Review Article | Emerging Therapeutics

Efficacy of statins in tissue healing following tooth extraction: a systematic review of animal studies

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Background: Statins, with their unique ability to stimulate bone formation and soft tissue healing, hold the potential to revolutionize dental care. The present study aims to delve into the profound effects of statins on bone and soft tissue healing in dental extraction sockets, offering a promising future for dental professionals and patients alike.

Methods: This systematic review aimed to understand the role of stains in tissue healing following dental extraction. This study was registered in the International Prospective Register of Ongoing Systematic Reviews (PROSPERO; CRD42022299247). A comprehensive electronic database search yielded 412 manuscripts. After a rigorous screening process, nine manuscripts met the eligibility criteria. The study sample consisted of 403 animals, with eight studies utilizing rat animal models and one conducted on mongrel dogs.

Results: Overall, the application of statin drugs holds promise for improving tissue healing outcomes following tooth extraction. The primary outcome variables across all studies were residual ridge height and width, messenger ribonucleic acid (mRNA) expression of transforming growth factor-beta 1 (TGF-β1), bone morphogenetic protein-2 (BMP-2), and vascular endothelial growth factor (VEGF), bone and gingival healing, inflammatory response, and bone turnover (BT), bone formation in tooth extraction socket, and osteogenic healing in a tooth extraction socket.

Conclusions: The findings of this study underscore the significant potential of statin drugs to enhance tissue healing outcomes following tooth extraction. This discovery opens new and exciting possibilities for improving dentistry patient care, potentially transforming how we approach post-extraction healing.

Keywords: Tooth extraction; extraction sockets; statins; dental implants; soft tissue healing

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Introduction

Tooth extraction starts a cascade of events, including inflammation, epithelialization, and remodeling. The socket heals via secondary intention and continues to remodel for up to one year following extraction (1). Autografts, allografts, xenografts, synthetic materials, and osteoinductive growth factors are currently used in clinical practice (2). Although the risk of disease transmission is sporadic, some patients may not prefer bone from another human or animal. Furthermore, due to the low concentration of bone growth proteins, they lack the osteoinductive capability (3). Similarly, synthetic materials have shortcomings, such as different resorption rates and a lack of intrinsic growth factors (4). The exponential development in regenerative medicine and tissue engineering has led to the use of recombinant human bone morphogenetic protein (rhBMP)-2, platelet rich plasma (PRP) products, progenitor cells, and various scaffolding systems to help with the delivery of some of these cellular elements (5-8).

Research and development in this arena have constantly evolved. Three-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA) has appeared as a promising alternative to promote bone healing and regeneration in the past decade. HMG-CoA (statin) is a key regulatory enzyme in the cholesterol biosynthesis (9). Statins stimulate bone formation through early expression of vascular endothelial growth factors (VEGFs), causing angiogenesis and differentiation of mesenchymal cells into bone-forming cells (10,11). Statins also play a role in the upregulation of the gene expression of extracellular matrix proteins, namely bone morphogenetic protein-2 (BMP-2), osteocalcin, bone sialoprotein, and type 1 collagen, to accelerate new bone formation, while downregulating the gene expression for collagenase-1, and collagenase-3 (12). Statins have been shown to promote new bone formation in the tooth extraction sockets (13). Its application around implants has demonstrated increased osteogenesis osseointegration and soft tissue healing around implants (14-16). Studies have suggested that a single local injection of statin at tooth extraction can potentially decrease the risk of developing medication-related osteonecrosis of like lesions (17-19). Most studies have been conducted on animal models, documenting the healing potential of topical application of the statins in the extraction sockets and around implants (13,14,19-25). This review evaluated the effect of statins on bone and soft tissue healing. The specific aim was to assess bone and soft tissue healing in dental extraction sockets following the local application of statins. We present this article in accordance with the PRISMA reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-24-140/rc) (26).

Highlight box

Key findings

- Local statin administration in tooth extraction sockets demonstrates enhanced bone repair, increased new bone formation, maintenance of height and width of residual alveolar ridge, upregulated messenger ribonucleic acid expression of growth factors, enhanced neo-vascularization, reduced inflammation and alveolar bone loss.

What is known and what is new?

- Previously, several materials were used to augment healing near a tooth extraction socket. Disadvantages like costs involved, risk of disease transmission and donor site morbidity have failed to establish a gold standard.
- Findings of this review demonstrate that statins preserve alveolar ridge and increase the healing of a tooth extraction socket, ensuring healthy a periodontium and osseo-integration. Reduced progression of medication related osteoradionecrosis of jaw like-lesion has also been observed, further enhancing scope of statin drugs in dentistry.

What is the implication, and what should change now?

- Further randomized controlled trials are warranted to establish sound guidelines for using statins in this regard.

Methods

Reporting format

The study's focused question was, "Does local administration of statins enhance healing in the socket following dental extraction?". This study was registered in the International Prospective Register of Ongoing Systematic Reviews (PROSPERO; CRD42022299247). Due to high heterogenicity, a meta-analysis was not performed.

