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The Role of Statins in Periodontal Therapy- A Review

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Reviews

History

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ABSTRACT

Periodontitis is an inflammatory mechanism causing step by step destruction of the periodontal tissues and alveolar bone. Periodontal treatment is intended to restore the tissues damaged by the disease. Various periodontal procedures have been introduced to lower the destruction; statins are being one among them. They are cholesterol-reducing drugs which have shown to promote bone formation and proven to be effective in periodontal therapy. However, statins have numerous actions, with anti-inflammatory and immunomodulatory effects, as well as the capacity to accelerate new bone formation. The pleiotropic effects of statins have been assessed for their prospective advantage in the therapy of several inflammatory and immune-mediated diseases including periodontitis. Such features could be beneficial for periodontal therapies. This article goes through the history and effects of statins and explores its potential role in periodontal regenerative therapy.

Keywords: Statins, Periodontitis, Simvastatin, Rosuvastatin, Periodontal Regeneration.

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Introduction

Periodontal disease is an incendiary infection affecting the aiding tissues of the dentition, produced by a group of pathogens. In 2017, the World Workshop classified Periodontitis based on multidimensional staging and grading system, Periodontitis as a manifestation of systemic diseases and necrotizing periodontal diseases. The prevalent form of periodontitis is chronic periodontitis, which is usually associated with the pocket formation and depletion of bone but the terminologies as “chronic” or “aggressive” has been grouped under a single category as Periodontitis.[1] Elimination of bacterial infection and restraining the advancement of inflammatory process are the fundamental treatment objectives. Traditional non-surgical periodontal therapy primarily involves scaling and root planing. However, it has its own limitations as it is difficult for debridement to approach fields like deep pockets, furcations, and grooves on the tooth surfaces, which concludes in partial debridement of these areas. Local application of antiseptics, antibiotics and laser assisted therapy are some of the alternative options that have been recommended to traditional non-surgical therapy. Controlled device containing tetracycline which desired for placement into the periodontal pocket and deliver the effective agent into the periodontal pocket.[2] Other antibiotics such as doxycycline and minocycline are also approved for the local drug delivery systems.

Lately, some statins like simvastatin (SMV), atorvastatin (ATS) and rosuvastatin (RSV) also have been considered as an ancillary remedy to non-surgical periodontal therapy. Statins were initially imported as cholesterol-reducing drugs, which performed by hindering the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase by intruding into liver and interfering in cholesterol synthesis and reduces the prevalence of cardiovascular disease. Excluding their cholesterol-lowering property, statins also have additional properties such as:

1. Anti-inflammatory properties
2. Antioxidative properties
3. Antibacterial properties
4. Pleiotropic effects, such as blocking the release of pro-inflammatory mediators and matrix metalloproteinases (MMP’s)

Due to the pleiotropic, non-hypolipidemic effects of statins, these could potentially be utilized as an adjunct therapeutic agent for periodontal disease therapy. By employing either systemic or local delivery systems, few studies have explored the biological mechanisms that may be involved in the anti-inflammatory effects of statins on periodontal tissues. In this way, the conventional periodontal treatment approach could be augmented with statins to decrease periodontal inflammation and promote bone tissue formation.[3] Local delivery of statins has proven to have additional assistance to traditional non-surgical periodontal treatment by few studies in contrast to conventional scaling and root planing alone.[4] Thus, the objective of the review is to appraise the usage of statins that showed additional benefits with non-surgical periodontal treatment in contrast to phase 1 therapy alone

Table 1. History of Statins

YEAR	INVENTION
1784	François Poulletier, a French doctor-chemist obtained real cholesterol from gallstones. Later after three years, another French physicist, Michel E. Chevreul, termed them cholesterin
1888	Friedrich Reinitzer, an Austrian botanist formulated the atomic formula of cholesterol
1927–1928	Heinrich O. Wieland and Adolf Windaus gave the structure of cholesterol
1950	The fundamental objective of the trial done by Dawber was to constrain the biosynthesis of cholesterol in the human system and HMG-CoA reductase (HMGR) develop into a pure objective
1959	Triparanol, the first cholesterol-reducing agent that constrained cholesterol formation was popularized into medical use in the United State of America
1964	Bloch and Lynen - The cholesterol formation pathway
1976	An HMG-CoA reductase inhibitor named Compactin was identified
1978	Alfred Alberts and colleagues discovered a new HMG-R inhibitor and later named it has lovastatin
1986–1987	Lovastatin was inured FDA approval for the initial commercial use
1989	Different statins named simvastatin and pravastatin were formed
2003	Atorvastatin turned into the popular statin in the history of pharmaceutics
2010	Atorvastatin, Fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin all these statins become available in markets

