Efficacy of Local and Systemic Statin Delivery on the Osseointegration of Implants: A Systematic Review

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Purpose: *In indexed literature, a systematic review of the efficacy of statins in enhancing osseointegration is lacking. The aim of this systematic review was to assess the efficacy of local and systemic statin delivery on the osseointegration of implants.* ***Materials and Methods:*** *To address the focused question, "Does local and systemic statin delivery affect osseointegration around implants?", indexed databases were searched from 1965 through November 2015 using various keywords. Letters to the Editor, case reports/case series, historic reviews, and commentaries were excluded. The pattern of this systematic review was customized to primarily summarize the pertinent data.* ***Results:*** *Nineteen studies were included. All studies were experimental and were performed in animal models. In seven studies, statins were delivered systemically via oral, intraperitoneal, intraosseous, subcutaneous, and percutaneous routes. Among the 12 studies, where statins were delivered locally, statin-coated implants were used in seven studies, whereas in the remaining studies, statins were delivered via topical application on the bone cavities. The follow-up duration ranged between 1 and 12 weeks. Results from 18 studies showed that statin administration enhanced new bone formation (NBF) around implants and/or bone-to-implant contact. One study showed that statin-coated implant surfaces impaired osseointegration. Seven studies reported that statin administration enhanced NBF around implants in osteoporotic rats.* ***Conclusion:*** *On experimental grounds, local and systemic statin delivery seems to enhance osseointegration; however, from a clinical perspective, further studies are needed to assess the role of statins in promoting osseointegration around dental implants.* Int J Oral Maxillofac Implants 2017;32:497–506. doi: 10.11607/jomi.4955

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A critical factor that influences the overall success and survival of implants is osseointegration.[1] With modernization in implant dentistry, a variety of adjunct therapies have been proposed in an attempt to enhance osseointegration of implants and bone-to-implant contact (BIC). One such adjunct therapy is the use of hydroxymethylglutaryl-coenzyme A reductase inhibitors (or statins). Statins are cholesterol-lowering drugs, which inhibit hepatic cholesterol biosynthesis, thereby reducing serum cholesterol concentrations and lowering the risk of cardiovascular diseases.[2,3] Statins have been classified in two types: *(1)* lipophilic statins (such as atorvastatin, cerivastatin, fluvastatin, lovastatin, pitavastatin, and simvastatin) and *(2)* hydrophilic statins (such as pravastatin and rosuvastatin).[4] In addition to the cholesterol-lowering effect,[5] preclinical studies have shown that statins reduce osteoclastic activity,[6,7] stimulate osteoblast differentiation in vitro,[8,9] and increase bone formation by enhancing the expression of bone morphogenetic protein (BMP)-2 in osseous tissues.[10] Statins have also been reported to increase angiogenesis and osteogenesis by promoting tendon-bone healing.[11,12]

In a study by Mundy et al,[13] subcutaneous administration of simvastatin increased the expression of BMP-2 and enhanced new bone formation (NBF) in the calvaria of mice; also, it increased cancellous bone

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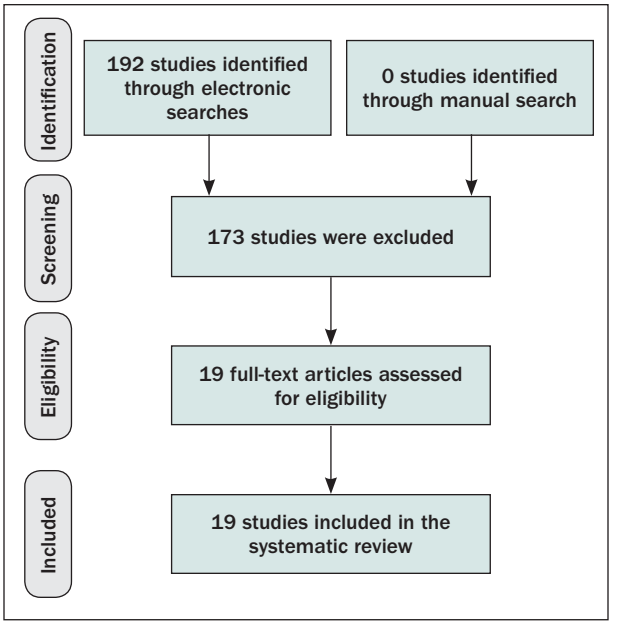

Fig 1 Article selection flow chart for the systematic review according to PRISMA guidelines.

volume when orally administered to rats. Similarly, in the study by Fang et al,[14] NBF around implant surfaces and BIC were assessed in rats with induced osteoporosis. The results showed that under experimental osteoporosis, simvastatin-coated implants exhibited significantly higher NBF and BIC compared with non-coated implant surfaces. Results of an in vitro study[15] also showed that statins enhance proliferation and differentiation of osteoblasts. Similar results were reported in another in vitro investigation.[9] However, in a study by Pauly et al,[16] impaired osseointegration around simvastatin-coated implants was reported.

To the authors' knowledge from indexed literature, the role of statins in enhancing osseointegration has not been systematically reviewed. Therefore, the aim of the present systematic review was to assess the efficacy of local and systemic statin delivery on the osseointegration of implants.