Patients, interventions, control, outcome (PICO)

(P): experimental animal models in which tooth extraction was performed; (I): statin drug administration in the tooth extraction socket; (C): no statin drug administration in the tooth extraction socket; (O): tissue healing.

Table 1 SYRCLE risk of bias

Domain	Adachi *et al.*, 2020 (19)	Rakhmatia *et al.*, 2018 (24)	Liu *et al.*, 2009 (21)	Li *et al.*, 2019 (13)	Mansour *et al.*, 2014 (14)	Willett *et al.*, 2017 (23)	Yasunami *et al.*, 2015 (22)	Sanda *et al.*, 2021 (25)	Wu *et al.*, 2008 (20)	Overall
Sequence generation	High	High	Low	Low	High	High	High	High	Low	High
Baseline characteristics	Low	High	Low	Low	Low	High	Low	Low	Low	High
Allocation concealment	High	High	High	High	High	High	High	High	High	High
Random housing	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Performance blinding	Unclear	High	High	High	High	High	High	High	High	High
Random outcome assessment	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Detection blinding	High	High	High	High	High	High	High	High	High	High
Incomplete outcome data	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Selective outcome reporting	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Other sources of bias	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low

SYRCLE, Systematic Review Centre for Laboratory Animal Experimentation.

Eligibility criteria

The following were the eligibility criteria of the included studies: (I) original studies; (II) animal studies; (III) presence of intervention (tooth extraction with statin administration) and control groups (tooth extraction without statin administration); (IV) English language. The following exclusion criteria were applied: (I) case reports and series; (II) commentaries; (III) letters to the editor; (IV) review articles; (V) *in-vivo* or human studies.

Search strategy and data extraction

Indexed databases were searched electronically in PubMed, Cochrane Library, EMBASE, Ovid Medline, Scopus, Web of Science, EBSCOhost, and JSTOR by two authors (K.K. and M.K.). Relevant studies up to and including December 2023 were included. A combination of the following terms was used to identify pertinent studies: (I) tooth extraction; (II) dental extraction; (III) exodontia; (IV) statins; (V) HMG CoA reductase inhibitors and text words; (VI) tissue repair; (VII) tooth socket healing; (VIII) bone regeneration; (IX) alveolar ridge preservation; and (X) animal experiments. A combination of the following keywords was used: (I) statins AND tooth extraction; (II) statins AND dental extraction; (III) statins AND exodontia; (IV) HMG CoA reductase inhibitors AND tooth extraction; (V) HMG CoA reductase inhibitors AND dental extraction; and (VI) HMG CoA reductase inhibitors AND exodontia. Boolean operators (OR and AND) combined keywords to expand search results. Disagreements during the process were solved through discussion between the authors and consultation of a third author (P.G.).

Data collection, statistical analysis, and risk of bias

Data variables including study design, age range, study groups, group allocations, study duration, the primary site of the evaluation, primary parameters of the review, type of statin, dose, delivery method, frequency, and site of application were included to answer the research question by authors P.G., M.K., and J.K. The Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) was used to evaluate the studies' bias. Specifically, the SYRCLE risk of bias tool, adapted from the Cochrane Risk of Bias tool for animal intervention studies, eased a thorough assessment of study quality, enhancing the credibility of preclinical evidence (*Table 1*; *Figures 1,2*).

