Review

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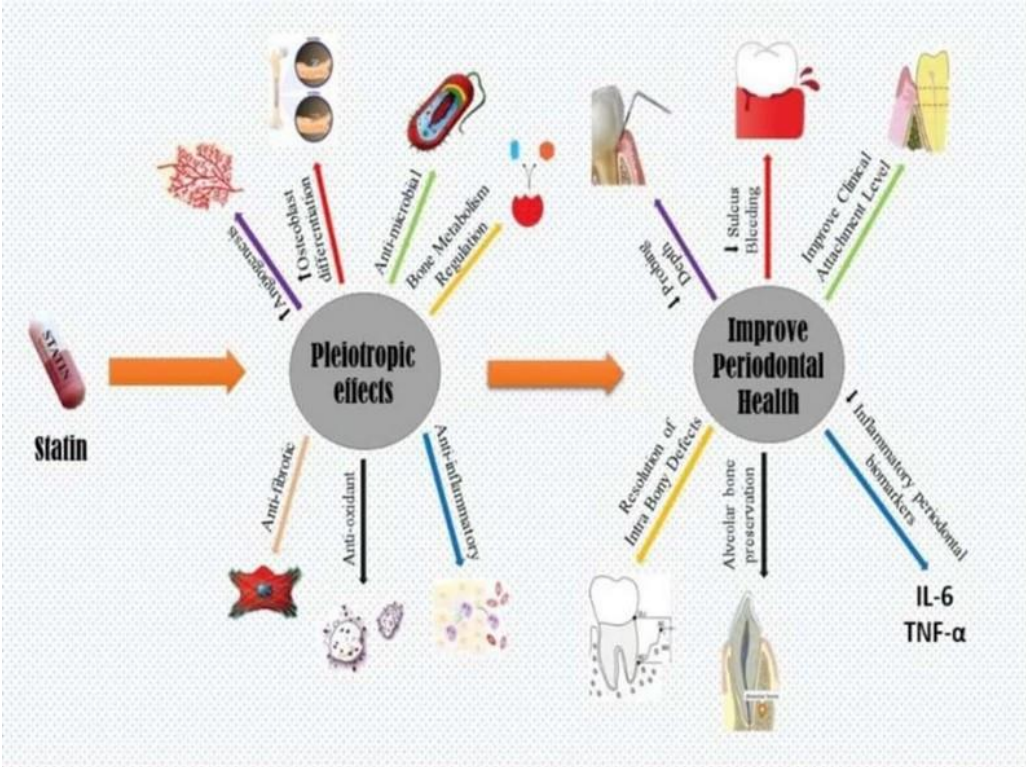
Statins as Potential Therapy in Periodontal Diseases: Mechanisms, Clinical Evidence, and Challenges

Hamza Alasbily[(1)], Hanan M.Ghaith[(2)], Salim Albarghathi[(3)], Ali Alkaseh[(4)], Wael Albhbah[(4)], Omar Aldokali[(4)], Ahmed Busasiyah[(4)], Luqman Dihoom[(4)]

[(1)] Department of Basic Medical Science, Faculty of Dentistry, Benghazi University, Benghazi, Libya, [(2)] 2Department of Periodontology, Faculty of Dentistry, Benghazi University, Benghazi, Libya. [(3)]Department of Pharmacology, Faculty of Medicine-Almarj, Benghazi University, Benghazi, Libya.
[(4)]Faculty of Dentistry, Benghazi University, Benghazi, Libya.

✉ Correspondence to: hamzah.mustafa@uob.edu.ly



Abstract: Statins, well recognized for their lipid-lowering and cardiovascular benefits, have emerged as prospective adjuncts in the treatment of periodontal diseases. Their pleiotropic actions, encompassing anti-inflammatory, immunomodulatory, and osteogenic properties, align with the therapeutic objectives of periodontal care. Clinical studies demonstrate their efficacy in enhancing periodontal outcomes, such as probing depth reduction, clinical attachment level gain, alveolar

bone preservation, and improvements in periodontal inflammation biomarkers, particularly when used alongside existing periodontal therapies. Despite these encouraging outcomes, challenges persist. Systemic side effects, variability in pharmacological actions among different statins, and the absence of commercially available localized delivery systems restrict their wider application. Furthermore, interactions with existing therapies and patient-specific factors, such as comorbidities, necessitate meticulous consideration. This review explores the potential mechanisms of action, reviews clinical evidence, and examines the challenges associated with incorporating statins into periodontal therapy.