MATERIALS AND METHODS

Focused Question

Based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, a specific question was constructed according to the Participants, Interventions, Control, Outcomes (PICO) principle (Fig 1). The addressed focused question was "Does local and systemic statin delivery affect osseointegration around implants?":

- (P) Participants: It was essential for subjects to have undergone implant treatment.
- (I) Types of interventions: The intervention of interest was the effect of statin administration on osseointegration.
- (C) Control intervention: Implant placement without adjunct statin administration
- (O) Outcome measures: BIC and NBF around the implant with and without statin delivery

Eligibility Criteria

The eligibility criteria were as follows: *(1)* original studies (clinical and experimental); *(2)* inclusion of a control group (osseointegration around implants without statin administration); and *(3)* intervention: effect of statin administration on osseointegration. Letters to the Editor, historic reviews, commentaries, case series, and case reports were excluded.

Literature Search Protocol

PubMed/Medline (National Library of Medicine, Washington, DC), EMBASE, Scopus, Web of Knowledge, and Google Scholar databases were searched from 1965 up to and including November 2015 using various combinations of the following keywords: *(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; rosuvastatin + implants; *(9)* fluvastatin + osseointegration; *(10)* fluvastatin + implants. Titles and abstracts of studies identified using the aforementioned protocol were screened by two authors (S.V.K. and F.J.) and checked for agreement. Full texts of studies judged by title and abstract to be relevant were read and independently evaluated for the stated eligibility criteria. Reference lists of potentially relevant original and review articles were hand searched to identify any studies that could have remained unidentified in the previous step. Once again, the articles were checked for disagreement via discussion among the authors (Fig 1). The pattern of the present systematic review was customized to mainly summarize the relevant data.

The initial search yielded 192 studies. Removal of duplicated studies and articles that did not fulfill the eligibility criteria reduced the count to 19 articles,[14,16–33] which were included and processed for data extraction.

Quality Assessment

Quality assessment of studies that were included was performed in an attempt to increase the strength of the present systematic review. The 19 studies[14,16–33] that were included underwent a quality assessment

with the Critical Appraisal Skills Program (CASP) Cohort Study Checklist.[34] The CASP tool uses a systematic approach based on 12 specific criteria, which are: *(1)* study issue is clearly focused; *(2)* cohort is recruited in an acceptable way; *(3)* exposure (statin administration) is accurately measured; *(4)* outcome (osseointegration and/or NBF around implants) is accurately measured; *(5)* confounding factors are addressed; *(6)* follow-up is long and complete; *(7)* results are clear; *(8)* results are precise; *(9)* results are credible; *(10)* results can be applied to the local population; *(11)* results fit with available evidence; and *(12)* there are important clinical implications. Each criterion was given a response of either "Yes", "No", or "cannot tell". Each study could have a maximum score of 12. CASP scores were used to grade the methodologic quality of each study assessed in the present systematic review.

RESULTS

General Characteristics of the Included Studies

In total, 19 studies[14,16–33] were included. All studies[14,16–33] were prospective and were performed in animals. Thirteen studies[14,16,17,19,21,23,25,27,28,30–33] were performed in female rats, and one study[29] was performed in male rats. Male and female rabbits were used in three studies[18,20,22] and one study,[26] respectively. One study[24] was performed in dogs; however, the sex of study animals remained unidentified. In seven studies,[17,19,21–23,25,31] statins were delivered systemically. In 12 studies,[14,16,18,20,24,26–30,32,33] statins were delivered locally, out of which statin-coated implants were used in seven studies,[14,16,18,29,30,32,33] and in five studies,[20,24,26–28] the statins were topically applied in the bone cavities.

In all studies,[14,16–33] the follow-up period ranged between 1 and 12 weeks. In 12 studies,[16–18,20–22,24–29] the role of statins in the promotion of NBF around implants was assessed in healthy animals, whereas in seven studies,[14,19,23,30–33] the effectiveness of statins on implant osseointegration was assessed in rats with induced osteoporosis.

Systemic Delivery of Statins

In six studies,[17,19,21–23,31] simvastatin was delivered systemically with a dosage ranging between 0.25 mg/kg/day and 50 mg/kg/day. In the studies by Ayukawa et al,[17,21] simvastatin was administered intraperitoneally. Başarir et al,[22] Du et al,[23] and Tan et al[31] delivered simvastatin subcutaneously, orally, and intraosseously, respectively. In the study by Tao et al,[19] the method used for simvastatin administration was not reported. Fluvastatin was administered percutaneously in the study by Masuzaki et al[25] (Table 1).

Topical Delivery of Statins

In two studies,[27,28] a propylene glycol alginate vehicle gel with fluvastatin concentrations ranging between 3 and 300 µg was injected into the bone cavity prior to the implant placement to evaluate the effectiveness of fluvastatin in the promotion of NBF around implants. In one study,[24] simvastatin was formulated as granules in a cellulosic polymeric matrix and locally packed into the bone after implant placement; Faraco-Schwed et al[20] investigated the effects of topical simvastatin gel (7.5 mg) application on the removal torque of titanium implants placed in rabbit tibiae. Monjo et al[26] evaluated rosuvastatin effectiveness on implant osseointegration using an absorbable collagen sponge as a carrier, with concentrations ranging between 8.7 and 259.1 µg (Table 2).

Implants with Statin-Coated Surfaces

In seven studies,[14,16,18,29,30,32,33] simvastatin was applied as a coating onto the implant surfaces, with a concentration ranging from 5.5 to 535 µg (Table 2).