Results

Study selection and general characteristics of study

An electronic database search found 412 manuscripts. After

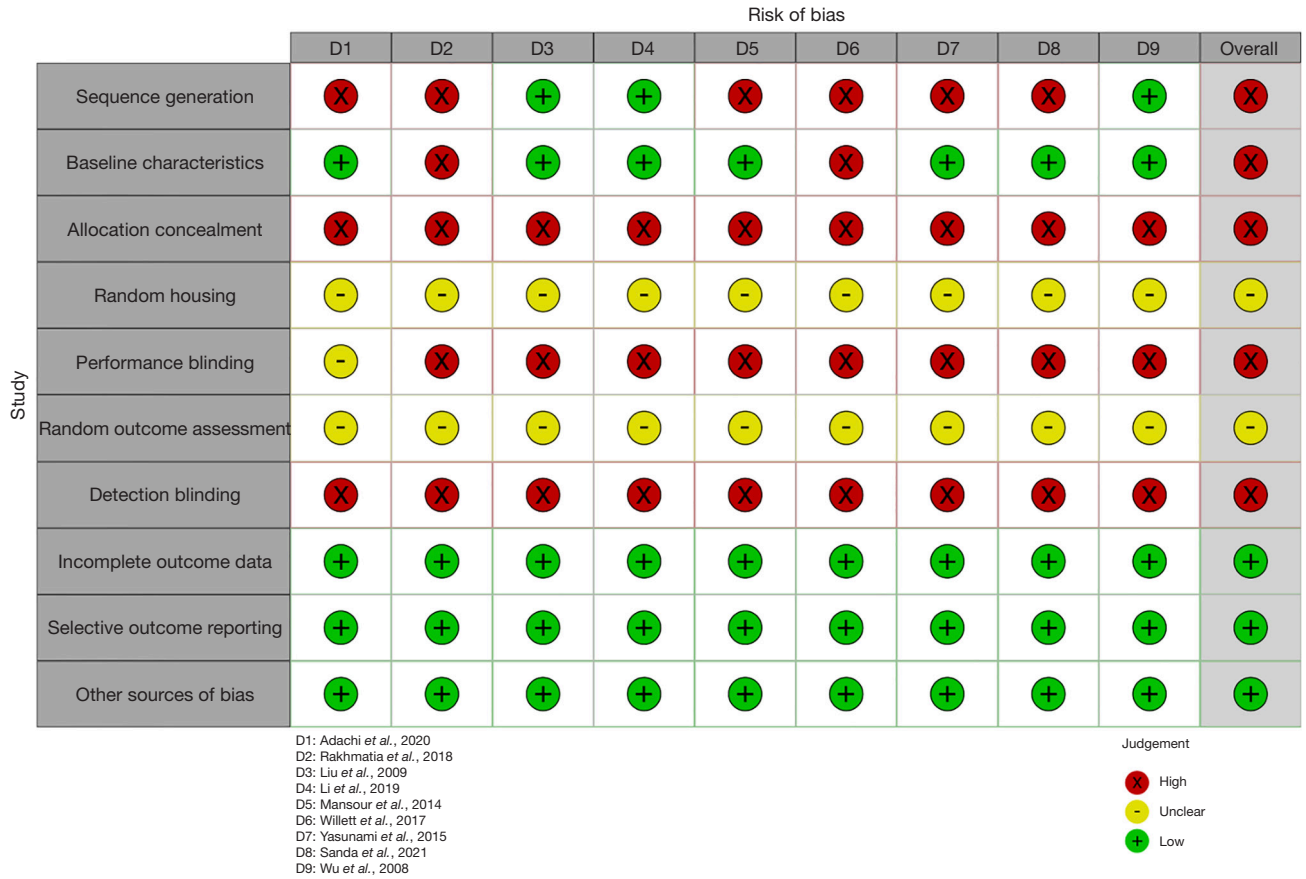

Figure 1 Traffic plot.

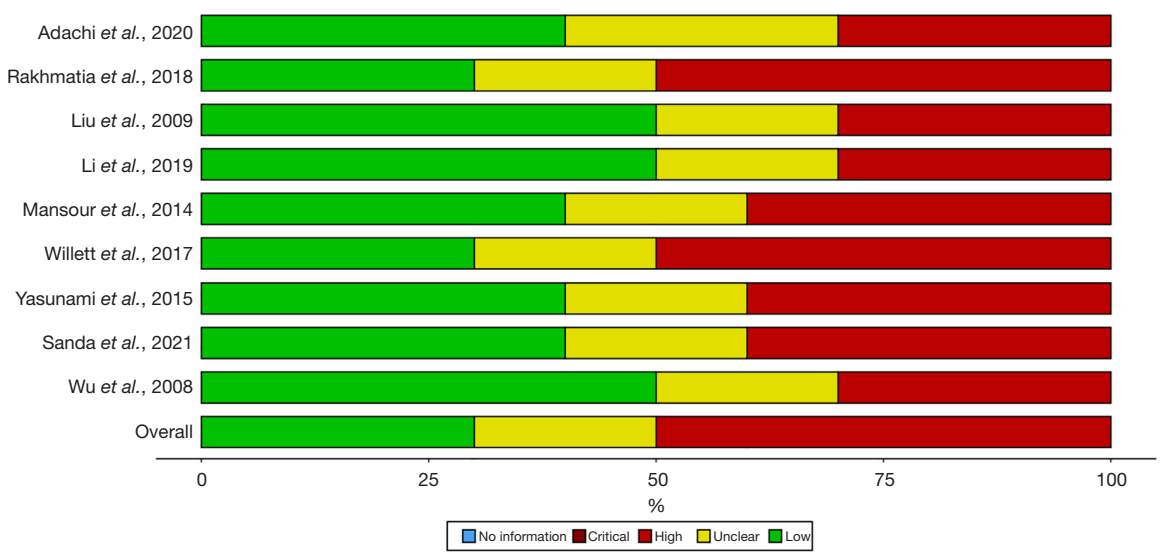

Figure 2 Risk of bias of included studies.