Keywords: Periodontal Diseases, Periodontal Therapy, Gingivitis, Scaling and Root Planing, Clinical Attachment Level, Statins, Pleiotropic Effects.

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Introduction

Periodontal diseases are microbially induced, host-mediated inflammatory conditions that lead to damage of the tooth-supporting apparatus. Gingivitis, the mildest form of periodontal disease, is characterized by bleeding, swelling, and pain. It is reversible with proper oral hygiene and regular dental care. If left untreated, it can progress to periodontitis, a destructive and irreversible disease that involves the loss of periodontal attachment and supporting bone [1]. Periodontitis is a fairly common pathology, with a prevalence of nearly 60% over the last decade (2011–2020). Its severe stage affects approximately 24% of the population, emphasizing the need for timely preventive and therapeutic measures to improve periodontal health [1,2]. The pathogenesis of periodontal diseases involves various local and systemic factors. These conditions originate from the accumulation of bacterial biofilms, including Porphyromonas gingivalis, Tannerella forsythia, Prevotella intermedia, and Treponema denticola [1,3,4]. Periodontal pathogens possess virulence factors that contribute to tissue destruction both directly, through invasion and toxic byproducts, and indirectly, by triggering host immune responses. This activation induces the release of cytokines, chemokines, and other pro-inflammatory mediators, recruiting neutrophils to eliminate the pathogens. Consequently, additional inflammatory mediators, including cytokines and reactive oxygen species, are released, exacerbating periodontal tissue damage [4,5]. Although bacterial biofilm is the primary cause of periodontal diseases, genetic, environmental, and behavioral factors also increase the risk [6]. Risk factors can be categorized as modifiable (e.g., tobacco smoking, poor oral hygiene, diabetes, and pregnancy) and non-modifiable (e.g., age and genetic predispositions). A key modifiable risk

factor is tobacco smoking. Tobacco smoking increases the risk of periodontal disease, leads to a more severe disease course, and reduces the response to periodontal therapies. The link between smoking and periodontal disease decreases with smoking cessation [7,8].

In recent years, efforts to improve the classification of periodontal and peri-implant diseases led to a new system introduced in 2017 by the American Academy of Periodontology, in collaboration with the European Federation of Periodontology. In this system, periodontitis is further characterized by staging and grading [9]. Staging depends on the disease severity at presentation and the complexity of disease management. Grading, on the other hand, measures the rate of progression based on evidence of associated risk factors such as smoking and diabetes mellitus [1,9,10].

Complications of periodontitis may result in attachment loss, tooth mobility, disability due to impaired chewing function, and eventually lead to tooth loss. Furthermore, it may impact systemic health [11,22]. Periodontitis is now widely recognized as being linked to an increased risk of various systemic diseases and conditions, including diabetes, insulin resistance, cardiovascular disease, adverse pregnancy outcomes, arterial hypertension, chronic renal failure, and obesity. The systemic impact of periodontal diseases is thought to be mediated by the release of inflammatory mediators into circulation, as bacteria and their products enter the bloodstream through the sulcular epithelium, inducing vascular responses and contributing to systemic inflammation [3,13,14]. These interactions underscore the importance of periodontal disease treatment, not only for oral health but also for overall health [15].

The treatment of periodontitis involves various interventions, with conventional treatment including scaling and root planing (SRP), home oral hygiene, and the control of modifiable risk factors, such as smoking cessation, diabetes management, and dietary changes. Adjunctive treatments, such as antibiotics (e.g., amoxicillin and metronidazole) and non-steroidal anti-inflammatory drugs (NSAIDs) (e.g., ibuprofen), may be used to enhance treatment outcomes by reducing inflammation and controlling bacterial infection. In more advanced cases, surgical intervention may be required. However, these treatment modalities have limitations in cases involving deep periodontal pockets, inaccessible areas, or severe periodontitis [1,6,16].

