prevention and treatment are based on lowering the serum concentration of atherogenic lipoproteins and triglycerides. Statins are one of the most commonly used drugs for this purpose. As structural analogs, they inhibit cholesterol synthesis in liver cells by inhibiting the enzyme 3-hydroxy-3-methylglutaryl-CoA (HMGCoA) reductase. People treated with statins generally continue with this therapy for the rest of their lives. Statins consumption is on the rise and in some countries, those drugs can be bought without a prescription [1].

Statins are rapidly absorbed and the maximum plasma concentration is within 4 hours [2]. The optimal time to take a statin is in the evening before bedtime when the synthesis of endogenous cholesterol is most intense [3]. They are metabolized largely by cytochrome P450 (CYP450). This metabolic pathway is particularly important for lipophilic statins that are highly susceptible to oxidative reactions at cytochrome P450 [4]. Elimination after metabolization in the liver is done mainly by bile. Therefore, hepatic dysfunction is a risk factor for statin-induced myopathy. Hydrophilic statins that bypass the metabolic pathway *via* cytochrome P450 are excreted largely unchanged by the liver and kidneys.

Statins are generally well tolerated and serious side effects are very rare. Mild and transient side effects that may occur include bloating, constipation, diarrhea, abdominal pain, general weakness, and dizziness [5].

Caution should be exercised with regard to dental procedures in patients receiving warfarin therapy because statins may increase the concentration of warfarin in plasma and dose adjustment of warfarin is sometimes required [6]. It is important to note that macrolides, although rarely prescribed in dental clinics, can increase plasma statin concentrations and consequently cause myopathy. It is recommended that statins are discontinued during macrolide therapy if treatment with another group of antibiotics is not possible [7].

Statins have an antibacterial effect against oral pathogens, especially against *Aggregatibacter actinomycetemcomitans* and *Porphyromonas gingivalis* [8]. They also have an antifungal effect against *Candida albicans*, *Aspergillus fumigatus*, and Zygomycetes. Statins modulate the immune response to inflammation and sepsis and reduce the CRP inflammatory parameter by reducing the level of inflammatory interleukin 6. They also increase the level of bone morphogenic protein-2 (BMP-2), stimulate osteoblast activity in bone matrix formation, and promote osseointegration of dental implants [9, 10]. There are several factors that may influence implant and osseointegration such as type of implant-abutment connection. Menini et al. do research on internal versus external connections. They measured peri-implant marginal bone level (MBL) changes, plaque index (PI), probing depth (PD), and bleeding on probing (BoP), evaluated at implant insertion and at 3, 6, and 12 months post-loading. After 12 months, both implant connections showed good clinical features, without inflammation or bone resorption [11]. Animal studies have shown that simvastatin promotes angiogenesis, osteoblast differentiation, and periodontal ligament cell development in both topical and systemic administrations. Angiogenesis and fibrinogenesis are prompted by stimulation of vascular endothelial growth factor (VEGF) in a not yet fully elucidated way [12, 13]. Studies in the United States have shown that more than one-third of the adult population over the age of 45 use systemic statin therapy, putting these drugs in a position to be used as essential therapeutics in dentistry, especially in oral surgery, dental implantology, and periodontology [14].

2. Materials and methods of search strategy

2.1 Literature search strategy

The keywords used in the web search were: (1) statins + osseointegration; (2) statins + implants; (3) statins + implants + osseointegration; (4) BIC + statins; (5) BIC + statins + osseointegration; (6) simvastatin + osseointegration; (7) simvastatin +

implants; (8) rosuvastatin + osseointegration + implants; (9) fluvastatin + osseointegration; and (10) fluvastatin + implants (**Figure 1**).

Keywords were entered into PubMed, Cochrane Central, and Google Scholar databases. The search inclusion criteria were published studies from the creation of the databases to the end of April 2021. Articles that do not have English abstract with the following keywords were eliminated: statins + endodontics, statins + pulpitis, statins + direct pulp coverage, and statins + stem cells. This was done by reviewing the reference list of included articles to identify the potential of an acceptable study. *In vitro* studies investigating oral and perioral microorganisms found in the oral cavity were included in the review. Studies published in languages other than English language were included only if an abstract was available in English. Studies inclusion criteria in this systematic review were if they met the following eligibility