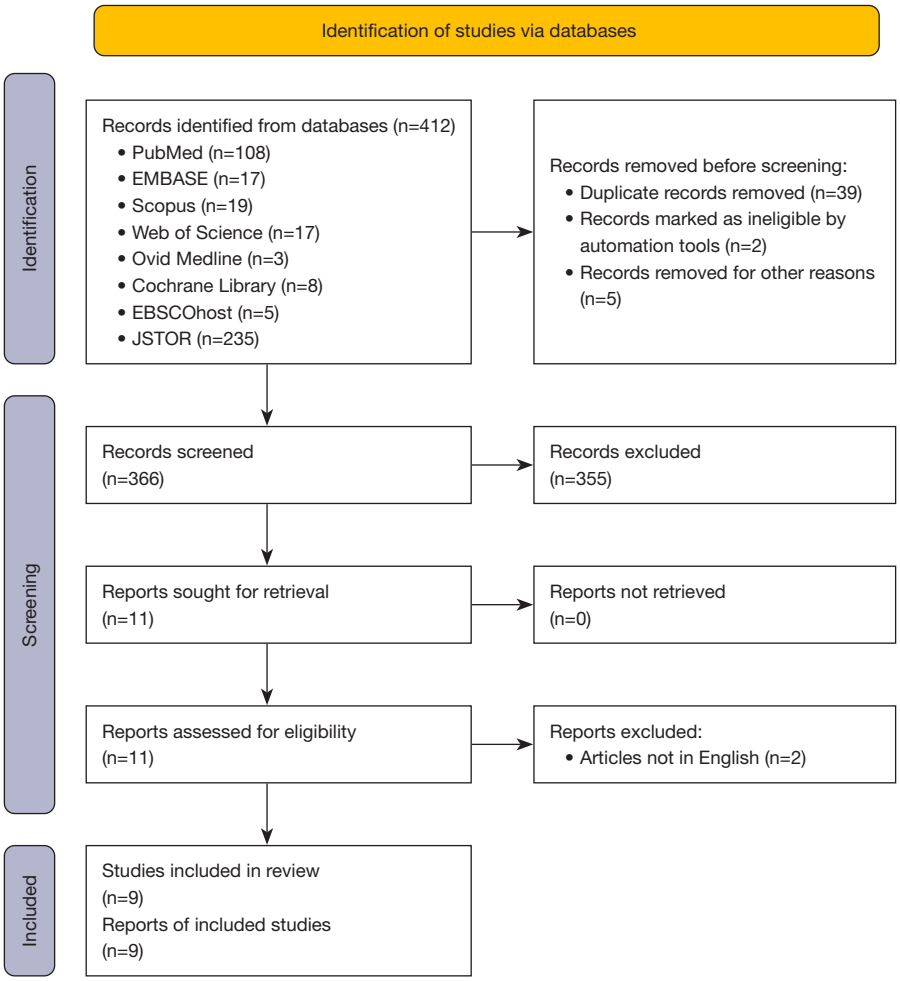

Figure 3 Study flowchart based on the PRISMA guidelines.

the removal for the following reasons: duplicate records (n=39), records marked as ineligible by automation tools (n=2), records removed for other reasons (n=5), 366 manuscripts remained. Following this title, abstract screening, and eligibility criteria, manuscripts met the inclusion and exclusion criteria of the present systematic review (*Figure 3*).

Animal model characteristics

Our study sample formed 403 animals. Eight studies utilized rat animal models (13,19-25), whereas one was performed on mongrel dogs (14). Seven studies reported the gender of animals (13,19-21,23-25). Their age ranged from 1 to 24 months. Of the nine studies, only five reported random group allocations for their study animals (13,19-21,25). The study duration ranged between 14 to 84 days (*Table 2*).

Statin administration

Out of the nine studies, five utilized local administration of simvastatin in the sockets of study group animals (13,14,20,21,23). The remaining four studies applied fluvastatin in the socket (19,22,24,25). The concentration of simvastatin across the studies ranged from 0.01 to 2.2 mg, with two studies employing simvastatin at a 1 mg/scaffold dosage (20,21). The concentration of fluvastatin across the studies ranged from 0.1 to 10 mg/kg (19,24,25). One study used fluvastatin-impregnated poly (lactic-co-glycolic acid) (PLGA) microspheres containing 20 or 40 $\mu g \cdot kg^{-1}$ of fluvastatin (22). The frequency of administration consisted of a single application of the statin drug in the extraction sockets of the study animal (13,14,20,21,23,24). Some authors injected the statin drug in the gingivobuccal fold (22) and near tooth extraction sockets (25) (*Table 3*).