Statins are among the most widely prescribed medications globally and play a major role in managing hypercholesterolemia and preventing atherosclerotic cardiovascular disease (ASCVD). Their primary mechanism of action involves the competitive inhibition of HMG-CoA reductase, a key enzyme in cholesterol biosynthesis. This inhibition reduces hepatic cholesterol production, resulting in the upregulation of low-density lipoprotein (LDL)

receptors and enhanced clearance of circulating LDL cholesterol. Consequently, statins significantly reduce cardiovascular morbidity and mortality. Statins include several members, such as simvastatin, atorvastatin, rosuvastatin, and pravastatin, each characterized by unique pharmacological properties. Statins are commonly used among various patient populations, including individuals with diabetes, coronary artery disease, familial hypercholesterolemia, metabolic syndrome, and chronic kidney disease. Statins demonstrate broad efficacy across diverse populations, ranging from young adults with genetic dyslipidemias to elderly individuals requiring intensive cardiovascular risk reduction [17-20].
The pharmacokinetics of statins exhibit significant inter-drug and patient-specific variations. Most statins undergo extensive first-pass metabolism in the liver, which is their primary site of action. Lipophilic statins (e.g., atorvastatin, simvastatin) easily penetrate both hepatic and extrahepatic tissues, while hydrophilic statins (e.g., rosuvastatin, pravastatin) are more liver-specific. In addition, genetic variations among patients contribute to differences in drug efficacy and the risk of adverse effects. Although statins are generally well-tolerated, they are associated with adverse effects, including myopathy, elevated liver enzymes, and a slight increase in the risk of new-onset diabetes. Myopathy, a dose-dependent condition, is more commonly observed with lipophilic statins [17-20].

In addition to their lipid-lowering effects, statins exhibit pleiotropic actions that extend beyond cholesterol reduction. These include anti-inflammatory, antioxidant, and endothelial-stabilizing properties. These effects are mediated through the inhibition of isoprenoid intermediates in the mevalonate pathway, decreasing the prenylation of proteins critical for cellular signaling. Consequently, statins improve endothelial function, attenuate vascular inflammation, and stabilize atherosclerotic plaques. Emerging evidence also suggests their potential to modulate immune responses, offering possible therapeutic benefits for conditions such as rheumatoid arthritis and systemic lupus erythematosus [17,18,21,22].

The scope of statin therapy has extended beyond cardiovascular health, fueled by their anti-inflammatory, immunomodulatory, and other pleiotropic effects. This expansion has generated interest across various medical disciplines, including dentistry, ophthalmology, oncology, and neurology. Preliminary studies suggest potential benefits in these fields, with ongoing research investigating their roles in managing chronic inflammatory conditions and preventing cancer progression. The multifaceted properties of statins position them as promising candidates for novel therapeutic applications, though many of these emerging uses remain investigational and require robust clinical validation [17,18,21,22].

Over the past few years, several pharmacological agents, such as probiotics, bisphosphonates, metformin, anticytokines, and statins, have been investigated for their potential role in periodontal therapy [23-28]. Among these, statins have drawn significant interest due to their reported benefits beyond lipid regulation. Studies have examined both systemic and local applications of statins in periodontology, assessing their impact on chronic periodontitis risk, periodontal tissue health, and alveolar bone regeneration. Additionally, their adjunctive use in surgical and non-surgical periodontal therapies has been explored.

This review discusses the potential mechanisms through which statins may exert periodontal benefits, summarizes clinical evidence supporting their use, and highlights the challenges associated with their application in periodontal therapy. Furthermore, it provides a comparative analysis of statins with other pharmacological agents investigated for periodontal treatment, offering insight into their relative efficacy and therapeutic potential. The literature was gathered from well-established scientific databases, including PubMed/Medline, Scopus/Web of Science, DOAJ, and Google Scholar, as well as recognized publisher platforms (e.g., MDPI, Elsevier, Wiley, Springer), to ensure a comprehensive and reliable evaluation of statins in this context.

Proposed Mechanisms of Statins in Periodontal Therapy

Promotion of Angiogenesis and Osteoblast Differentiation

Statins have been observed to promote angiogenesis and support osteoblast activity, both of which are essential for periodontal bone repair. By modulating vascular endothelial growth factor (VEGF) expression, they may enhance periodontal tissue perfusion, particularly in ischemic and inflamed areas. Furthermore, statins enhance osteoblast activity and proliferation by increasing the expression of bone morphogenetic proteins (BMPs) and activating the Runt-related transcription factor 2 (Runx2) pathway, which is critical for osteogenic differentiation. In addition to promoting bone formation, they impede osteoclast-mediated bone resorption by regulating the receptor activator of nuclear factor-kappa B ligand (RANKL)/osteoprotegerin (OPG) ratio and inhibiting both osteoclastogenesis and osteoblast apoptosis. The synergistic effects on bone regeneration and the suppression of bone resorption suggest that statins may play a vital role in mitigating the progression of periodontitis, where alveolar bone destruction is a defining characteristic. [29–34].