Implant-Related Characteristics of the Included Studies

Titanium implants were used in all studies.[14,16–33] Five studies[14,18,20,25,32] reported the total number of implants placed in the subjects, which ranged between 16 and 96 implants. In 14 studies,[16,17,19,21–24,26–31,33] the total number of implants placed was not reported. In 13 studies[14,17,20,21,23,25–30,32,33] and in four studies,[16,19,22,31] implants were placed in the tibiae and femur, respectively; in the study by Kwon et al,[18] implants were placed in the tibia and femur. Mansour et al[24] placed implants in dogs' mandibles.

In 17 studies,[14,17–25,27–33] dimensions (diameter × length in millimeters) of implants used ranged between 1 × 1.5 and 1.5 × 20 mm. Monjo et al[26] used a coin-shaped titanium implant that was 6.25 × 1.95 mm. In the study by Pauly et al,[16] titanium Kirschner wires with a 1.4-mm diameter were used; however, the length remained unidentified. Cylindrical and screw-type implants were placed in eight studies[17,19,21,22,24,25,27,28] and eight studies,[14,20,23,29–33] respectively; in one study,[18] the shape of the implants used was not reported. In 11 studies,[14,18–20,22–24,29,30,32,33] rough-surfaced implants were used; in four studies,[17,21,25,28] the implants had smooth surfaces. The implant surface characteristics were not reported in four studies[16,26,27,31] (Table 3).

Assessment of Osseointegration

In 12 studies,[14,16,17,21–23,25,27,28,30,32,33] osseointegration was assessed using histomorphometric analysis. In 10 studies,[16,18–20,22,25,27,28,30,31] biomechanical testing was performed to assess the strength of newly formed bone around implants. In six studies,[18,19,26,29–31] NBF

Table 1 Systemic Delivery of Statin

Study	Study animals (mean age)	Study groups	Statin dose and route of administration	Follow-up	Analysis methods
Ayukawa et al[21]	10 Female rats (4.2 months)	Group 1: 5 Control Group 2: 5 SIM	SIM 10 mg/kg/day Intraperitoneal	4 wk	HIST Histology
Ayukawa et al[17]	60 Female rats (4.2 months)	Group 1: Control Group 2: SIM 0.125 mg Group 3: SIM 1 mg Group 4: SIM 5 mg Group 5: SIM 10 mg	SIM Group 2: 0.125 mg/kg/day Group 3: 1 mg/kg/day Group 4: 5 mg/kg/day Group 5: 10 mg/kg/day Intraperitoneal	4 wk	HIST ELISA Histology
Başarir et al[22]	20 Male rabbits (NA)	Group 1: Control Group 2: SIM	SIM 50 mg/kg/day Subcutaneous injection	6 wk	HIST Biomechanical SEM Histology
Du et al[23]	54 Female rats (3 months)	Group 1: 18 Sham Group 2: 18 OVX Group 3: 18 OVX + SIM	SIM 5 mg/kg/day Oral	4 and 12 wk	HIST
Masuzaki et al[25]	40 Female rats (2.2 months)	Group 1: Control Group 2: PLGA Group 3: PLGA + FLU 0.5 mg Group 4: PLGA + FLU 1 mg	FLU Group 3: 0.5 mg/kg Group 4: 1 mg/kg 2 mL percutaneous PLGA microspheres	2 and 4 wk	HIST Biomechanical Histology
Tan et al[31]	48 Female rats (3 months)	Group 1: 16 OVX + SIM 5 mg Group 2: 16 OVX + SIM 10 mg Group 3: 16 OVX	SIM 1 Intraosseous injection Group 1: 5 mg (100 µL) Group 2: 10 mg (100 µL)	4 wk	DXA Micro-CT Histology Biomechanical
Tao et al[19]	50 Female rats (3 months)	Group 1: 10 OVX Group 2: 10 OVX + SIM Group 3: 10 OVX + PTH Group 4: 10 OVX + PTH + SIM	SIM Groups 2 and 4: 5 mg/kg/day NA	12 wk	Histology Micro-CT Biomechanical

NBF = new bone formation; BIC = bone-to-implant contact; micro-CT = microcomputed tomography; SIM = simvastatin; FLU= fluvastatin; PTH = parathyroid hormone; PLGA = poly(lactic-co-glycolic acid); BV/TV = bone volume fraction; BCR = bone contact ratio; BD = bone density; DXA= dual-energy x-ray absorptiometry; SEM = scanning electron microscope; ELISA = enzyme-linked immunosorbent assay; OVX = ovariectomized; NA = not available.

around implants was assessed using three-dimensional microcomputed tomography (micro-CT). In 13 studies,[14,17,19,21,22,24–26,28,29,31–33] osseointegration was assessed using histology. Başarir et al[22] used scanning electron microscopy to assess NBF around implants. Ayukawa et al[17] assessed the amount of osteocalcin as a marker of bone resorption, using enzyme-linked immunosorbent assay. Dual-energy x-ray absorptiometry was performed in the study by Tan et al.[31] Monjo et al[26] used a polymerase chain reaction to assess an in vivo BMP-2 gene expression.

Main Outcomes

Systemic Delivery of Statins. Results from all studies[17,19,21–23,25,31] where the statins were administered systemically showed that simvastatin and fluvastatin enhanced NBF and/or BIC around implants (Table 1).