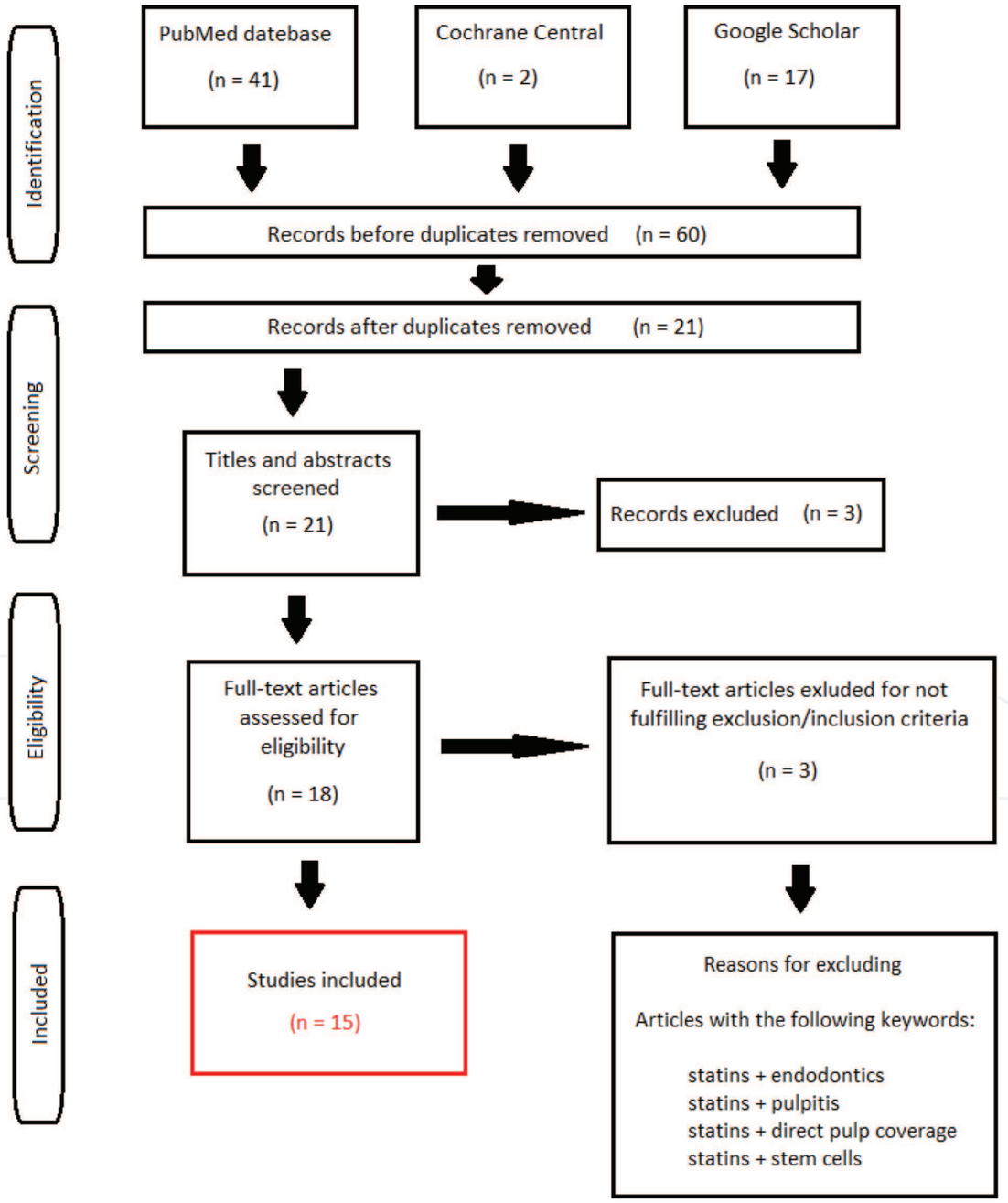

Figure 1.
Flowchart of article selection process in the review.

criteria: original studies in English (clinical and animal trials); evaluation of titanium implants influenced by statins; the presence of a control group; and outcome data considering bone implant contact (BIC), mechanical tests, or other histological evaluation. Studies exclusion criteria was articles using implants inserted into the medullar cavity, Letters to the editor, reviews, case series, case reports, and *in vitro* studies were also exclusion criteria for this chapter.

2.2 Review and identification of acceptable studies

In the initial phase, one author reviewed abstracts of all papers to identify the studies that could have the inclusion criteria. If the abstract met the inclusion criteria, then the full text of the paper was obtained, evaluated, and cited in the review paper. The second author checked all the listed works and the criteria for inclusion or exclusion of certain articles.