Table 2 General characteristics of included studies

Author, year	Study design	Animal	Number	Sex	Age range	Study groups	Group allocation	Study duration	Evaluation site	The primary parameter of evaluation
Wu *et al.*, 2008 (20)	Experimental	Wistar rats	60	M	7–8 weeks	1. Exp group (n=30): statin-PLGA; 2. scaffold group; 3. control group (n=30); 4. PLGA scaffold group	Random	84 days	Mand right central incisor	Residual ridge height
Liu *et al.*, 2009 (21)	Experimental	Wistar rats	48	M	7–8 weeks	1. Exp group statin group, n=NR; 2. control group (n=NR)	Random	28 days	Mand right incisor	mRNA expression of TGF-beta 1, BMP-2, and VEGF
Mansour *et al.*, 2014 (14)	Split mouth experiment	Mongrel dogs	10	NR	18–24 months	1. Left/experiment side (n=10); 2. right/control side (n=10)	NA	84 days	Mand third premolars	Bone regeneration and neovascularization
Yasunami *et al.*, 2015 (22)	Experimental	Wistar rats	100	NR	6 weeks	1. Exp group 1 (n=5): FS-PLGA 80 group; 2. Exp group 2 (n=5): FS-PLGA 160 group; 3. Exp group 3 (n=5): PLGA-without statin; 4. control group (n=5): no administration	NA	28 days	Max right first molar	Bone and gingival healing
Willett *et al.*, 2017 (23)	Experimental	Sprague-Dawley rats	50	F	10–12 months	1. Exp group (n=9): BMM + statin group; 2. comparator site (n=9): untreated control group	NA	28 days	Max right first molar	Residual ridge height and width, inflammatory response, and BT
Rakhmatia *et al.*, 2018 (24)	Experimental	Rats	48	M	4 weeks	1. Exp group 1 (n=NA): HAFS group; 2. Exp group 2 (n=NA): COFS group; 3. control group 3 (n=NA)	NA	28 days	Mand right incisor	Bone formation in tooth extraction socket
Li *et al.*, 2019 (13)	Experimental	Male Wistar rats	36	M	NA	Exp group (n=12): statin-loaded hydrogel microsphere group; control group (n=12): blank microsphere group	Random	56 days	Mand right central incisor	Osteogenic healing in a tooth extraction socket
Adachi *et al.*, 2020 (19)	Experimental	Wistar rats	30	F	4 weeks	1. Exp group 1 (n=6): low statin conc group; 2. Exp group 2 (n=6): medium statin conc group; 3. Exp group 3 (n=6): high statin conc group; 4. control group (n=6): MRONJ group	Random	14 days	Maxi's right first molar	Bone and gingival healing
Sanda *et al.*, 2021 (25)	Experimental	Wistar rats	21	F	4 weeks	Exp group 1 (n=7): low statin conc group; Exp group 2 (n=7): high statin conc group; control/saline group (n=7)	Random	14 days	Max right first molar	Epithelial continuity and new bone formation

M, male; NR, not reported; F, female; NA, not available; Exp group, experiment group; PLGA, poly (lactic-co-glycolic acid); FS-PLGA, fluvastatin-poly (lactic-co-glycolic acid); BMM, bone mineralized matrix; HAFS, hydroxyapatite containing statin; COFS, carbonate apatite containing statin; MRONJ, medication-related osteonecrosis of jaws; TGF-beta 1, transforming growth factor-beta1; BMP-2, bone morphogenic protein-2; VEGF, vascular endothelial growth factor; BT, bone turnover.

Table 3 Characteristics of statins

Author, year	Type of statin	Dosage of statin	Statin delivery method	Frequency of administration	Site of application
Wu *et al.*, 2008 (20)	Simvastatin	1 mg/scaffold	Implanting statin-PLGA scaffolds into the extraction socket	Once after tooth extraction	Extraction socket of mandibular right incisor
Liu *et al.*, 2009 (21)	Simvastatin	1 mg/scaffold	Implanting statin-PLGA scaffolds into the extraction socket	Once after tooth extraction	Extraction socket of mandibular right incisor
Mansour *et al.*, 2014 (14)	Simvastatin	2.2 mg	Implanting statin granules into the extraction socket	Once at the time of implant placement	Left mandibular third premolars extraction socket
Yasunami *et al.*, 2015 (22)	Fluvastatin	1. Group 1: FS-PL 80 (PLGA containing 20 $\mu g \cdot kg^{-1}$ fluvastatin); 2. Group 2: FS-PL 160 (PLGA containing 40 $\mu g \cdot kg^{-1}$ fluvastatin)	Injection of statin-incorporated PLGA microspheres	Once after tooth extraction	Gingivobuccal fold at the site of tooth extraction
Willett *et al.*, 2017 (23)	Simvastatin	0.2 mg	Packing BMM-statin graft into the tooth extraction socket	Once after tooth extraction	Extraction socket of the maxillary right first molar
Rakhmatia *et al.*, 2018 (24)	Fluvastatin	0.5 mg	Filling statin-associated Granules in tooth extraction socket	Once after tooth extraction	Extraction socket of mandibular right incisor
Li *et al.*, 2019 (13)	Simvastatin	0.01 mg	Filling the tooth socket with statin-PLGA gelatin hydrogel microspheres	Once after tooth extraction	Extraction socket of the mandibular right central incisor
Adachi *et al.*, 2020 (19)	Fluvastatin	Group 1: 0.1 mg/kg; Group 2: 1.0 mg/kg; Group 3: 10 mg/kg	Injection into the vicinity of the socket after tooth extraction	Once after tooth extraction	Vicinity of the maxillary right first molar extraction socket
Sanda *et al.*, 2021 (25)	Fluvastatin	1. Low concentration group: 1.0 mg/kg; 2. high concentration group: 10 mg/kg	Injection in the vicinity of the tooth extraction socket	Once after tooth extraction	Vicinity of the maxillary right first molar extraction socket

FS-PL, fluvastatin-poly (lactic-co-glycolic acid); PLGA, poly (lactic-co-glycolic acid); BMM, bone mineralized matrix.