Antimicrobial Actions

Statins have demonstrated significant antimicrobial properties, particularly against Porphyromonas gingivalis, a primary pathogen linked to periodontal disease. Research

indicates that statins suppress biofilm metabolic activity, reducing bacterial loads within periodontal pockets. Their antibacterial effects are linked to enhanced bacterial clearance from the infected site and the induction of microbial cell apoptosis. Moreover, the hydrophobic nature of statins disrupts bacterial membranes in a 'soap-like' manner, resulting in bacterial death. In addition to P. gingivalis, statins demonstrate antimicrobial activity against other oral pathogens, including Veillonella parvula, Streptococcus mutans, Capnocytophaga ochracea, Tannerella forsythia, Aggregatibacter actinomycetemcomitans, streptococci, and Actinomyces naeslundii. This broad-spectrum antimicrobial activity helps address the dysbiosis characteristic of periodontal disease, thereby improving periodontal health by restoring a more balanced microbial environment [35–37].

Regulation of Bone Metabolism

Statins have been shown to stimulate the production of bone-related enzymes, including alkaline phosphatase and osteocalcin, which are crucial for bone mineralization and osteoblast activity. Additionally, statins reduce the levels of matrix metalloproteinases (MMPs), enzymes responsible for degrading extracellular matrix components and contributing to tissue destruction in periodontal disease. Through this dual mechanism, statins support both bone preservation and regeneration, making them a potentially valuable tool in periodontal therapy by offering bone protection and regeneration [29,32].

Anti-inflammatory Actions

Statins exert significant anti-inflammatory and immunomodulatory effects, which are crucial for mitigating chronic inflammation in periodontal diseases. These effects are primarily mediated by the suppression of pro-inflammatory cytokines, including interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), which are key regulators of the inflammatory cascade. Furthermore, statins inhibit the recruitment of monocytes, which are critical contributors to the inflammatory response, thereby modulating the overall inflammatory process. These properties enhance the potential of statins as an adjuvant therapy for managing periodontal diseases by reducing inflammation, promoting tissue repair, and preventing the progressive destruction of periodontal structures [17,29,38,39].

Anti-oxidant Effects

Statins exhibit significant antioxidant properties by primarily reducing oxidative stress and inhibiting the generation of reactive oxygen species (ROS). They enhance the activity of key antioxidant enzymes, including glutathione peroxidase and superoxide dismutase, which

neutralize ROS. Moreover, statins inhibit lipid peroxidation, preventing the oxidative modification of lipids—a critical phase in oxidative tissue damage. By targeting Nicotinamide Adenine Dinucleotide Phosphate NADPH oxidase, a major source of ROS, and modulating cellular redox balance, statins reduce oxidative stress at both vascular and systemic levels, underscoring their direct role as antioxidants, independent of their other pleiotropic effects [17,40,41].

Anti-Fibrotic Actions

Statins have demonstrated notable anti-fibrotic effects across various organ systems, which may benefit the management of periodontal diseases. Preclinical studies have confirmed their efficacy in mitigating fibrosis in pulmonary, hepatic, and cardiovascular tissue models. Statins achieve these effects by suppressing pro-fibrotic pathways, including the differentiation of fibroblasts into myofibroblasts a key process in fibrosis development. Furthermore, statins inhibit the excessive accumulation of extracellular matrix components, particularly collagen, thereby minimizing tissue scarring [42–45]. These anti-fibrotic properties complement the previously discussed mechanisms, such as their anti-inflammatory and antioxidant effects. By addressing multiple pathways of tissue damage and repair, statins hold significant promise as adjunctive agents in the treatment of periodontal disease.

Clinical evidence

Emerging evidence from various studies supports the potential of statins as adjunctive treatments for periodontal disease. These studies have evaluated the efficacy of statins—administered both systemically and locally (or subgingivally)—in individuals with periodontal conditions. Statins have demonstrated positive effects, particularly in improving clinical outcomes, such as reductions in probing depth (PD) and gains in clinical attachment level (CAL), as observed in numerous studies.