3. Effects of statins in animal studies literature review

A total of 60 articles were found. When duplicates and those that did not meet the criteria were excluded, there were 15 publications left that were included in the research.

Table 1 shows the results of this review. A total of 15 papers were included in the analysis. In seven studies, statins were shown to increase the formation of new bone. In two studies, statins promoted better osseointegration of dental implants and in one, there were no significant differences. In five studies, use of statins led to improved contact between the bones and the surface of the implant, and in three

Authors	Test subjects	Number of implants	Implant site	Implant used	Statins: type and dosage	Results
Kellesarian, Al Amri, Al-Kheraif, Ghanem, Malmstrom, Javed [14]	19 laboratory animals: 13 female rats, 1 male rat, 5 dogs of unspecified gender	-	-	Titanium	Simvastatin (per os, s.c., i.o.): 0.25 and 50 mg/kg/day; fluvastatin: 3–300 μg	Better osseointegration and better contact of implant surface with newly formed bone
Fang, Zhao, He, Liu, Yang [15]	36 female rats	72	Distal tibia	Titanium 4 × 2.2 mm	Simvastatin HA surface coat of 1 implant (10^{-7} M and 10^{-6} M)	Increased formation of new bone, better BIC
Kwon, Yang, Lee [16]	3 male rabbits	16	Tibia, femoral head	Titanium 3.5 × 8 mm	Simvastatin 535 μg, surface of 1 implant	Significantly larger volume of newly formed bone and better contact of implant
Faraco-Schwed, Mangueira, Ribeiro, Antao Ada, Shibli [17]	16 male rabbits	32	Tibia	Titanium 3.25 × 8.5 mm	Simvastatin gel 0.25 mg/mL and 30 mg/mL, topically to bone	Significantly better contact of implant after 4 and 8 weeks

Authors	Test subjects	Number of implants	Implant site	Implant used	Statins: type and dosage	Results
Mansour, Al Ashwah, Koura [18]	10 dogs	20	Mandible	Titanium 3.5 × 10 mm	Simvastatin 150 mg topically on 1 implant	Significantly higher volume of newly formed bone
Nyan, Hao, Miyahara, Noritake, Rodriguez, Kasugai [19]	24 male rats	36	Tibia	Titanium 1.8 × 5 mm	Simvastatin 25 and 50 μg to surface of 1 implant	Significantly larger volume of newly formed bone, better contact of newly formed bone and implant surface, larger volume of mineralized newly formed bone
Pauly, Back, Kaeppler, Haas, Schmidmaier, Wildemann [20]	80 female rats	80	Femur	Titanium 1.4 × 5 mm	Simvastatin 5.5 and 90 μg to surface of 1 implant	Significantly larger volume of newly formed bone and better contact of implant surface and newly formed bone, significantly better contact of implant
Yang, Song, Guo, Zhao, Liu, He [21]	48 male rats	96	Tibia	Titanium 2.2 × 4 mm	Simvastatin 10^{-6} M and 10^{-7} M to surface of 1 implant	Histomorphometric analysis showed significantly larger volume of newly formed bone and better implant surface contact with newly formed bone
Moriyama, Ayukawa, Ogino, Atsuta, Koyano [22]	60 rats	60	tibia	Titanium 1 × 1.5 mm	Fluvastatin 3 and 75 μg, simvastatin 15 μg topically on surface of 1 implant	Larger volume of newly formed bone; no significant difference in BIC
Moriyama, Ayukawa, Ogino, Atsuta, Todo, Takao et al. [23]	126 female rats	126	Tibia	Titanium 1 × 1.5 mm	Fluvastatin 3 μg (group 3), 15 μg (group 4), 75 μg (group 5), 300 μg (group 6) topically on surface of 1 implant	Volume of newly formed bone lower in group 6 in comparison to other groups after week 1; volume of newly formed bone and BIC larger in group 5 in comparison to other groups after week 2