Topical Delivery of Statins. Results from five studies[20,24,26–28] where the statins were administered topically into the bone cavities showed that simvastatin, fluvastatin, and rosuvastatin enhanced NBF and/or BIC around implants (Table 2).

Implants with Statin-Coated Surfaces. Results from six studies[14,18,29,30,32,33] showed that simvastatin improved NBF, bone volume fraction, or BIC and biomechanical properties. However, Pauly et al[16] evaluated the effectiveness of titanium Kirschner wires coated with a high dose (90 µg/implant) of simvastatin in the promotion of NBF in rat femurs, reporting impaired osseointegration under local application of simvastatin-coated implants after 8 weeks.

Quality Assessment of Included Studies

Quality assessment showed that all studies[14,16–33] were conducted on experimental animals, and the total quality score ranged from 8 to 11. The most common shortcoming among all studies[14,16–33] was the short-term and incomplete follow-up of the experimental

Outcome
Group 2 presented higher BCR and BD compared with group 1.
Groups 4 and 5 presented significantly higher BCR and BD compared with groups 1, 2, and 3. No significant difference between the groups in cortical bone area
Group 2 presented significantly higher NBF and fixation strength compared with group 1.
Group 3 presented higher BIC and BD in cancellous bone compared with group 2. No significant difference between 3 groups in cortical bone
Groups 3 and 4 presented higher BCR, NBF, and bending test rates compared with groups 1 and 2.
Groups 1 and 2 presented significantly higher BMD, BV/TV, implant fixation, trabecular number, and thickness compared with group 3.
Group 4 presented significantly higher BV/TV, BIC, BCR, and push-out force compared with groups 1, 2, and 3.

groups. Furthermore, as all studies[14,16–33] were performed in animals, the application of these results to the human population is still limited. Thus, although, on average, the quality of included animal studies on the impact of statin administration on the osseointegration of implants was good, the limitations of short-term follow-up and a lack of clinical studies limit the clinical application of these study outcomes. Quality assessment of the individual papers is summarized in Table 4.

DISCUSSION

To the authors' knowledge from indexed literature, the present study is the first one to systematically review the efficacy of local and systemic administration of statins in enhancing osseointegration and NBF around implants. Results from ~95% of the studies[14,17–33] showed that local and systemic statin administration is effective in enhancing osseointegration and NBF around implants. These results seem persuasive enough to conclude that local and systemic administration of statins enhances osseointegration. However, it seems difficult to replicate these experimental results in a clinical setting for a number of reasons. First, it seems challenging to establish a precise route of administration for statin delivery in humans. For example, in the studies by Ayukawa et al,[17,21] simvastatin was administered systemically via intraperitoneal injections, whereas in other studies, statins were systemically administered using subcutaneous,[22] oral,[23] intraosseous,[31] and percutaneous[25] routes. Second, the dose formulation and frequency of statin delivery that could yield the most predictive outcome varied between the studies[17,21–28,31]; Tan et al[31] administered a single simvastatin dosage of 5 or 10 mg to study subjects, whereas in studies by Ayukawa et al[17] and Başarir et al,[22] statins were delivered at dosages of 0.125 mg/kg/day for 4 weeks, and up to 50 mg/kg/day, for 6 weeks, respectively. Since statins are metabolized in the liver,[36] it is hypothesized that in a clinical scenario, higher concentrations of statins (compared with those reported in the studies[14,16–33] included in the present systematic review) would most likely be needed to induce osteogenesis and NBF around dental implants. Gutierrez et al[37] suggested that topical application of statins is 50 to 80 times more effective in inducing bone formation. This reflects that in a clinical scenario, there is a lack of agreement regarding the route of administration, dosage, and frequency of statin delivery in the included studies, and this needs to be further optimized.

It is notable that the experimental studies[14,16–33] were performed for a maximum follow-up period of 12 weeks. It remains unclear whether adjunct use of statins (either systemic or local) in patients receiving dental implants would increase BIC and contribute to long-term (at least 5 years or longer) success and survival of dental implants. Further long-term clinical studies are needed in this regard. The authors, however, emphasize that a longer follow-up for the studies included in the present systematic review[14,16–33] would have provided stronger evidence regarding the efficacy of statin administration on the osseointegration of implants.

Studies[38,39] have shown that systemic diseases such as osteoporosis jeopardize osseointegration, leading to a reduction of implant stability. The beneficial effects of statins in the treatment of osteoporosis have been confirmed in vivo and in clinical studies.[40,41] However, controversial results exist, associated with different factors such as type, route of administration, and dosage of statins, suggesting that statins may have no

