

Do Statin Medications Improve Periodontal Health and/or Outcomes? A Systematic Review

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Focused Clinical Question:

For adult patients (aged ≥ 30 years) with chronic periodontitis, does the use of 3-hydroxy-3-methyl-glutaryl coenzyme A reductase inhibitors (statins) improve periodontal health?

Clinical Scenario:

A 59-year-old female with a history of hyperlipidemia presents for periodontal maintenance care. She has been taking a statin medication for 4 years, during which time she received comprehensive periodontal therapy, including regenerative surgery in two quadrants. Post-surgical evaluation revealed substantial gains in clinical attachment and probing depth reduction. Radiographically, significant fill of the intrabony defect was observed. Before treatment, she was very anxious about losing more teeth and is now curious about the stability of her periodontal treatment. For clinical and radiographic presentation of the patient, see Figures 1 and 2.

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Key Words: Adult; chronic periodontitis; hydroxymethylglutaryl-CoA reductase inhibitors, therapeutic use; hyperlipidemia; treatment outcome.

Background

Chronic periodontitis (CP) is an inflammatory disease induced by the presence of bacterial pathogens and their byproducts. The observed tissue and bone breakdown results from a long-standing inflammatory response mounted by the immune system of the host.¹ Traditionally, treatment of CP has focused on both non-surgical and surgical removal of bacterial plaque and calculus by mechanical means, with the aim to reduce the amount of local factors that trigger the immune response. More recently, the approach has shifted from a focus solely on controlling the exogenous bacterial factors to the goal of controlling the responses of the host to these triggers and encouraging regeneration of tissue—in other words, host modulation.²

Manipulation of the proinflammatory state with pharmacologic therapies has been investigated.^{2,3} Many of the substances (i.e., non-steroidal anti-inflammatory drugs, statins, bisphosphonates) used are commonly prescribed drugs that periodontal patients are already taking as a part of a concurrent systemic disease treatment.² Examples of such substances are the 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors, commonly known as statins. These drugs act as competitive inhibitors of the

enzyme HMG-CoA reductase, thereby preventing a crucial step in cholesterol synthesis in the liver.⁴ This effectively lowers cholesterol and secondarily decreases the incidence of cardiovascular disease.⁴

Because inflammation plays a role in cardiovascular disease, the anti-inflammatory properties of statins have been studied previously.⁵ In addition to their cholesterol-lowering effects, they have pleiotropic features, such as inhibiting the release of proinflammatory mediators, specifically cytokines (i.e., tumor necrosis factor- α , chemokines, interleukin [IL] family) and matrix metalloproteinases (MMPs).⁶ MMPs have long been associated with collagen and extracellular matrix degradation in periodontal disease. There are four categories of MMPs—collagenases, gelatinases, stromelysins, and membrane type—with collagenases (MMP-1, MMP-8, MMP-13) and gelatinases (MMP-2, MMP-9) being most often implicated in periodontitis.^{7,8} Statins have been shown to reduce the expression of lipopolysaccharide (LPS)-induced MMP-1, MMP-8, and MMP-9 in monocytes⁹ and reduce the expression of MMP-9 in osteoblastic cells.¹⁰ LPS is a well-known component of the cell membrane of Gram-negative bacteria, which are also the predominant type of microorganism found in periodontal disease.¹¹ Animal studies demonstrated the effect of statins on alveolar bone loss and gingival inflammation. In a ligature-induced periodontitis model in rats, oral simvastatin (SMV) administration reduced alveolar bone loss and decreased the levels of the proinflammatory cytokines MMP-1 and MMP-8, as well as receptor activator of nuclear factor- κ B (RANK) and RANK ligand.¹² In another animal study, both alveolar bone loss

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FIGURE 1 Initial clinical presentation.



FIGURE 2a Lower right quadrant before comprehensive periodontal treatment with concurrent systemic statin administration. **2b** Lower right quadrant 2 years after comprehensive periodontal treatment with concurrent systemic statin administration.

and osteoclastogenesis were significantly reduced when SMV was administered to rats with LPS-induced periodontitis.¹³ These findings in animal studies support previously published evidence on the effect of statins on improved bone mineral density and bone formation with statin use in humans.¹⁴ Accordingly, there is biologic plausibility that the anti-inflammatory and bone formation-promoting actions

of statins could positively affect periodontal treatment outcomes in humans.