History of statins

The history of statins goes back to the late 1950s where Triparanol was the first cholesterol reducing agent that was popularized in medical use in the USA. In 1978, Alfred Alberts and his colleagues discovered a new HMG-CoA reductase inhibiting agent named Lovastatin and by 1980s it got the Food and Drug Administration (FDA) approval for commercial use. Late 1980s was the discovery of simvastatin and pravastatin and by 2000, atorvastatin became the popular drug in use. All the statins were made available in the markets by 2010. (Table 1)

Classification of Statins

The classification of statins was processed according to certain criteria which are differences in structure and ring structure that affect the pharmacological properties of statins then the capability of drug to lower the cholesterol levels (Fluvastatin is least effective and Atorvastatin and Rosuvastatin are the most effective)[5]

The different criteria for classification of statins are:

1. *According to the methods of manufacture of statins:*
   a. Type 1 Fermentation (Simvastatin, Lovastatin, Pitavastatin, and Pravastatin)
   b. Type 2 Synthetic (Atorvastatin, Fluvastatin, and Rosuvastatin).
2. *According to the solubility of statin:*
   a. Hydrophilic (Pravastatin, Rosuvastatin and Pitavastatin)
   b. Lipophilic (Fluvastatin, Atorvastatin, Simvastatin and Lovastatin).

The interaction of these drugs with other drugs were included as Rosuvastatin and Pravastatin counts in the human body are minor and cannot be altered by alternative drugs considering the enzymes present in the liver that eradicate Rosuvastatin and Pravastatin are not inhibited through innumerable number of the drugs when compared to other statins. Because of this mechanism, the levels of these drugs are inhibited from elevating and prominently to increasing toxicity like myopathy. Recently, Rosuvastatin and Atorvastatin are seen as the exceedingly puissant and Fluvastatin the slightest puissant statins.

Statins are soluble in both aqueous environment and viscous environment. The water-soluble statins are eliminated from the body and unmetabolized by the liver. Fat soluble statins are fragmented down in the liver by cytochrome P450 system and water-soluble statins contribute to minor interactions with other drugs.

Structure of Statin

The structures of statins can be generally categorized into three parts as a target enzyme substrate analog, HMG-CoA, the substrate analogue linked to an intricate hydrophobic ring framework involved in the reductase enzyme which is conclusive of the statin and the solubility properties of the drugs is defined by side groups on the rings.

Mechanism of Action

Cholesterol is synthesized in the cytoplasm and membrane of the endoplasmic reticulum of virtually all tissues in humans including the liver, intestine, adrenal cortex, and reproductive tissues. The mode of action of statins is by inhibiting a process in the body's formation of cholesterol. The common output of the liver is cholesterol but occasionally when the liver produces excessive amount of cholesterol. This reaction is inhibited by statins that commences with the abridgment of acetyl-CoA with acetoacetyl-CoA to form HMG-CoA in a reaction catalyzed by HMG-CoA synthase. The HMG-CoA reductase enzyme then converts HMG-CoA to mevalonate. After the production of mevalonate there are various reactions that follow to produce cholesterol. Statins inhibit the HMG-CoA reductase enzyme associated with liver's cholesterol production thus hinder the liver's capability to produce low-density lipoprotein. This process causes an elevation

in count of the low-density lipoprotein receptors on the periphery of liver cells, proceed in more cholesterol being eliminated from the blood and decrease in risk for high cholesterol-associated diseases. (Figure 1)

Pleiotropic Effects of Statins

Apart from lipid lowering properties, this drug has additional non-lipidic effects that are responsible for its pharmacological silhouette demonstrated in clinical trials. New studies have shown various properties of statins on non-lipidic biological scopes known as "pleiotropic effects" of statins, which include the antioxidant effect,[6] antithrombotic effect[7], anti-inflammatory effect[8], immunomodulatory properties[9] and the osteo-modulatory effects.[10]All these properties of statins indicate that it is enhancing one of the first host modulation agents in periodontics. The biologically significant amount of antioxidant and anti-inflammatory effects of SMV is accepted to be important in treatment of periodontitis.[11] Free radical scavenging activity of statins in human body have been established in few studies. Interaction with lipids, proteins and deoxyribonucleic acid is prevented by direct scavenging of reactive oxygen species. In this regard, Fluvastatin is more active against peroxyl radical, and SMV and ATS are more active against hydroxyl radical. Various pleotropic effects of statins prove that it is a possible host modulating agent in the regimen of periodontal infections in humans.