Table 2 Local Delivery of Statins

Study	Study animals (mean age)	Study groups	Statin dose and route of administration
Implants with statin-coated surface			
Fang et al[14]	36 Female rats (NA)	Group 1: 12 OVX + HA + SIM 10^{-7} M Group 2: 12 OVX + HA + SIM 10^{-6} M Group 3: 12 OVX + HA	SIM coating solution Group 1: 10^{-7} M Group 2: 10^{-6} M
Kwon et al[18]	4 Male rabbits (NA)	Group 1: Control Group 2: HA Group 3: HA + SIM	SIM Group 3: 535 μg
Nyan et al[29]	24 Male rats (4 months)	Group 1: 6 Control Group 2: 6 MAO coating Group 3: 6 MAO + SIM 25 μg coating Group 4: 6 MAO + SIM 50 μg coating	SIM coating solution Group 3: 25 μg SIM Group 4: 50 μg SIM
Pauly et al[16]	80 Female rats (6 months)	Group 1: 20 Control Group 2: 20 PDLLA Group 3: 20 PDLLA + SIM 5.5 μg Group 4: 20 PDLLA + SIM 90 μg	SIM coating solution Group 3: 5.5 μg SIM Group 4: 90 μg SIM
Stadlinger et al[30]	224 Female rats (6 months)	Group 1: 32 Sham Group 2: 32 Sham + conditioned implant Group 3: 32 OVX Group 4: 32 OVX + conditioned implant Group 5: 32 OVX + collagen Group 6: 32 OVX + SIM Group 7: 32 OVX + ZA	SIM coating solution Group 6: 35 μg SIM
Yang et al[32]	48 Female rats (NA)	Group 1: OVX + SIM 10^{-7} M Group 2: OVX + SIM 10^{-6} M Group 3: OVX	SIM coating solution Group 1: 10^{-7} M Group 2: 10^{-6} M
Zhao et al[33]	16 Female rats (NA)	Group 1: OVX Group 2: OVX + SIM 10^{-6} M coating	SIM coating solution Group 2: 10^{-6} M
Topical delivery of statins			
Faraco-Schwed et al[20]	16 Male rabbits (11–15 months)	Group 1: 4 SIM + 28 days Group 2: 4 SIM + 56 days Group 3: 4 Control + 28 days Group 4: 4 Control + 56 days	SIM 0.25 mL gel (30 mg/mL) 7.5 mg
Mansour et al[24]	10 Dogs (18–24 months)	Group 1: SIM Group 2: Control	SIM 2.2 mg × 150 mg total weight Granules in cellulosic polymeric matrix
Monjo et al[26]	18 Female rabbits (2.2 months old)	Group 1: Sham Group 2: ACS Group 3: ACS + RSV1 Group 4: ACS + RSV2 Group 5: ACS + RSV3	RSV ACS RSV1: 8.7 ± 1.8 μg RSV2: 52 ± 4.4 μg RSV3: 259.1 ± 8.8 μg
Moriyama et al[27]	60 Female rats (2.2 months)	Group 1: 12 Control Group 2: 12 PGA Group 3: 12 PGA + FLU1 Group 4: 12 PGA + FLU2 Group 5: 12 PGA + FLU3	FLU PGA carrier FLU 1: 0.1 mg/mL (3 μg) FLU 2: 0.5 mg/mL (15 μg) FLU3: 2.5 mg/mL (75 μg)
Moriyama et al[28]	126 Female rats (2.2 months)	Group 1: 21 Control Group 2: 21 PGA Group 3: 21 FLU1 Group 4: 21 FLU2 Group 5: 21 FLU3 Group 6: 21 FLU4	FLU PGA carrier FLU 1: 0.1 mg/mL (3 μg) FLU 2: 0.5 mg/mL (15 μg) FLU3: 2.5 mg/mL (75 μg) FLU4: 10 mg/mL (300 μg)

SIM = simvastatin; FLU = fluvastatin; RSV = rosuvastatin; HIST = histomorphometric; BCR = bone contact ratio; ZA = zoledronic acid; BD = bone density; ELISA = enzyme-linked immunosorbent assay; SEM = scanning electron microscope; BIC = bone-to-implant contact; BV = bone volume; PLGA = poly (lactic-co-glycolic acid); ACS = absorbable collagen sponge; PGA = propylene glycol alginate; MBV = mineralized bone volume; BV/TV= bone volume fraction; DXA = dual-energy x-ray absorptiometry; Micro-CT = microcomputed tomography; MAO = micro-arc oxidation; HA = hydroxyapatite; PDLLA = poly(D,L-lactide); PTH = parathyroid hormone; OVX = ovariectomized.

Follow-up	Analysis methods	Outcome
2, 4, and 12 weeks	Histology HIST	Groups 1 and 2 presented higher BIC and NBF compared to group 3.
4 weeks	MicroCT Biomechanical	Group 3 presented significantly higher removal torque and NBF compared to groups 1 and 2.
2 and 4 weeks	MicroCT Histology	Groups 3 and 4 presented higher BV, BIC and MBV compared to groups 1 and 2.
8 weeks	HIST Biomechanical	Group 4 presented a significant decrease in fixation strength, BIC and NBF compared to groups 1 and 2.
2 and 4 weeks	HIST MicroCT Biomechanical	Group 6 presented a significant increase in BIC, BV/TV, and BD compared to groups 3, 4, and 5.
1,2,4, and 12 weeks	HIST Histology	Groups 1 and 2 presented a significant increase in NBF and BIC compared to group 3.
4 and 12 weeks	HIST Histology	Group 2 presented a significant increase in NBF and BIC compared to group 1.
4 and 8 weeks	Biomechanical	Group 2 presented significantly higher removal torque values compared to group 4. No significant difference between groups 1 and 3.
4 and 12 weeks	Histology	Group 1 presented higher NBF compared to group 2.
4 weeks	PCR MicroCT Histology	Group 3 presented higher NBF and increased BMP-2 messenger RNA levels compared to the rest of the groups.
1 and 2 weeks	HIST Biomechanical	Group 5 presented significantly higher BV and push-out strength compared with groups 1 and 2. No significant difference in BIC among 5 groups.
1,2, and 4 weeks	Histology HIST Biomechanical	MBV and push-in strength at week 1 were significantly lower in group 6 compared to the rest of the groups. At week 2, BIC and MBV were higher in group 5 compared to groups 1 and 2.