Tooth extraction, medication-related osteonecrosis of jaws (MRONJ), dental implants, soft tissue healing

Nine studies examined the effects of statin drugs on extraction sockets. Two assessed statins' preventative and therapeutic effect on MRONJ. One evaluated statins' healing potential around the dental implant, and three assessed soft tissue healing at the extraction site.

Primary outcome variables

Primary outcome variables were measured by applying the following tools: dual-energy X-ray absorptiometry (DXA) (20), micro-computed tomography (micro-CT) (19,22-25), soft X-ray photography (13), histomorphometry (19,25) and histology (13,14,19-25). Primary outcome variables used across all the studies were residual ridge height, messenger ribonucleic acid (mRNA) expression of transforming growth factor-beta 1 (TGF-β1), BMP-2, and VEGF, bone regeneration and neovascularization, bone and gingival healing, residual ridge height and width, inflammatory response, and bone turnover (BT), bone formation in tooth extraction socket, osteogenic healing in a tooth extraction socket, epithelial continuity, and new bone formation (13,14,19-25) (*Table 4*).

Residual ridge height

Study by Wu *et al.* reported a significantly greater height of the residual alveolar ridge in the experimental compared to the control group at 2, 4, 8, and 12 weeks after simvastatin application following tooth extraction. At 12 weeks, the relative height of the residual alveolar ridge in the control group was 0.922±0.018 compared to 0.960±0.026 in

Table 4 Characteristics of outcome variables

Author, year	Measurement technique(s)	Primary findings	Secondary findings	Additional findings	Conclusion
Wu *et al.*, 2008 (20)	DXA and histological examination	The relative height of the residual ridge was significantly higher in the Exp group at weeks 2, 4, 8, and 12	BMD was higher in Exp groups at weeks 4, 8, and 12	Bone deposition line, density of bone trabecula, and new bone formation were higher in the Exp group at the end of 12 weeks	Local administration of statin-PLGA scaffold resulted in new bone formation in the tooth socket and maintained the height of the residual alveolar ridge
Liu *et al.*, 2009 (21)	In situ hybridization	Histologically, mRNA expression of TGF-beta 1, BMP-2, and VEGF was upregulated in the Exp groups at weeks 1, 2, and 4	Histologically, significant mRNA expression of VEGF was identified at weeks 1 and 2 in the Exp group	In general, expression of TGF-beta 1, BMP-2, and VEGF mRNA in fusiform stroma cells was identified in both groups	Temporal upregulation of growth factors TGF-beta 1, BMP-2, and VEGF aligned with the temporal increase in new bone formation
Mansour *et al.*, 2014 (14)	Histology	larger areas of newly formed bone at the implant-bone interface, and enhanced neovascularization in the Exp group at 3 months	In the Exp group, bone notches created by implant serrations were identified to be almost filled with new bone	Numerous osteocytes and dense collagen bundles were identified in the Exp group at 3 months	Simvastatin application increased new bone formation, neovascularization, and osseointegration in the experimental group
Yasunami *et al.*, 2015 (22)	Histology and Micro-CT	Increased bone mineralization and extensive connective tissue formation in the extraction socket in both FS groups	Connective tissue area, vertical bone height, bone density, and bone volume were significantly higher in FS groups on day 28	New bone formation with minimal signs of inflammation was identified in all groups at the extraction socket	Single PLGA-statin administration promotes extraction socket healing
Willett *et al.*, 2017 (23)	Histology and Micro-CT	The BMM-statin group showed higher interproximal bone and enhanced ridge width	Higher bone surface density and lower inflammation density were observed in the BMM-statin group	Higher osteoblast and lower osteoclasts percentage was identified in the BMM-statin group	The BMM-SIM group showed reduced alveolar bone loss and lower degree of inflammation, and an increase in the width of the total alveolar ridge
Rakhmatia *et al.*, 2018 (24)	Histology and Micro-CT	Greater bone formation, bone growth, and bone volume were identified in statin-containing groups	Bone volume and BMD were higher in statin-containing groups when compared to the control group	Mostly, Tb. Th and Tb. Sp were greater in statin-containing groups when compared to the control group	Fluvastatin used as an adjunct effectively proved to promote bone formation
Li *et al.*, 2019 (13)	Soft X-ray photographs and histology	At week 8, socket bone density in the statin-associated group was highest	Newly formed bone tissue was highest in the statin-associated group at the end of the experiment	Statin—the associated group demonstrated a consistent and stable increase in newly formed bone from weeks 1 through 8	Simvastatin-loaded gelatin hydrogel microspheres in tooth extraction sockets have the potential for bone repair and regeneration

Table 4 (*continued*)