Authors	Test subjects	Number of implants	Implant site	Implant used	Statins: type and dosage	Results
Ayukawa, Okamura, Koyano [24]	30-week-old female rats	20	Both tibia	Titanium 1 × 1.5 mm	Experimental group was intraperitoneally administered 10 mg/kg of simvastatin, control group received the isotonic saline instead	In both group newly formed bone was seen to be in direct contact with the implant surface; however, unmineralized connective tissue, including fibroblast-like cells and blood vessels, was occasionally seen on implant surface in experimental group
Xu, Shi, Xu, et al. [25]	30 male rats	30	Maxilla	Titanium implants, diameter 0.8 mm	Oral simvastatin group-25 mg/kg simvastatin, the local simvastatin group-0.8 mg/0.05 ml simvastatin around the implant every day	Bone tissue was markedly higher with local simvastatin administration relative to oral simvastatin administration
Jun, Oh, Park, Jung, Li, Moon [26]	12 rabbits	48	Both tibia	Titanium, diameter 3.1 mm	Group C: implants placed without any treatment in rabbits Group U: implants irradiated with UV immediately before implantation, but not coated with simvastatin Group S: implants immersed in simvastatin solution for 24 h in separate sealed containers without UV exposure in rabbits Group SU: implants first immersed in simvastatin solution for 24 h and then irradiated with UV immediately before surgery in rabbits	Ultraviolet (UV) or SIM treatment of SLA titanium implants accelerates osseointegration in tibias with or without xenogenic bone graft materials. The combination of both treatments did not show synergy

Authors	Test subjects	Number of implants	Implant site	Implant used	Statins: type and dosage	Results
Dundar, Bozoglan [27]	16 female rats	16	Tibia	Titanium 2.5 × 4 mm	Test group (8)-5 mg of simvastatin was applied to the bone sockets control group-no simvastatin	No statistically significant differences in ratios of the test group and control group in terms of implant osseointegration ($p > 0.05$)
Apostu, Lucaciu, Mester, Oltean-Dan, Gheban, Rares Ciprian Benea [28]	80 female rats	80	Femur	Titanium Ti90Al6V4 alloy nails	Group I (ovariectomy); Group II (sham ovariectomy); Group III (alendronate 3 mg/kg twice a week + ovariectomy); Group IV (simvastatin 5 mg/kg daily + ovariectomy); and Group V (tibolone 5 mg/kg daily + ovariectomy)	Tibolone could offer the best results in a way of osseointegration

Table 1.
A total of 15 papers that were included in the analysis with their number of test subjects, number of implants that were placed in the study, place where implant was inserted, surface of implant and dosage used in each animal research, and final conclusion of each study.

studies, less mobility of the implant could be demonstrated. In two studies, there were no significant differences in contact between bone and implant, regardless of the statin use.

One study demonstrated more bone formation if simvastatin was administered topically than systemically orally. Tibolone also showed good results in osseointegration compared to simvastatin.

Kellesarian et al. [15] reviewed studies performed on 19 laboratory animals in which simvastatin was administered systemically and locally, specifically orally, subcutaneously, and intraosseously. Better osseointegration and better contact of the implant surface with the newly formed bone were demonstrated in the simvastatin group. A total of 13 studies were performed on female rats, 1 study was on male rats, and 5 studies were performed on dogs of indeterminate sex. Statins were used topically in 12 studies, statins were applied directly to bone cavities in five studies and they were applied systemically in two studies. The dose of systemically administered statins was between 0.25 and 50 mg/kg/day. In two studies, propylene glycol and fluvastatin were used at a dose of 3–300 μg and were applied to the bone bed of the implant before implant placement. Titanium implants were used in all studies.

Studies by Fang et al., Kwon et al., and Faraco-Schwed et al. [16–18] reported that the total number of implants placed in subjects ranged between 16 and 96 implants

per research. The total number of implants utilized was not reported in 14 studies. Implants were placed in the tibia and femur in 13 and in 4 studies, respectively. In a study by Kwon et al., 16 implants were placed in the tibia and femur [17]. Fang et al. in their research study work on 36 female rats divided into 3 groups. In the first group, the surface of implants implanted in the tibia is covered with a mixture of hydroxylapatite and simvastatin in the amount of SIM 10^{-7} M (M = 1 mol/liter), in the second group, the surface of implants is covered with the same combination only in the amount of 10^{-6} M, and in the third group, only hydroxylapatite is applied on the surface of implants. Histomorphometric analysis was performed after 2, 4, and 12 weeks and better contact of the newly formed bone with the implant surface was found as well as a higher volume of newly formed bone in the first two groups as opposed to the third group [16]. Kwon et al. performed the research on 3 male rabbits, divided into three groups. A total of 16 implants measuring 3.5 × 8 mm are placed in the tibia and femur. The first group is control and implants are placed without additional surface treatment. In the second group, implants surface is coated only with hydroxylapatite and in the third group, implants surface is covered with hydroxylapatite and simvastatin and a concentration of 535 μg.