Reduction in Chronic Periodontitis Risk

Emerging clinical evidence suggests that statins may reduce the risk of chronic periodontitis. A population-based retrospective cohort study in Taiwan assessed the association between antihyperlipidemic agents and chronic periodontitis risk in patients with hyperlipidemia. The study included individuals newly diagnosed with hyperlipidemia between 2001 and 2012 from the 2000 Longitudinal Generation Tracking Database, with a follow-up

period of five years. The findings indicated a 25% reduction in chronic periodontitis risk among those receiving statin-fibrate combination therapy, with an even greater risk reduction observed in patients using statins or fibrates for more than three years [46].

Improving Periodontal Health with Subgingivally Delivered Statins

Statins have shown significant clinical and radiographic benefits when used as adjuncts to conventional periodontal treatment. A 2024 systematic review by Greethurst AR et al. (2024) evaluated the effects of subgingivally administered statins across 18 randomized controlled trials (RCTs) involving 1,171 participants. The analysis assessed key periodontal parameters, including PD**,** CAL**,** bleeding on probing (BoP), and bone fill. The findings indicated that statin therapy resulted in notable improvements, such as greater CAL gains, reduced PD, and lower bleeding index (BI), primarily due to their anti-inflammatory properties. Additionally, radiographic evidence showed increased alveolar bone density and reduced bone loss in statin-treated groups compared to placebo [47].

Improving Surgical Periodontal Outcomes

The role of statins in enhancing surgical periodontal outcomes has been investigated. A meta-analysis assessed the impact of local and/or systemic statin use as adjuncts to both non-surgical and surgical periodontal therapies. Of the four studies reviewed, three reported significant positive effects from intra-surgical statin application, demonstrating both clinical and radiographic improvements. Notably, these improvements were observed with local statin use, but not with systemic application. Additionally, no adverse events were reported following statin use [48].

Improving Non-Surgical Periodontal Outcomes

Statins have been explored for their potential to enhance the outcomes of non-surgical periodontal therapy. A randomized clinical trial by Shalaby R et al. (2020) evaluated the efficacy of systemic atorvastatin (20 mg/day) as an adjunct to SRP in 30 patients with chronic periodontitis. Over a six-month follow-up, the atorvastatin group demonstrated significant improvements in CAL**,** PD, and intra-bony defect depth compared to the placebo group. Additionally, atorvastatin-treated patients exhibited a statistically significant increase in salivary OPG levels, although no significant differences were observed in BoP. These findings suggest that systemic statin therapy may aid in periodontal regeneration when combined with conventional treatment [49].

Enhancing Intrabony Defect Healing

Statins have demonstrated potential in promoting intrabony defect healing when used as adjuncts to non-surgical periodontal therapy. A systematic review by Cecoro G et al. analyzed 20 RCTs involving 1,212 patients and 1,289 defects, evaluating the efficacy of locally delivered statins in combination with SRP**.** The meta-analysis revealed significant improvements in CAL**,** PD**,** and intrabony defect resolution when statins were added to SRP**,** compared to SRP alone. Among the statins evaluated, atorvastatin and rosuvastatin showed superior outcomes, while simvastatin did not reach statistical significance. These results highlight the potential of locally administered statins as a promising adjunct in the management of periodontal intrabony defects [50].

Alveolar Bone Preservation and Regeneration

Statins have exhibited efficacy in preserving and regenerating alveolar bone. Intra-alveolar application of statins following tooth extraction has proven to be both effective and safe for maintaining alveolar bone, with various concentrations and carriers yielding positive outcomes without significant adverse effects. Moreover, the local application of statins after SRP has resulted in notable improvements in clinical parameters and substantial bone fill. These findings highlight the bone-stimulating properties of statins, reinforcing their role in alveolar bone regeneration [51–55].

Reduction in Periodontal Inflammation Biomarkers

Statins have shown notable anti-inflammatory effects, offering potential benefits in managing periodontal diseases. A case-controlled cross-sectional study involving 74 patients with periodontitis and/or dyslipidemia assessed the impact of statin therapy on periodontal biomarkers. Participants were divided into three groups: Group A (34 patients with periodontitis not on statin therapy), Group B (40 patients with periodontitis on statin therapy), and Group C (30 healthy controls). The results showed that statin therapy in patients with periodontitis significantly reduced serum levels of IL-6**,** CRP**,** TNF-α, and MDA, compared to non-statin users. Statin therapy also led to improvements in periodontal indices when compared to non-users [56]. Furthermore, these findings were corroborated by a reduction in the expression of MMPs, particularly MMP**-**2 and MMP-9, in periodontal tissues. There was also an increase in OPG and a decrease in RANKL. These results suggest that statins help mitigate the inflammatory response, providing protection against periodontal tissue destruction [29,57].