Table 3 Characteristics of the Implants in Included Studies

Study	No. of implants	Implant dimensions (diameter × length in mm)	Location of implant placement	Implant shape	Implant surface characteristics (median roughness)
Ayukawa et al[21]	Ti implants NA	1 × 1.5	Tibia	Cylinder	Smooth (0.438 μm)
Ayukawa et al[17]	Ti implants NA	1 × 1.5	Tibia	Cylinder	Smooth (0.438 μm)
Başarir et al[22]	Ti implants NA	5 × 10	Femur	Cylinder	Rough
Du et al[23]	Ti implants NA	2 × 5	Tibia	Screw	Rough
Fang et al[14]	72 Ti implants	2.2 × 4.0	Tibia	Screw	Rough
Faraco-Schwed et al[20]	32 Ti implants	3.25 × 8.5	Tibia	NA	Rough
Kwon et al[18]	16 Ti implants	3.5 × 8	Tibia and femur	Screw	Rough
Mansour et al[24]	Ti implants NA	3.5 × 10	Mandible	Cylinder	Rough
Masuzaki et al[25]	40 Ti implants	1 × 1.5	Tibia	Cylinder	Smooth (0.5 μm)
Monjo et al[26]	Ti implants NA	6.25 × 1.95	Tibia	Coin-shaped	NA
Moriyama et al[27]	Ti implants NA	1 × 1.5	Tibia	Cylinder	NA
Moriyama et al[28]	Ti implants NA	1 × 1.5	Tibia	Cylinder	Smooth (0.438 μm)
Nyan et al[29]	Ti implants NA	1.8 × 5.0	Tibia	Screw	Rough
Pauly et al[16]	Ti implants NA	1.4 × NA	Femur	Wire	NA
Stadlinger et al[30]	Ti implants NA	1.7 × 3	Tibia	Screw	Rough
Tan et al[31]	Ti implants NA	1.5 × 10	Femur	Screw	NA
Tao et al[19]	Ti implants NA	1.5 × 20	Femur	Cylinder	Rough
Yang et al[32]	96 Ti implants	2.2 × 4.0	Tibia	Screw	Rough
Zhao et al[33]	Ti implants NA	2.2 × 4.0	Tibia	Screw	Rough

benefit and in some instances, may impair bone repair.[42,43] Moreover, several factors, such as duration of the osteoporosis, age of the patient, and undergoing medication, can affect implant osseointegration.[39,44] Thereby, in a clinical scenario, delivery of statins (either locally or systemically) may not be sufficient enough to induce NBF around implants in patients with osteoporosis. The authors of the present systematic review believe that further clinical studies are needed to assess the role of statins in osteoporotic patients.

Confounding parameters, such as poorly controlled diabetes mellitus, stress, immunodeficiency, increasing age, female gender, deficient oral hygiene, and tobacco habits may also impair healing and are significant risk factors of alveolar bone loss.[45–50] Since all studies[14,16–33] included in this systematic review were performed in animals, it remains to be determined whether or not statin administration in a clinical scenario would facilitate NBF in patients with poor plaque control, elderly individuals, patients who are systemically compromised, and habitual tobacco product users. Hence, additional studies are warranted in this regard.

Interestingly, Pauly et al[16] showed that local application of statins around implant surfaces impaired osseointegration and NBF; moreover, 20% of the animals in the test group with 90 μg simvastatin–coated implants

Table 4 CASP Quality Assessment of the Reviewed Papers

Study	Item												Total quality score (0 to 12)
	1	2	3	4	5	6	7	8	9	10	11	12	
Ayukawa et al[21]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	10
Ayukawa et al[17]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	10
Başarir et al[22]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	10
Du et al[23]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	11
Fang et al[14]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	11
Faraco-Schwed et al[20]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	11
Kwon et al[18]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	10
Mansour et al[24]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	11
Masuzaki et al[25]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	10
Monjo et al[26]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	10
Moriyama et al[27]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	10
Moriyama et al[28]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	10
Nyan et al[29]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	10
Pauly et al[16]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	No	No	8
Stadlinger et al[30]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	10
Tan et al[31]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	10
Tao et al[19]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	11
Yang et al[32]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	11
Zhao et al[33]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	11

showed osteolysis next to the implant surfaces. Some possible explanations can be hypothesized for these findings. First, there was a possible risk of infection after the implant placement in the rats' femur; peri-implant infections have been reported to impair osseointegration and increase implant failure after surgical procedures.[51,52] It is worth mentioning that Pauly et al[16] ruled out the possibility of a microbiologic analysis of the osseous tissues, which could have revealed valuable information from a microbial with reference to impaired osteogenesis. This was a relatively short-term study (14 days).[16] It is therefore tempting to speculate that microbiologic analysis of osseous tissues could have reflected the presence of a peri-implant infection. Moreover, Pauly et al[16] used titanium Kirschner wires coated with a poly(D,L-lactide) solution, and no characteristics of the implant surface topography were reported. The authors of this systematic review hypothesize that in the Pauly study,[16] the use of a smooth-surface simvastatin-coated implant may have impaired osseointegration.