Follow-up after 4 weeks was done by micro-CT analysis and biomechanical examination during which a significantly higher volume of newly formed bone and less implant mobility were observed in the third group [17]. Faraco-Schwed et al. conducted a study in which they topically administered statins to 16 male rabbits divided into 4 groups. They used 32 titanium implants implanted in the tibia measuring 3.25 × 8.5 mm. The first group received 0.25 mL of simvastatin gel (30 mg/mL) topically over 28 days, the second group over 56 days, while the third and fourth groups represented the control group. Biomechanical control after 4 and 8 weeks showed significantly less mobility in the second group compared to the fourth, while in the first and third groups there were no statistically significant differences [18].

Mansour et al. studied 10 dogs that received titanium implants in the mandible measuring 3.5 × 10 mm. The duration of the study was 18 months. The first group received simvastatin 150 mg topically *via* implant surface and the second group was the control. Histological analysis of the preparation after 4 and 12 weeks showed a significantly higher amount of newly formed bone in the first compared with the control group [19].

Nyan et al. used 24 male rats divided into 6 groups. The first group was the control. The second group used implants where the surface was treated only by the micro-oxidation technique, while the third group used implants where the surface was treated with micro-oxidation and coated with simvastatin (SIM) in the amount of SIM 25 μg and in the fourth group, the amount of simvastatin used to cover the surface of implants was 50 μg. Micro-CT analysis and histological analysis were performed after 2 and 4 weeks and the results showed significantly higher volume of newly formed bone, better contact of newly formed bone, and implant surface as well as a larger volume of mineralized newly formed bone. Titanium implants measuring 1.8 × 5.0 mm were implanted in the animals' tibia [20].

Pauly et al. divided 80 female rats into 4 groups. The first group was control, while the second group used implants where the surface was treated only with poly D, l-lactide acid (PDDLA) and the third and fourth groups used PDLLA + simvastatin 5.5 μg and PDLLA + simvastatin 90 μg per implant surface. Histological and biomechanical analysis after 8 weeks showed a significantly higher volume of newly formed bone as well as better contact between the surface of the implant and the newly formed bone and significantly less mobility of the implant in the third and fourth groups. Titanium implants measuring 1.4 × 5 mm implanted in the femur were used in the study [21].

Yang et al. implanted 96 titanium implants in a total of 48 female rats with removed ovaries. The implants measured 2.2 × 4.0 mm. The first group underwent ovariectomy, while rats in the other two groups underwent ovariectomy and the surface of implants was coated with a concentration of simvastatin 10^{-7} M for the first group and in the second group with 10^{-6} M. Histomorphometric analysis after 1, 2, 4, and 12 weeks showed a significantly higher volume of newly formed bone and better contact of the implant surface with the newly formed bone in the first two groups [22].

Moriyama et al. conducted their two studies on a total of 186 female rats. The first study was conducted on 60 rats divided into 5 groups that received titanium implants measuring 1 × 1.5 mm in the tibia. Throughout all five groups, authors combined different amounts of propylene glycol alginate (PGA) and fluvastatin (FLU) at different concentrations topically across the implant surface. The first group was the control, while the second group received only PGA, the third group topically received PGA and FLU 3 μg on the surface of the implant, the fourth group received PGA + SIM 15 μg on the surface of implant, and the fifth group received PGA and FLU 75 μg on the surface of the implant. Histomorphometrically, group 5 showed a significantly higher volume of newly formed bone compared to other groups, while there was no significant difference in the quality of contact between the implant surface and the newly formed bone in all five groups. The second study was performed on 126 female rats divided into 6 groups, 21 subjects each. The first group subjects did not receive any topical statin administration and it formed the control group. The second group received topically only PGA, the third group received FLU in the amount of 3 μg; the fourth group received FLU 15 μg, the fifth group FLU 75 μg, and the sixth group received FLU in the amount of 300 μg on the surface of the implant. All animals had titanium implants measuring 1 × 1.5 mm in the tibia. After the first week, the volume of the newly formed bone was lower in group six compared to other groups and after the second week, the volume of newly formed bone and bone contact with the implant was higher in the fifth group compared to other groups [23, 29].