Comparison of Statins with Other Potential Therapies in Periodontal Treatment

Several pharmacological agents have been investigated for their potential benefits in periodontology. Among these, bisphosphonates, metformin, and probiotics have shown promising outcomes. While statins primarily exert anti-inflammatory and osteogenic effects, promoting bone regeneration and periodontal healing, probiotics benefit periodontal health through distinct mechanisms. They help restore microbial balance and enhance host immune responses, effectively managing microbial dysbiosis. However, unlike statins, probiotics do not directly influence bone metabolism or angiogenesis, limiting their regenerative potential [23].

Bisphosphonates, known for inhibiting osteoclast-mediated bone resorption, effectively preserve alveolar bone in periodontitis. However, they do not stimulate new bone formation, limiting their regenerative capabilities. Moreover, their long-term use is controversial due to the associated risk of osteonecrosis of the jaw (ONJ). In contrast, statins, with their bone-forming and anti-inflammatory properties, may present a safer alternative in regenerative periodonta therapy [24,25].

Beyond probiotics and bisphosphonates, metformin has emerged as a promising agent with both anti-inflammatory and bone-regenerative effects. By activating Adenosine Monophosphate-Activated Protein Kinase AMPK, metformin reduces oxidative stress and enhances osteogenic activity, particularly benefiting diabetic periodontitis by improving glycemic control. However, concerns such as gastrointestinal side effects and the potential risk of lactic acidosis remain. While both metformin and statins enhance bone metabolism, statins additionally promote angiogenesis and exert lipid-lowering effects, potentially offering broader systemic benefits [26].

Given the unique advantages of each pharmacological agent, their selection should be tailored to specific periodontal conditions. Statins may be favored for promoting bone regeneration and reducing inflammation, probiotics for managing microbial dysbiosis, bisphosphonates for addressing severe bone loss, and metformin for treating diabetes-associated periodontitis.

Challenges in Using Statins for Periodontal Therapy

The clinical application of statins in periodontal therapy presents several challenges. While systemic administration offers cardiovascular benefits, it can also lead to adverse effects, including myalgia, liver enzyme abnormalities, and, in rare cases, rhabdomyolysis. These risks are particularly concerning in individuals with comorbid conditions like diabetes,

where long-term use may be impractical. Moreover, systemic administration may not achieve the therapeutic concentrations needed in the oral cavity to effectively treat periodontal diseases. Although targeted delivery of statins to periodontal tissues has the potential to minimize systemic side effects and enhance therapeutic efficacy, current delivery technologies remain inadequate. Additionally, variability in the pharmacokinetics and biological actions of different statins, along with the potential for drug interactions with other medications and concurrent periodontal treatments, poses further concerns [17,29,51].

Future Directions

The successful implementation of statins in periodontal therapy requires advancements in formulation, particularly with targeted delivery systems to enhance local efficacy and minimize systemic side effects. Long-term clinical studies with larger cohorts and extended follow-up are needed to assess the durability of benefits and identify risks. Comparative studies with other adjunctive treatments, such as probiotics, bisphosphonates, and metformin, will help clarify the relative advantages of statins. Additionally, further research into the molecular mechanisms by which statins affect periodontal regeneration, including angiogenesis, osteogenesis, and immune modulation, is necessary to support their use. Considering patient-specific factors like genetic variability and concurrent medications will also be crucial for optimizing treatment strategies. By addressing these research gaps, we will strengthen the evidence base for statins, facilitating their more precise and effective application in periodontal practice.

Conclusions

Statins demonstrate considerable promise as adjunctive treatments in periodontal therapy due to their anti-inflammatory, immunomodulatory, and osteogenic properties. Clinical evidence highlights their potential to improve periodontal outcomes when combined with traditional therapies. However, their widespread implementation may be limited by systemic side effects, pharmacological variability, and the absence of targeted delivery systems tailored for periodontal treatment. To fully harness their therapeutic potential, it is crucial to enhance statin formulations, optimize delivery methods, and account for individual patient factors. Advancements in these areas could facilitate the effective incorporation of statins into clinical periodontal practice.

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