Application of Statins in Periodontal Therapy

The primary aim of periodontal therapy is inhibiting the fragmentation and replacing periodontal apparatus to their initial form and structure. SMV proves to hinder bone resorption which is negligible compared to its anabolic effect on maturation of osteoblasts and new bone formation.[12] It also carries antioxidant as well as anti-inflammatory properties that facilitate healing of periodontal intrabony defects. The anti-inflammatory effect could be due to the depletion of isoprenoids by statins that inhibit the IL-1 and IL-6 mediators along with lowering the LDL cholesterol levels.[13] A study conducted by Meisel et al explained that the statins were effective modifiers in the relationship between periodontitis and its inflammatory counterparts in systemic circulation.[14] The locally delivered statins such as SMV and ATS possess potential benefits in periodontal regenerative therapy due to the above-mentioned properties.[15,16] Moreover, solutions of SMV in adequate concentration have been added with bone grafts to increase the regenerative potential.[17,18]

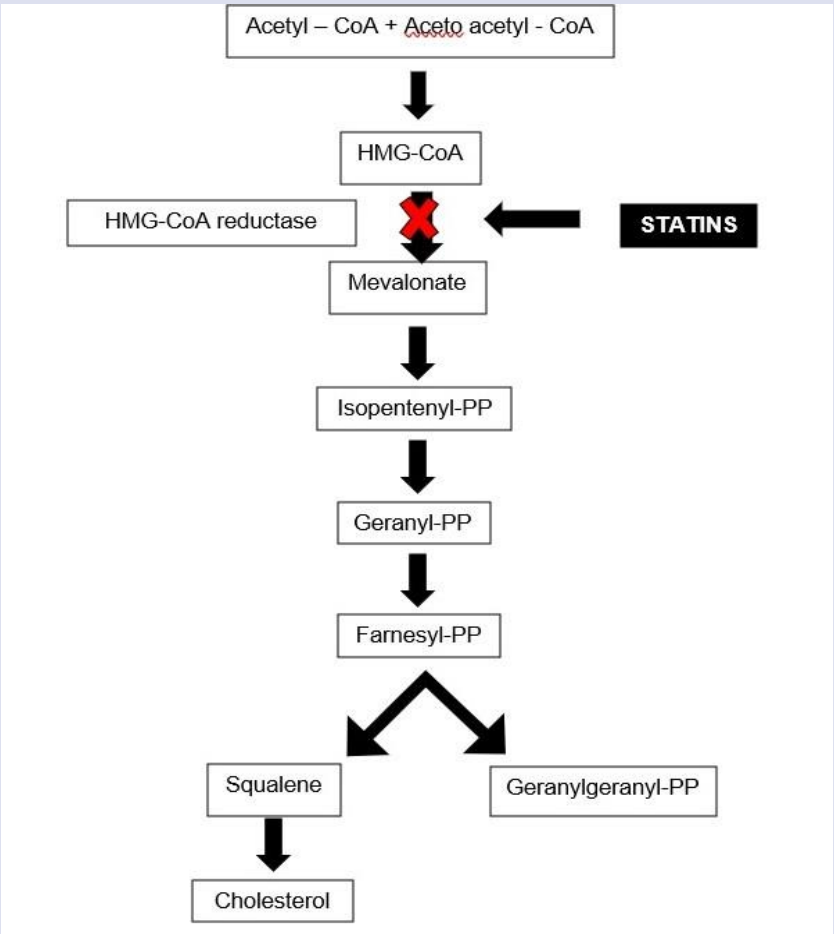

Figure 1. Melvonate Pathway.

Obesity is generally in conjunction with dyslipidemia with increased blood triglyceride levels and low-density lipoprotein levels. The excess release of proinflammatory cytokines may develop damage to the periodontal tissue; meantime, the increased systemic inflammation seen in obesity is contributed by the cytokines released in periodontitis. In a large patient population this overlap of obesity, hyperlipidemia, and periodontal disease have found benefits from statin therapy.[19]

Comprehensive research has been operated on the link uniting periodontal diseases and cardiovascular diseases.

A study was conducted to assess the relation among periodontal health and common parameters like probing depth (PD) and gingival index (GI).[20] It was illustrated that the parameters were greater in subjects with dyslipidemia, whereas subjects employed with ATS had lesser GI scores and PD levels which were correlated with reduction in total cholesterol and blood triglyceride levels.

In yet another study conducted on patients with atherosclerosis and managed with high doses of atorvastatin, it was concluded that there was a convincing reduction in periodontal inflammation when measured by c reactive protein levels and a positron emission tomography scan after 12 weeks of therapy.[21] Few other studies have observed the molecular effects of statins in periodontitis, and it has been demonstrated that administration of statins led to decreased levels of interleukin 1β, tumor necrosis factor α and MMP's in periodontitis patients.[10,22]These proinflammatory mediators are responsible for most of the host tissue damage seen in periodontitis patients. Few studies have proven that statins have the capability to elevate levels of both osteoprotegerin (OPG) levels and bone morphogenetic protein 2 (BMP-2), that play a major developmental component in the formation of bone.[23,24] A clinical trial based on the effect of local statin administration on periodontal disease was illustrated that the use of topical simvastatin gel in adjunct to non-surgical periodontal therapy resulted in greater intra bony defect fill and clinical attachment level (CAL) with decreased PD level and GI scores than the placebo group.[25] Local employment of statins such as RSV and ATS achieved clinical improvements such as PD reduction and CAL gain in addition to non-surgical periodontal regime when compared to scaling and root planing alone.[26]