CONCLUSIONS

On experimental grounds, local and systemic statin delivery seems to enhance osseointegration; however, from a clinical perspective, further randomized controlled trials are needed to assess the role of statins in promoting osseointegration around dental implants.

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REFERENCES

1. Walton TR. An up-to-15-year comparison of the survival and complication burden of three-unit tooth-supported fixed dental prostheses and implant-supported single crowns. Int J Oral Maxillofac Implants 2015;30:851–861.
2. Gadi R, Figueredo VM. Low-density lipoprotein cholesterol lowering therapies: What is on the horizon? J Cardiovasc Med (Hagerstown) 2015;16:1–10.
3. Goldstein JL, Brown MS. Regulation of the mevalonate pathway. Nature 1990;343:425–430.
4. Hamelin BA, Turgeon J. Hydrophilicity/lipophilicity: Relevance for the pharmacology and clinical effects of HMG-CoA reductase inhibitors. Trends Pharmacol Sci 1998;19:26–37.
5. Gomaraschi M, Adorni MP, Banach M, Bernini F, Franceschini G, Calabresi L. Effects of established hypolipidemic drugs on HDL concentration, subclass distribution, and function. Handb Exp Pharmacol 2015;224:593–615.

6. Moon HJ, Kim SE, Yun YP, et al. Simvastatin inhibits osteoclast differentiation by scavenging reactive oxygen species. Exp Mol Med 2011;43:605–612.
7. Yamashita M, Otsuka F, Mukai T, et al. Simvastatin inhibits osteoclast differentiation induced by bone morphogenetic protein-2 and RANKL through regulating MAPK, AKT and Src signaling. Regul Pept 2010;162:99–108.
8. Walter MS, Frank MJ, Rubert M, Monjo M, Lyngstadaas SP, Haugen HJ. Simvastatin-activated implant surface promotes osteoblast differentiation in vitro. J Biomater Appl 2014;28:897–908.
9. Yang F, Zhao SF, Zhang F, He FM, Yang GL. Simvastatin-loaded porous implant surfaces stimulate preosteoblasts differentiation: An in vitro study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011;111:551–556.
10. Yueyi C, Xiaoguang H, Jingying W, et al. Calvarial defect healing by recruitment of autogenous osteogenic stem cells using locally applied simvastatin. Biomaterials 2013;34:9373–9380.
11. Dolkart O, Liron T, Chechik O, et al. Statins enhance rotator cuff healing by stimulating the COX2/PGE2/EP4 pathway: An in vivo and in vitro study. Am J Sports Med 2014;42:2869–2876.
12. Oka S, Matsumoto T, Kubo S, et al. Local administration of low-dose simvastatin-conjugated gelatin hydrogel for tendon-bone healing in anterior cruciate ligament reconstruction. Tissue Eng Part A 2013;19:1233–1243.
13. Mundy G, Garrett R, Harris S, et al. Stimulation of bone formation in vitro and in rodents by statins. Science 1999;286:1946–1949.
14. Fang W, Zhao S, He F, Liu L, Yang G. Influence of simvastatin-loaded implants on osseointegration in an ovariectomized animal model. Biomed Res Int 2015;2015:831504.
15. 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;30:191–199.
16. Pauly S, Back DA, Kaeppler K, Haas NP, Schmidmaier G, Wildemann B. Influence of statins locally applied from orthopedic implants on osseous integration. BMC Musculoskelet Disord 2012;13:208.
17. Ayukawa Y, Ogino Y, Moriyama Y, et al. Simvastatin enhances bone formation around titanium implants in rat tibiae. J Oral Rehabil 2010;37:123–130.
18. Kwon YD, Yang DH, Lee DW. A titanium surface-modified with nano-sized hydroxyapatite and simvastatin enhances bone formtion and osseintegration. J Biomed Nanotechnol 2015;11:1007–1015.
19. Tao ZS, Zhou WS, Tu KK, et al. The effects of combined human parathyroid hormone (1-34) and simvastatin treatment on osseous integration of hydroxyapatite-coated titanium implants in the femur of ovariectomized rats. Injury 2015;46:2164–2169.
20. Faraco-Schwed FN, Mangueira LM, Ribeiro JV, Antao Ada S, Shibli JA. Removal torque analysis of implants in rabbit tibia after topical application of simvastatin gel. J Oral Implantol 2014;40:53–59.
21. Ayukawa Y, Okamura A, Koyano K. Simvastatin promotes osteogenesis around titanium implants. Clin Oral Implants Res 2004;15:346–350.
22. Başarir K, Erdemli B, Can A, Erdemli E, Zeyrek T. Osseointegration in arthroplasty: Can simvastatin promote bone response to implants? Int Orthop 2009;33:855–859.
23. Du Z, Chen J, Yan F, Xiao Y. Effects of Simvastatin on bone healing around titanium implants in osteoporotic rats. Clin Oral Implants Res 2009;20:145–150.
24. Mansour G, Al Ashwah A, Koura A. Evaluation of simvastatin grafting around immediate dental implants in dogs. Implant Dent 2014;23:195–199.
25. Masuzaki T, Ayukawa Y, Moriyama 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;31:3327–3334.
26. Monjo M, Rubert M, Wohlfahrt JC, Rønold HJ, Ellingsen JE, Lyngstadaas SP. In vivo performance of absorbable collagen sponges with rosuvastatin in critical-size cortical bone defects. Acta Biomater 2010;6:1405–1412.