Table 4 (*continued*)

Author, year	Measurement technique(s)	Primary findings	Secondary findings	Additional findings	Conclusion
Adachi *et al.*, 2020 (19)	Micro-CT and morphometry, and histology and histomorphometry	1. New bone formation was identified in all statin-administered groups. 2. The shorter length of necrotic bone and shorter distance between edges of epithelial surfaces at tooth extraction socket was identified in FS-H and FS-M groups	1. The area of necrotic bone and the necrotic bone ratio were significantly smaller in the FS-H group. 2. Bone volume and tissue volume were significantly larger in the FS-H group	Soft tissue closure of extraction socket was identified only in the FS-H group	Fluvastatin administration after tooth extraction can potentially lower chances of developing MRONJ-like lesions (by aiding in tissue healing and new bone formation)
Sanda *et al.*, 2021 (25)	Micro-CT, morphometry, histology and histomorphometry	FS-administered groups showed epithelial continuity and new bone formation	1. Decreased necrotic bone ratio and reduced inflammation were identified in the FS-administered groups. 2. BV/TV was significantly larger in the FS-administered groups	Complete epithelial recovery in the FS-H and FS-L groups was observed	Single local administration of FS in the MRONJ site demonstrated epithelial closure, new bone formation, and reduction of necrotic bone

DXA, dual X-ray absorptiometry; CT, computed tomography; Exp group, experiment group; TGF-beta 1, transforming growth factor-beta1; BMP-2, bone morphogenic protein-2; VEGF, vascular endothelial growth factor; BMM, bone mineralized matrix; FS-H, high statin concentration group; FS-M, medium statin concentration group; FS, fluvastatin; BMD, bone mineral density; BV, bone volume; TV, turnover volume; Tb. Th, trabecular thickness; Tb. Sp, trabecular separation; FS-L, low statin concentration group; PLGA, poly (lactic-co-glycolic acid); SIM, simvastatin; MRONJ, medication-related osteonecrosis of jaws.

the experimental group (20). Radiographic images were reviewed to measure the height of the residual alveolar ridge (20). Study by Willett *et al.* concluded that bone mineralized matrix + simvastatin conjugate preserved the most interproximal bone height (P<0.01) based on the micro-CT measurements (23).

Bone density (BD), socket BD (SBD), and bone mineral density (BMD)

In addition to residual alveolar height Wu *et al.* also studied BMD. The authors reported that BMD values were significantly higher in the experimental than in the control group at 4, 8, and 12 weeks (20). Study by Willett *et al.* demonstrated that bone mineralized matrix infused with simvastatin preserved BD. The authors utilized micro-CT measurements to determine their findings (23). Study by Li *et al.* noted that the BD of the simvastatin-loaded microsphere hydrogel group was higher on the soft X-ray photographs than that of the simvastatin-free hydrogel group (13). Yasunami *et al.* examined the effect of sustained-release, fluvastatin-impregnated PLGA microspheres on bone healing. They concluded, based on their analysis of histological images, that at day 28, BD was significantly increased in PLGA containing 20 $\mu g \cdot kg^{-1}$ fluvastatin and PLGA containing 40 $\mu g \cdot kg^{-1}$ fluvastatin when compared with the control and (PLGA) microspheres (22). Study by Rakhmatia *et al.* noted that the BMD of the carbonate apatite-containing statin (COFS) group was higher than that of the other groups, thereby promoting bone healing in the socket (24).

mRNA expression of TGF-β1, BMP-2 and VEGF

Study by Liu *et al.* examined the effect of simvastatin on mRNA expression of TGF-β1, BMP-2, and VEGF in tooth extraction sockets via *in situ* hybridization. The authors noted that expression of TGF-β1 and BMP-2 mRNA in the tooth extraction sockets experimental group was significantly up-regulated after 1, 2, and 4 weeks (TGF-β1, P<0.05) and (BMP-2, P<0.01). Similarly, expression of VEGF mRNA was significantly increased after one and two weeks compared with that in the control group, indicating its positive influence on alveolar bone remodeling (21).

Osseointegration in immediate implants

Another study aimed to assess the regenerative potential of simvastatin as a grafting material proximal to immediate dental implants. The authors found that simvastatin granules allowed for osteogenesis around immediate implants, resulting in osseointegration via bone regeneration with neovascularization through histologic analysis (14).

MRONJ

One study investigated the ability of fluvastatin to prevent the development of MRONJ-like lesions (19). A significantly shorter length of necrotic bone was exposed in the oral cavity in the medium [1.0 mg/kg; medium statin concentration group (FS-M)] concentrations of fluvastatin and high concentrations [10 mg/kg; high statin concentration group (FS-H)] of fluvastatin FS-H groups than in the MRONJ group (Steel test, MRONJ *vs.* FS-M: P=0.028; MRONJ *vs.* FS-H: P=0.041). Furthermore, the distance between the edges of the epithelial surfaces was significantly shorter in the FS-M groups (19). Bone volume fraction calculated on micro-CT images was significantly more significant in the FS-H group than in the MRONJ group (19). Similarly, another study concluded that the distance between the edges of the epithelium, the length and area of the exposed necrotic bone, and the necrotic bone ratio were significantly smaller in the fluvastatin-administered group compared with the saline group (25).