Statins are among the most prescribed and top-selling drugs in the United States each year.¹⁵ This is especially true among middle-aged adults, in whom systemic diseases, such as hyperlipidemia, atherosclerosis, and other cardiovascular diseases, tend to be most common. CP, too, has a higher prevalence among adults aged ≥ 30 years.¹⁶ Because age is a risk indicator for both atherosclerosis and CP, use of statin therapy could be a potentially convenient and cost-effective strategy to address both chronic diseases simultaneously.

Although statins have potentially dangerous adverse effects, including elevated liver enzymes and rhabdomyolysis, their incidence is relatively rare.¹⁷ This makes the drug an ideal choice for concomitant therapeutic use for periodontal disease. With the above purported actions of statins in inflammation, it is biologically plausible to expect beneficial effects of statins in patients with CP. The aim of this review is to examine the effects of statins, used both systemically and locally, on treatment outcomes for CP.

Search Strategy

A literature search of PubMed and the Cochrane Database was performed using the following MeSH terms: ((“periodontal diseases”[MeSH Terms] OR (“periodontal”[All Fields] AND “diseases”[All Fields]) OR “periodontal diseases”[All Fields] OR (“periodontal”[All Fields] AND “disease”[All Fields]) OR “periodontal disease”[All Fields]) AND (“hydroxymethylglutaryl-coa reductase inhibitors”[Pharmacological Action] OR “hydroxymethylglutaryl-coa reductase inhibitors”[MeSH Terms] OR (“hydroxymethylglutaryl-coa”[All Fields] AND “reductase”[All Fields] AND “inhibitors”[All Fields]) OR “hydroxymethylglutaryl-coa reductase inhibitors”[All Fields] OR “statins”[All Fields])) AND (“1980”[PDAT]: “3,000”[PDAT])

Search Outcome

The literature search yielded 49 papers related to the search topic. Forty-six full-text articles were reviewed. Three papers were written in languages other than English. Of the 46 reviewed papers, four randomized clinical trials (RCTs)¹⁸⁻²¹ and seven cross-sectional or cohort studies²²⁻²⁸ were selected for inclusion (Tables 1 and 2). The remaining papers were eliminated because of lack of human participants or lack of direct evaluation of periodontal conditions.

Discussion

This review of the literature revealed a paucity of clinically controlled trials and a noticeable heterogeneity in design among cross-sectional and cohort studies regarding the