27. Moriyama Y, Ayukawa Y, Ogino Y, Atsuta I, Koyano K. Topical application of statin affects bone healing around implants. Clin Oral Implants Res 2008;19:600–605.
28. Moriyama Y, Ayukawa Y, Ogino Y, et al. Local application of fluvastatin improves peri-implant bone quantity and mechanical properties: A rodent study. Acta Biomater 2010;6:1610–1618.
29. Nyan M, Hao J, Miyahara T, Noritake K, Rodriguez R, Kasugai S. Accelerated and enhanced bone formation on novel simvastatin-loaded porous titanium oxide surfaces. Clin Implant Dent Relat Res 2014;16:675–683.
30. Stadlinger B, Korn P, Tödtmann N, et al. Osseointegration of biochemically modified implants in an osteoporosis rodent model. Eur Cell Mater 2013;25:326–340; discussion 339–340.
31. Tan J, Yang N, Fu X, et al. Single-dose local simvastatin injection improves implant fixation via increased angiogenesis and bone formation in an ovariectomized rat model. Med Sci Monit 2015;21:1428–1439.
32. Yang G, Song L, Guo C, Zhao S, Liu L, He F. Bone responses to simvastatin-loaded porous implant surfaces in an ovariectomized model. Int J Oral Maxillofac Implants 2012;27:369–374.
33. Zhao S, Wen F, He F, Liu L, Yang G. In vitro and in vivo evaluation of the osteogenic ability of implant surfaces with a local delivery of simvastatin. Int J Oral Maxillofac Implants 2014;29:211–220.
34. Zeng X, Zhang Y, Kwong JS, et al. The methodological quality assessment tools for preclinical and clinical studies, systematic review and meta-analysis, and clinical practice guideline: A systematic review. J Evid Based Med 2015;8:2–10.
35. Advisory Task Force on Bisphosphonate-Related Ostenonecrosis of the Jaws, American Association of Oral and Maxillofacial Surgeons. American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaws. J Oral Maxillofac Surg 2007;65:369–376.
36. Dongiovanni P, Petta S, Mannisto V, et al. Statin use and non-alcoholic steatohepatitis in at risk individuals. J Hepatol 2015;63:705–712.
37. Gutierrez GE, Lalka D, Garrett IR, Rossini G, Mundy GR. Transdermal application of lovastatin to rats causes profound increases in bone formation and plasma concentrations. Osteoporos Int 2006;17:1033–1042.
38. Giro G, Chambrone L, Goldstein A, et al. Impact of osteoporosis in dental implants: A systematic review. World J Orthop 2015;6:311–315.
39. Piarulli G, Rossi A, Zatti G. Osseointegration in the elderly. Aging Clin Exp Res 2013;25(suppl):s59–s60.
40. Huang W, Shang WL, Li DH, Wu WW, Hou SX. Simvastatin protects osteoblast against H2O2-induced oxidative damage via inhibiting the upregulation of Nox4. Mol Cell Biochem 2012;360:71–77.
41. 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;40:1581–1587.
42. Oryan A, Kamali A, Moshiri A. Potential mechanisms and applications of statins on osteogenesis: Current modalities, conflicts and future directions. J Control Release 2015;215:12–24.
43. Bone HG, Kiel DP, Lindsay RS, et al. Effects of atorvastatin on bone in postmenopausal women with dyslipidemia: A double-blind, placebo-controlled, dose-ranging trial. J Clin Endocrinol Metab 2007;92:4671–4677.
44. Devlin H. Identification of the risk for osteoporosis in dental patients. Dent Clin North Am 2012;56:847–861.
45. Javed F, Al-Askar M, Samaranayake LP, Al-Hezaimi K. Periodontal disease in habitual cigarette smokers and nonsmokers with and without prediabetes. Am J Med Sci 2013;345:94–98.
46. Javed F, Altamash M, Klinge B, Engström PE. Periodontal conditions and oral symptoms in gutka-chewers with and without type 2 diabetes. Acta Odontol Scand 2008;66:268–273.
47. Javed F, Tenenbaum HC, Nogueira-Filho G, et al. Periodontal inflammatory conditions among gutka chewers and non-chewers with and without prediabetes. J Periodontol 2013;84:1158–1164.
48. Javed F, Näsström K, Benchimol D, Altamash M, Klinge B, Engström PE. Comparison of periodontal and socioeconomic status between subjects with type 2 diabetes mellitus and non-diabetic controls. J Periodontol 2007;78:2112–2119.
49. Renvert S, Persson GR. Patient-based assessments of clinical periodontal conditions in relation to alveolar bone loss. J Clin Periodontol 2004;31:208–213.
50. Javed F, Al-Rasheed A, Almas K, Romanos GE, Al-Hezaimi K. Effect of cigarette smoking on the clinical outcomes of periodontal surgical procedures. Am J Med Sci 2012;343:78–84.
51. Bafail AS, Alamri AM, Spivakovsky S. Effect of antibiotics on implant failure and postoperative infection. Evid Based Dent 2014;15:58.
52. Clementini M, Rossetti PH, Penarrocha D, Micarelli C, Bonachela WC, Canullo L. Systemic risk factors for peri-implant bone loss: a systematic review and meta-analysis. Int J Oral Maxillofac Surg 2014;43:323–334.