Discussion

This systematic review assessed statins' effect on healing following tooth extraction. The findings of this systematic review are threefold: (I) local application of statin preserves the residual alveolar bone by promoting bone formation and allows for soft tissue healing at the extraction site; (II) statins facilitate osteogenesis around immediate dental implants, resulting in their osseointegration; (III) statins have preventative and therapeutic effects on MRONJ. Several authors have studied the mechanism of statin-induced bone formation.

This study investigates the potential of statin drugs in enhancing tissue healing and bone regeneration in tooth extraction sockets. The loss in height and width of the residual alveolar ridge post-extraction is well-documented. A systematic review revealed that local administration of simvastatin carried by PLGA promoted new bone formation in the tooth socket and preserved residual alveolar ridge height in rats. This effect is attributed to

simvastatin's osteoinductive and anti-resorption properties. Studies by Wu *et al.* (20) and Yasunami *et al.* (22) further proved increased bone mineralization and connective tissue formation following simvastatin administration. Furthermore, statins have been reported to promote angiogenesis, inflammation reduction, and antibacterial activity, contributing to enhanced tissue healing post-extraction. Bisphosphonates (BPs) and denosumab have been associated with MRONJ in osteoporotic and cancer patients, showing a need for caution in dental procedures. Similar findings of statin drugs enhancing tissue healing in tooth extraction sockets have been observed in clinical studies (27-29). Interestingly, an animal study investigated the potential of statins to reduce the risk of developing jaw osteoradionecrosis and showed that a single injection of fluvastatin can reduce the risk of medication-related osteonecrosis following tooth extraction (19). A recent study experimentally explored the benefits of atorvastatin in managing MRONJ in rats (30). The study's observations resonate with the current review's findings that statin drugs potentially positively affect bone metabolism by stimulating osteoblastic activity in the site of interest. Notably, a recently published clinical study of 102 patients demonstrated a 32.4% improvement rate of osteoradionecrosis in their investigations. Although the findings are insufficient, the study concluded that statins may be a novel and effective treatment of jaw osteoradionecrosis (31). These recent novel findings, observed in experimental and clinical investigations, strengthen existing evidence to extend the scope of using statin drugs in dentistry, from tissue healing in tooth extraction sockets to managing complex dental conditions such as osteoradionecrosis of the jaw, thereby offering new hope for clinical practice. In contrast, statins have shown promising results in promoting bone formation, inflammation reduction, and tissue healing, making them potential candidates for managing tooth extraction sites. Sanda *et al.* reported epithelial continuity and new bone formation. They observed reduced necrotic bone in Fluvastatin-treated groups in rats (25), while the study by Adachi *et al.* reported reduced necrotic bone exposure and epithelial surface distances following fluvastatin administration post-extraction (19). Overall, the included studies suggest a positive influence of statins on soft and hard tissue remodeling at tooth extraction sites, highlighting their potential role in perfecting post-extraction healing processes.

This systematic review has limitations. First, due to the heterogeneity of the studies included, we could not perform a meta-analysis of the articles. Second, the chosen animal model may not fully replicate clinical conditions due to the use of rats at a developmental stage where growth is still ongoing. Therefore, future studies might consider using animal models that better align with the clinical context to enhance the validity and reliability of research outcomes. Despite these limitations, this study is significant because it is the first to review statin drug applications to promote tissue healing after tooth extraction. The application of statin drugs to promote tissue healing after tooth extraction has garnered attention due to their potential therapeutic benefits. Statins, primarily known for their cholesterol-lowering properties, have proved pleiotropic effects, including anti-inflammatory, angiogenic, and bone-stimulating properties. These attributes make them attractive candidates for enhancing wound healing processes.

Conclusions

In preclinical studies using animal models, local administration of statins, such as simvastatin and fluvastatin, has shown promising results in promoting tissue healing in tooth extraction sockets. These studies have reported increased new bone formation, reduced necrotic bone exposure, and enhanced epithelialization in statin-treated groups compared to control groups. Additionally, statins have been found to inhibit osteoclast formation and function, thereby potentially reducing bone resorption and preserving alveolar ridge height. While preclinical evidence is encouraging, further clinical research is needed to evaluate the efficacy and safety of statins in promoting tissue healing after tooth extraction in humans. Clinical trials assessing parameters such as wound closure, bone regeneration, and postoperative complications are called to confirm statin-based therapies' translational potential in dental practice. Moreover, investigations into best dosages, delivery methods, and long-term effects of statins on oral tissues are essential for their successful clinical implementation. Overall, the application of statin drugs holds promise for improving tissue healing outcomes following a tooth extraction, potentially offering new avenues for enhancing patient care in dentistry.

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Footnote

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