TABLE 1 RCTs

Reference	Patient Group	Study Type (Level of Evidence)	Methods	Key Results	Comments
Fajardo et al., 2010 ¹⁸	N = 38; 6 males and 24 premenopausal and 8 postmenopausal females with established periodontitis (at least three teeth with PD \geq 3 mm, gingival index of 2 or 3, ³⁶ PI of 2 or 3, ³⁷ GR, and at least 15 teeth present in the mouth)	Double-masked RCT	After receiving SRP plus OHI, patients were randomized to receive 20 mg ATV or a trivitamin preparation once daily; clinical measurements (PD, GR, BOP, attachment loss, dental mobility ³⁸ [0 = absent or 1 = present; recorded as percentage of mobile teeth]), radiographs, and laboratory blood values were taken at BL and 3 months.	Statistically significant improvements noted in the test group (ATV) for cholesterol levels, LDL, dental mobility, and CAB-CEJ measurements.	Although a short follow-up period was observed, ATV may have a positive effect on radiographic bone level, in addition to its positive blood chemistry actions.
Pradeep and Thorat, 2010 ¹⁹	N = 64; 33 males, 31 females aged 25 to 45 years; moderate to severe periodontitis (PD \geq 5 mm or CAL \geq 4 mm) and vertical bone loss \geq 3 mm on periapical radiographs	Double-masked RCT	Patients randomized to receive SRP plus placebo gel (control) or SRP plus SMV in situ gel (test) at one site per patient; clinical measurements (mSBI, full-mouth and site-specific PI, PD, and CAL) taken using an acrylic stent before SRP (at BL) and 1, 2, 4, and 6 months; IBD fill assessed at BL and 6 months; GCF samples taken at BL, 2, 4, and 6 hours, and 1, 2, 7, 14, 21, and 30 days.	Statistically significant decrease in PD, CAL, and mSBI in the test group versus the control group at 6 months; greater decrease in IBD depth from BL to 6 months in the test group versus the control group; GCF samples reveal the presence of drug at 30 days.	Local delivery of SMV gel results in controlled release of SMV over 30 days, which was shown to reduce bleeding (inflammation), PD, and CAL in patients with CP.
Pradeep et al., 2013 ²⁰	N = 38; patients with well-controlled diabetes with PD \geq 5 mm or CAL \geq 4 mm and \geq 3 mm vertical bone loss on periapical radiographs; \geq 20 teeth	Double-masked RCT	Patients received OHI and were randomized into groups to receive SRP plus placebo gel or SRP plus SMV gel at multiple sites; clinical measurements (PD, CAL, mSBI, and PI) were recorded using an acrylic stent at BL (before SRP) and 3, 6, and 9 months.	No difference in PI between the groups at any time (similar hygiene levels). Statistically significant decrease in PD and mSBI and gain in CAL for the test group versus the control group at 3, 6, and 9 months. Greater reduction in IBD for the test group versus the control group. Greater percentage defect fill for the test group versus the control group.	Local application of SMV gel resulted in significant reduction in inflammation, IBD fill, CAL, and PD for patients with type 2 diabetes. This effect was lower than that seen in a study of a population without diabetes but with CP. ¹⁹

association of HMG-CoA reductase inhibitors and periodontal disease. For the clinical trials, statin use, both systemically and locally, was associated with an improvement in periodontal parameters.¹⁸⁻²⁰ One of the trials¹⁸ showed a statistically significant improvement on tooth mobility and radiographic bone level with the once-daily use of systemically administered atorvastatin (ATV). However, these results should be interpreted with caution because of the

short follow-up period (3 months) and atypical method of assessing tooth mobility. Conversely, the radiographic bone level can be seen as statistically and, presumably, clinically significant, with the control group losing bone height (crest of alveolar bone–cemento-enamel junction [CAB-CEJ] at baseline [BL], 2.71 ± 1.43 mm versus 3 months, 2.80 ± 1.52 mm) and the test (ATV) group gaining bone height (CAB-CEJ at BL, 2.85 ± 1.50 mm versus 3 months,

TABLE 1 (Continued) RCTs

Reference	Patient Group	Study Type (Level of Evidence)	Methods	Key Results	Comments
Subramanian et al., 2013 ²¹	N = 71, aged 37 to 78 years; LDL cholesterol ≥ 60 mg/dL, triglycerides ≤ 350 mg/dL, statin naive or low-dose statin only	Double-masked RCT	Patients received either 10 or 80 mg ATV; patients were evaluated using FDG/PET-CT for arterial and periodontal activity at BL and 4 and 12 weeks.	Fifty-nine patients presented with periodontal imaging for analysis. Severe periodontal disease was indicated by higher target-to-background ratio. At 12 weeks, there was a significant reduction in periodontal inflammation in the 80-mg group compared with the 10-mg group. Improvements were more pronounced for patients with more inflammation and more periodontal disease severity at BL. Periodontal disease severity correlated with carotid inflammation.	Inflammation and periodontal disease quantified only by FDG/PET-CT evaluation. No recording of clinical parameters (e.g., PD, BOP, CAL).

PI = plaque index; GR = gingival recession; SRP = scaling and root planing; OHI = oral hygiene instruction; LDL = low-density lipoprotein; IBD = intrabony defect; FDG/PET-CT = 2-18F-fluoro-2-deoxy-D-glucose/positron emission tomography-computed tomography.