In their review paper, Moraschini et al. [30] also summarize and analyze similar studies as Kellesarian et al. The discussion explained the mechanism of action of statins on the process of osseointegration. Authors concluded that statins enhanced the action of bone-morphogenic protein-2 (BMP-2) which in turn acted on enhanced osteoblastic activity and the formation of new bone. Authors further claimed that in the above studies in which FLU was used in rats, no changes were observed in the form of an increase in the liver enzymes alanine aminotransferase (ALT) or aspartate aminotransferase (AST). The higher the dose used in the studies, the greater the volume of newly formed bone and better seal of newly formed bone and implant surface in the first 2 weeks, which was evident in the study by Moriyama et al.

Türer et al. divided 32 rats into 4 groups: group C-14 (control), group R-14, group C-28 (control), and group R-28. Each animal underwent a unilateral, standard vertical osteotomy on the right side of the mandible, extending from the tooth to the mandibular base. Sterile saline absorbent collagen sponge was applied to the fracture area in groups C-14 and C-28, while an absorbent collagen sponge with saline containing 1 mg rosuvastatin was applied to the fracture area in groups R-14 and R-28. Animals in groups C-14 and R-14 were euthanized on day 14 and the animals in groups C-28 and R-28 were euthanized on day 28 after surgery. Stereological analyses were performed. New areas of bone and connective tissue volume were measured. Stereological analysis showed that the R-14 group had significantly more new bone after 2 weeks compared to the C-14 group. The volume of connective tissue was also significantly higher in R-14. Differences in connective tissue volume and new bone

were not statistically significant upon comparison of groups C-28 and R-28. Topically applied rosuvastatin enhanced early bone regeneration in rats with mandibular fracture [31].

Keuroghlian et al. investigated mice with the assumption that hyperlipidemia negatively affected the osseointegration of dental implants because a high-fat diet had significant detrimental effects on bone density and volume. The authors placed a group of male mice on a high-fat diet and a control group on a regular diet. After 12 weeks, every animal received a titanium implant in the femur. Animals were humanely sacrificed 4 or 8 weeks after implantation, and the results showed that a high-fat diet significantly reduced bone density and strength and that osseointegration was poorer [32].

The work of Mahrous, who investigated the topical application of simvastatin in gel form for the treatment of peri-implant mucositis, was found in the Cochrane Central database. The author tested the proven anti-inflammatory effect of statins on the inflamed mucosa surrounding dental implants. The hypothesis was that 1.2% of simvastatin gel would reduce inflammation around the implant. The pilot study involved 44 subjects divided into a test and a control group. The test group received topically simvastatin gel that was applied with a blunt-tipped needle around the implant while the control group received a placebo. The inflammatory condition was determined at the beginning of the study, 24 hours later, after 1 week, and after 1 month by clinical indications for inflammation and biochemical markers of inflammation collected around the implant. The study included individuals of both sexes who had no signs of bone resorption around the implant by more than 1 mm as established by X-ray analysis. The results showed that the greatest reduction in inflammation occurred in the first 24 hours, but there were no statistically significant differences in the levels of cytokines IL-1β, IL-6, IL-8, and TNF-α between the test and control group as well as no significant differences in periodontal probing depth [24].

Ayukawa et al. performed the animal study on 10 female rats that were 30 weeks old. Ten titanium implants were placed in both tibias and measured 1 mm in diameter and 1.5 mm in length. Experimental group received intraperitoneally 10 mg/kg of simvastatin, and the control group received isotonic saline instead. Both groups showed that the newly formed bone was thought to be in direct contact with the implant surface. Despite direct contact of the new bone and implant surface, the experimental group showed occasional evidence of unmineralized connective tissue, including fibroblast-like cells and blood vessels, on implant surface [25].

Rongyao Xu et al. performed implants in oral cavity on 30 male rats that were postoperatively randomly divided into three groups. The first group received 25 mg/kg of simvastatin orally, the second group received simvastatin injections in the amount 0.8 mg/0.05 mL around the implant every day, and the third group was the control. Simvastatin promoted osseointegration of the implant. Rats that were treated with simvastatin had more newly formed bone that had a woven appearance than control group rats as revealed by H&E staining. In addition to that, the volume of bone tissue was significantly higher in rats that received simvastatin locally in comparison with the group that received simvastatin orally [26].