2.10 \pm 1.14 mm). The most significant improvement in common periodontal parameters was seen with the use of a locally delivered form of SMV, used as an adjunct to non-surgical periodontal therapy.^{19,20} Probing depth (PD), clinical attachment level (CAL), and inflammation (as measured by a modified sulcus bleeding index [mSBI]) all exhibited statistically and, presumably, clinically significant improvement over controls for both a systemically healthy¹⁹ and a diabetic²⁰ participant group; on average, more than twice the reduction in PD and CAL was seen in the SMV group (for both studies) when compared with the placebo group for all time points studied.^{19,20} Therapeutic treatment outcomes may be improved when administering a statin locally compared with systemically. The application of a statin on a localized level may eliminate the resultant dose decrease seen at bone sites after the first-pass liver metabolism.²⁹ Furthermore, in two of the above trials,^{19,20} gingival crevicular fluid (GCF) analysis of the treatment site demonstrated that the delivery vehicle allowed for an extended release of the drug for up to 30 days.

With regard to the cross-sectional and cohort studies, there was only a weak positive correlation of statins to improved periodontal parameters. Many of the studies showed an association with statin use and fewer periodontal pockets (defined as PDs of 3 to 4 mm).^{24,25,27} Parameters such as PD, CAL, and bleeding on probing (BOP) can serve as surrogate endpoints for the actual true endpoint of tooth loss. Interestingly, however, the retrospective studies evaluating the impact of statin therapy on tooth loss showed either no reduction in tooth loss²³ or weak association with tooth loss reduction²²—one in which a reduction in tooth loss was related to time of periodontal disease diagnosis

and time of statin medication being dispensed. For the study that did show a slight reduction in tooth loss,²² it was interesting to note that this relationship was not found to be dose dependent. One must regard the results of this retrospective cohort study, in which only insurance information was evaluated, with caution. Although the authors tried to control for the potential confounding factor of extractions attributable to non-periodontally related issues (i.e., consideration of total caries-related procedures), the lack of information regarding the reason for extraction does not permit a true understanding of periodontal tooth loss in statin users, because non-users may have had similar tooth loss rates that were unrelated to periodontal disease. Additionally, studies suggest that well-maintained, compliant patient populations may exhibit higher rates of tooth loss than poorly maintained populations—a trend that may provide insight into the lack of difference seen between the statin group and others.

Statins exert their inflammation-modulating effects on many levels, including the reduction of C-reactive protein levels,³⁰ blockage of the effects of proinflammatory cytokine IL-6,³¹ and suppression of tissue-degradative MMPs.⁹ Animal studies demonstrated the positive effects of statins on bone metabolism, specifically with regard to stimulation of bone morphogenetic protein-2³² and increased expression of vascular endothelial growth factor in osteoblasts.³³ Seto et al.³⁴ showed increased bone formation in rat calvaria after the topical administration of SMV, revealing its ability to maintain high osteoblastic function. In addition, it was demonstrated in another animal study that the application of SMV, in a cyclosporine A (CsA)-induced periodontal disease model, counteracted the deleterious effects of the CsA on bone turnover.³⁵