Hoon Yun et al. researched the effect of ultraviolet (UV) and simvastatin (SIM) treatment on the osseointegration of dental titanium implants in rabbit tibias at two different time points. Implants were sandblasted, large-grit, and acid-etched (SLA) and surface alterations due to simvastatin treatment were analyzed with an infrared spectrometer. Implants were divided into four groups depending on the type of surface treatment of implants. Twelve rabbits were implanted with two implants per

tibia. Implants were in contact with the surface of the bone and bovine bone was used as graft material for gap filling. Animals were humanely sacrificed after 2 or 4 weeks. Results showed that bone-to-implant contact (BIC) was increased with UV treatment and SIM immersion on non-grafted sides and both BIC and bone area (BA) were increased on grafted sides. BIC or BA did not increase with both treatments in comparison with a single treatment. As data were collected at two different time points, results showed that BIC in the non-grafted sides did not differ significantly among UV- and/or SIM-treated groups, but BA was significantly different among groups. Ultraviolet or simvastatin treatments on SLA titanium implants accelerated osseointegration in tibias with or without xenogenic bone graft materials. Joint implementation of both treatments did not show significant positive effects [27].

Dundar and Bozoglan conducted their research on 16 female rats during a 4-week experimental trial. The subject was divided into two groups: a test group (n = 8) that received local simvastatin and a control group (n = 8) that did not receive simvastatin treatment. A titanium implant was surgically implanted into the tibial metaphysis of all 16 animals. Ethanol solution in the amount of 100 μl containing 5 mg simvastatin was applied to the bone sockets before implantation. Results for bone-implant contact (BIC) showed no statistically significant differences among test and control groups with regard to implant osseointegration ($p > 0.05$) [28].

Apostu et al. evaluated and compared the effects of different treatments (simvastatin, alendronate, and tibolone) on improved osseointegration of titanium implants. Research was conducted on 80 female albino Wistar rats evenly divided into five groups: Group 1 underwent ovariectomy, group 2 underwent false ovariectomy, group 3 underwent ovariectomy and alendronate treatment, group 4 underwent ovariectomy and simvastatin treatment, and group 5 underwent ovariectomy and tibolone treatment. Three months post-ovariectomy, the authors performed bilateral titanium intramedullary nailing (Ti90A16V4 alloy nails) in all groups followed by a 12-week oral administration of alendronate (3 mg/kg twice a week), simvastatin (5 mg/kg daily), or tibolone (5 mg/kg daily). Micro CT, mechanical pull-out test, histology, and bone serum markers were examined after 12-week oral treatment. Upon review of all examination results, the authors concluded that the initial hypothesis that simvastatin, alendronate, and tibolone enhance osseointegration in ovariectomized rats with intramedullary titanium implants has been accepted. Tibolone showed the best results out of three treatments [33].

4. Pharmacokinetics of simvastatin

The chemical structure of all statins consists of the pharmacophore and its moiety containing a ring system with different substituents. The pharmacophore is shared among all statins, and it is a dihydroxyheptanoic acid segment that is very similar to the HMGCoA substrate [34]. The ring system consists of a complex hydrophobic structure covalently linked to the pharmacophore and it is involved in binding interactions with the HMG-CoA reductase enzyme [35]. There are different kinds of statins, which differ from each other in their hydrophobic ring structure and its substituents, covalently linked to the HMG-like moiety. These differences in structure affect the pharmacological properties of the statins [36].

The lipophilicity of the statins is considered important since the hepatoselectivity of the statins is related to their degree of lipophilicity. The higher the lipophilicity of statins, the greater level of exposure it gets to non-hepatic tissues, while the

more hydrophobic statins have a tendency to be more selective for the liver, whereas lipophilic statins passively and nonselectively diffuse into both hepatocytes and non-heptatocytes. The more hydrophobic statins largely rely on active transport into hepatocytes to exert their effects [37].

There are two forms of statins, lactone (inactive) and open-ring hydroxy acid (active) forms. The HMG-like moiety that all statins are in the inactive form as a lactone. Simvastatin and lovastatin are administered as lactone prodrugs and subsequently transformed into active metabolites. The remaining statins become in their active form as a β-hydroxy acid. *In vivo*, lactone statins are hydrolyzed to their hydroxy acid pharmacophores in the liver to achieve pharmacological activity [38].

We can divide statins into two groups: naturally or fungal-derived (type 1) and synthetic (type 2). One of the main differences between the type 1 and type 2 statins is the replacement of the fluorophenyl group of type 2 statins with the butyryl group in type 1 statins. These specific groups cause additional polar interactions and stronger and tighter binding to the HMGR enzyme. Functionally, the methylethyl group attached to the central ring of the type 2 statins replaces the decalin of the type 1 statins. The butyryl group of the type 1 statins occupies a region similar to the fluorophenyl group present in the type 2 inhibitors [39].

The hepatoselectivity is very important factor in liposolubility of the statins and their inhibitory effect on HMG-CoA reductase. Lipophilic statins enter the hepatocytes through passive diffusion, whereas hydrophilic statins undergo a carrier-mediated membrane [40].

Hydrophilicity depends on a transport process that takes the drug from the portal blood into hepatocytes using anion-transporting polypeptides (OATP). That molecules give better potential and selectivity for the liver cells. Hydrophilic statins—such as rosuvastatin and pravastatin—have higher potential to the liver metabolism, because they harder way of entering other tissues as lipophilic statins do. However, the balance between desired and undesired effects of lipophilic and hydrophilic statins remains not clearly established [41].

5. Effect of statin on bone metabolism

The bone tissue is a very dynamic formation that is always remodeled by bone cells osteoclasts and bone-forming osteoblasts.

Osteoblast cells are derived from mesenchymal stem cells and osteocytes derived from terminally differentiated osteoblasts [42, 43].

The biggest amount of lipids is present in bone marrow, and the lowest concentration of them in bone mineral matrix. Human bone contains 28–84% of neutral lipids, and only less than 3% of phospholipids [44].

Cholesterols have function in bone metabolism, in which membrane signal transducing platforms and play crucial roles in RANK-RANKL signal transduction during osteoclastogenesis.

High cholesterol levels also increase bone metabolism. High fat diets in mice caused osteoclastogenesis, and decrease in bone mass. The high-fat-fed antigen-induced arthritis (AIA) model also suggested that enhanced cathepsin K-positive osteoclasts contributed to more severe deterioration of the joints than in normal-diet-fed AIA rabbits [45–47].

Cellular cholesterol has important role in cellular metabolism of macrophages pathways. Macrophages have the same origin as osteoclasts. The low-density

lipoprotein receptor (LDLR) on macrophages promotes the internalization of ApoB-containing lipoprotein, resulting in high levels of intracellular cholesterol [48, 49].

Osteoporosis is an epidemic throughout the world and is associated with trauma fractures in the vertebral spine, femoral neck, and distal radius. Specifically, postmenopausal osteoporosis is connected with pathological bone fractures. That is very often a disease in elderly women. It is typically associated with low bone mass and poor bone density.

Bisphophonates, selective estrogen receptor modulators, calcitonin, and vitamin D analogues are most usefully drugs for osteoporosis. They can also stop further bone loss. All of these drugs are inhibitors of bone resorption that act mainly to stabilize bone mass. It is hard to say if they are also osteoinductive [50, 51].

Osteoporosis and atherosclerosis share the tendency to accelerate after menopause; both diseases are promoted by inflammatory processes, and many aspects of arterial calcification and bone formation are similar [52]. The relationship between osteoporosis and atherosclerosis is supported by the observation that the progression of aortic calcification is most severe in women with the most severe metacarpal bone loss. Factors that may promote both processes include estrogen deficiency and increased concentrations of proinflammatory cytokines, such as IL-1, IL-6, and TNF-a [49, 50].

6. Conclusion

A review of the results from the available literature shows that statins have a future in the use within oral surgery procedures and implantology where their osteogenic effect is most pronounced and their influence on the increase of the volume of newly formed bone and contact between implants and bone. Although studies have been conducted on small animals we believe that the potential of statins in bone formation is also high in humans. One of the studies also demonstrated the effectiveness of statins on bone fracture regeneration. We believe that local use of a statin applied to the bone bed of the implant, as well as topical application of a liquid statin to the implant surface, shows better osseointegration potential of the implant, as well as better contact of the implant with the more newly formed bone. A better effect on the soft tissues around the implant is also visible. It is possible that local statins increase level of bone morfogenic protein-2 (BMP-2) in bone metabolism, which affects higher level of newly formed bone. Future studies should establish safe and effective clinical protocols for statin application to promote osseointegration.

Conflict of interest

The authors declare that there is no conflict of interest.

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