TABLE 2 Human Cross-Sectional and Cohort Studies

Reference	Patient Group	Study Type (Level of Evidence)	Methods	Key Results	Comments
Cunha-Cruz et al., 2006 ²²	N = 1,021 HMO patients, aged 45 to 60 years at BL, with a diagnosis of CP (bone loss and multiple deep pockets diagnosed by a periodontist) ³⁹	Retrospective cohort	Qualifying patients had a diagnosis of CP, initial periodontal exam, and full-mouth series radiographs taken 6 months to 1 year before or after the initial examination for this study. Dental records and drug-dispensing data were combined to evaluate the effect of statin use: 1) any statin use during the 3 years of the study; 2) statin use for each of the 3 consecutive years (regular use) during the study; and 3) any statin use during the first 3 years after the initial exam. Mean follow-up period of 7.1 years.	Any statin use in the first 3 years after the periodontal exam resulted in significantly less (48%) tooth loss than no statin use. Regular statin use for 3 years during the study showed reduced tooth loss (37%) compared with no statin use, although it was not significant.	Statin use showed decreased tooth loss but no relation to duration of statin use. Investigators were unable to control for smoking during the study period.
Saver et al., 2007 ²³	N = 12,631 HMO patients, aged 48 to 62 years at the end of the study period who had been diagnosed with CP by a general dentist or periodontist in the last 3 years of the study period; Mild CP: bone loss \leq 30% of the tooth root, clinical AL, PD of 4 to 6 mm, or grade I furcation involvement; Moderate CP: bone loss 30% to 50% of the tooth root, AL, PD of 5 to 7 mm, and furcation involvement less than grade I; Severe CP: bone loss \geq 50% of the tooth root, possible immediate tooth loss, and PD \geq 7 mm	Retrospective cohort	Analyzed statin prescription patterns over a 7-year evaluation period (1996 to 2002) and related them to dental extractions.	Unadjusted results showed increased tooth loss for statin users. After adjusting for smoking and diabetes, statin use showed no effect on tooth loss (increased or decreased). Statin use did not show benefits for mild versus severe disease, nor for non-smokers versus former smokers versus current smokers.	Unable to see the effects of statins on clinical parameters (CAL, PD, BOP). Ultimately, tooth loss is the endpoint, but investigators were unable to provide specific information on the reason for tooth loss; however, the large sample size may negate potential variations.

Based on the results presented herein, there is promising, albeit preliminary, information regarding the benefits of statin use on periodontal treatment outcomes. The current widespread use of these medications in the adult population coupled with the increased prevalence of periodontal disease in this same population makes their use in periodontal therapy both practical and economical. The early evidence of the prospective RCTs are promising, especially given the benefit of a locally delivered method of administration that is associated with fewer side effects and a reduced need for patient compliance. However, the conclusions are

a reflection of a relatively small sample size and therefore need to be demonstrated in the larger population as a whole. Therefore, future endeavors might include large-scale, cross-sectional studies that correlate statin use with overall periodontal condition (i.e., National Health and Nutrition Examination Survey III data mining); such an analysis would provide a large enough sample size to control for confounders. With that correlation established, research should then be aimed at evaluating the benefit of HMG-CoA reductase inhibitors on periodontal disease through well-controlled, largely powered, prospective clinical trials

TABLE 2 (Continued) Human Cross-Sectional and Cohort Studies

Reference	Patient Group	Study Type (Level of Evidence)	Methods	Key Results	Comments
Lindy et al., 2008 ²⁴	N = 97 patients, aged ≥ 40 years, ≥ 14 teeth, diagnosed with advanced CP; Moderate CP: PD ≤ 4 to 6 mm; Advanced CP: PD ≥ 6 mm	Retrospective, cross-sectional	Extracted data from charts (2004 to 2005), including age, sex, smoking status, use of statins, diabetes status, and rheumatoid diseases. Also extracted visible PI, PD for present teeth (6 sites). Derived a novel PIBI based on data from moderate and deep pocket sites.	When compared with statin non-users (n = 76), patients using statins (n = 21) had 37% fewer pockets ≥ 4 mm. Statin users had 50% fewer pockets ≥ 6 mm compared with statin non-users. The PIBI was 40% less in statin users compared with non-users. There was a higher incidence of diabetes in the statin user group (28.6%) compared with the statin non-user group (18.4%). There was a higher incidence of smoking in the statin user group (28.6%) compared with the statin non-user group (3.9%).	Despite the higher incidence of smoking and diabetes in the statin user group, members of that group had significantly fewer moderate and advanced periodontal pockets. Results must be interpreted with caution because of the uneven distribution of patients in each group.
Saxlin et al., 2009 ²⁵	N = 2,032 non-smoking dentate adults aged 40 to 69 years without diabetes or rheumatoid diseases	Cross-sectional	Calibrated examiners performed periodontal evaluations using PD (4 sites per tooth) measurements to diagnose disease; disease status based on "deepened" pockets (≥ 4 mm) or "deep" pockets (≥ 6 mm); also evaluated BOP. Statin information garnered from health questionnaire.	One hundred thirty-four patients used statins. Among the total study population, statins showed a weak negative association with deepened (≥ 4 mm) pockets and with deep (≥ 6 mm) pockets showing slightly stronger negative association, but not to the point of statistical significance.	Statin medication was weakly negatively associated with the presence and severity of periodontal infection; this was seen in patients with plaque and increased BOP; in patients without plaque or BOP, there was a slight increase in the likelihood of deepened periodontal pockets with statin medication. Statin medication appears to have an effect on the periodontium and may be dependent on the inflammatory state of the tissues.

TABLE 2 (Continued) Human Cross-Sectional and Cohort Studies

Reference	Patient Group	Study Type (Level of Evidence)	Methods	Key Results	Comments
Meisel et al., 2011 ²⁶	N = 3,156 dentate adults aged ≥30 years	Cross-sectional	<p>Patients selected from a cluster sampling in the Study in Health of Pomerania study.</p> <p>Periodontal examination on a maximum 14 teeth performed on 4 sites per tooth, noting PD, AL, plaque, BOP, and number of teeth.</p> <p>Smoking, socioeconomic status, and medications were assessed by questionnaire; medications were verified by package inserts or prescriptions.</p> <p>Laboratory values attained for total cholesterol, LDL and HDL cholesterol, fibrinogen, and hemoglobin A1c (a measure of glycated hemoglobin).</p>	<p>Two hundred eighty patients were treated with statins.</p> <p>AL >4 mm was associated with increased risk of high LDL cholesterol; use of statins lowered this risk.</p> <p>The probability of having high C-reactive protein was lower with statins but not to statistical significance.</p>	Statins were seen as effect modifiers in the association of periodontitis (AL >4 mm) with high LDL cholesterol levels.
Sangwan et al., 2013 ²⁷	N = 140 adults with ≥16 teeth: 94 patients with hyperlipidemia (50 statin users, 44 non-pharmacologic therapy); 46 normolipidemic patients as controls	Cross-sectional	<p>Clinical examination included PI, GI, PD, and CAL.</p> <p>Biochemical measures included total cholesterol, HDL, LDL, and serum triglyceride.</p>	<p>The periodontal status of statin users did not differ significantly from normal lipid level patients.</p> <p>There was significantly higher PI and GI in hyperlipidemic statin non-users than statin users and normolipidemic patients.</p> <p>Mean PD values were statistically significantly higher in the hyperlipidemic non-statin users than the control group or hyperlipidemic statin users.</p> <p>PD and GI were significantly higher in the hyperlipidemic non-statin user group compared with the normolipidemic group and statin user group.</p>	This study evaluated patients divided according to lipid levels, enabling an assessment of the relationship of lipid levels to periodontitis and the potential modification by statin use.
Suresh et al., 2013 ²⁸	N = 30 adults aged 40 to 60 years with generalized CP (AL of 3 to 5 mm in >30% of sites); group 1 (n = 15), 20 mg/d ATV; group 2 (n = 15), control	Cross-sectional	<p>The clinical parameters recorded were PI, GI, and CAL.</p> <p>GCF samples analyzed for IL-1β using commercially available ELISA.</p>	<p>There was no difference in clinical parameters between those taking statins and control patients.</p> <p>GCF IL-1β levels in patients with CP on statin medication were lower than patients with CP not taking statin medication.</p>	<p>This study does not assess PDs or measurements of bone levels (i.e., radiographic assessment).</p> <p>The patients in this study were only taking statin medication for 6 months, which may have prevented the ability to detect differences in clinical parameters.</p>

HMO = health maintenance organization; AL = attachment loss; PI = plaque index; PIBI = periodontal inflammatory burden index; LDL = low-density lipoprotein; HDL = high-density lipoprotein; GI = gingival index; ELISA = enzyme-linked immunosorbent assay.

that showcase the improvement in clinical parameters in patients with periodontal disease. ■

Clinical Bottom Line

In adult patients (aged ≥ 30 years) with CP, the use of statins may show a positive effect on periodontal status (i.e., tooth loss, inflammation). Additionally, in patients undergoing non-surgical periodontal therapy, concomitant administration of statins may help improve periodontal outcomes.

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