Osteogenic properties of statin in periodontal therapy

SMV has been recorded to promote osteoblastic activity and hinder osteoclastic activity. Short-term exposure of alveolar bone to stains was enough to commence a cascade of bone regeneration by inducing the local generation of the BMP-2. The BMP-2 promoter has been employed as a mark to recognize new compounds that initiate the transcription and differentiation of osteoblasts.[27]

On oral administration of SMV, lowered action of serum tartrate-resistant acid phosphatase 5b was recorded, expressing the lowered osteoclast activity. Since osteoblasts and marrow adipocytes originate from a common mesenchymal progenitor, few adipogenic agents have recorded to overcome osteoblast differentiation. SMV augments alkaline phosphatase action and mineralization, including increasing the expression of bone sialoprotein, osteocalcin and Type I collagen, and it has demonstrated to have anti-inflammatory action by depleting the formation of IL-6 and IL-8.[28] Some of the recent studies involve comparing the efficacy of local delivery of 1.2 mg of ATV, RSV, or placebo gels for the regimen of intraosseous defects in subjects with chronic periodontal disease. A re-application of the gels was performed after 6 months to increase the bioavailability of the drug at the site. The mean reductions in the modified sulcus bleeding index (mSBI) and PD, the gain in the CAL, and the reduction in the intrabony defect depth were considerably more in the statin subjects than in the placebo gel subjects. At the same time, RSV treatment illustrated a larger beneficial effect than ATV at 6 and 9 months.[29] The clinical potency of locally administered 1.2% RSV and 1% Metformin (MF) gel as an addition to phase 1 periodontal treatment in the reduction of intraosseous defects in chronic periodontal patients concluded that additional local delivery of 1.2% RSV and 1% MF gel caused critical clinical attachment level gain, decline in probing pocket depths and enhanced bone fill compared to the placebo group.[30] The correlation capability of 1.2% ATV and 1.2% SMV, in addition to phase I therapy, in the regimen of intrabony defects inferred that ATV showed improved clinical measurements and greater proportion of radiographic defect depth reduction as compared to sites treated with SMV.[31]

Statins effect on periodontium

An important factor considered in healing of alveolar bone is the cells derived from periodontal ligament. The osteoblast like properties have been shown with help of in vitro studies and are accountable not only for osteogenesis and osteoclasia, but also for fibrogenesis and fibroclasis, and cementogenesis and cementoclasis.[32] The periodontal condition and immunoglobulin IgG subclasses against *Porphyromonas gingivalis* in subjects with pre- rheumatoid arthritis and early rheumatoid arthritis were compared to control group to institute a link between periodontal disease markers and rheumatic activity and the results showed that individuals with pre-rheumatoid arthritis (pre-RA) had increased inflammatory periodontal involvement and a critical link between IgG and *Porphyromonas gingivalis* and ACPAs in pre-RA and markers of rheumatoid arthritis (RA) activity in individuals with early rheumatoid arthritis (e-RA).[33] Another study compared the effect of phase I treatment on clinical measurements and GCF levels of tissue or blood vessel-type plasminogen activator (t-PA) and plasminogen activator inhibitor-2 (PAI-2) with periodontal subjects, presence, or absence of RA and results illustrated that phase 1 reduced the pretreatment GCF PAI-2 levels creating a link with the GCF plasminogen activator

inhibitor-2 amounts.[34] The considerable increased t-PA and PAI-2 GCF levels in periodontal subjects proposed that the plasminogen triggering action plays an aspect in the infection pathway of periodontal disease. By evaluating the effect of phase I therapy on the serum levels of RA-related inflammatory markers in subjects with chronic periodontal disease presented that phase I therapy may help in the regulation of RA-related inflammatory markers in subjects with chronic periodontitis.[35]

Retrospective studies have evaluated the possible effect of daily statin dose on periodontal clinical parameters and/or tooth loss which were inconclusive.[36,37]Whereas various preclinical and clinical studies studied the action of local and/or systemic benefit of statins as addition to non-surgical and/or surgical periodontal treatment have been published.[38,39] The studies concluded by proving that statins are effective against *A. actinomycetemcomitans* and *Porphyromonas gingivalis* which are the important species of bacteria involved in periodontal pathogenesis. Moreover, statins have proven to hinder the tissue degrading enzymes and in exerting a pro-proliferative action on mesenchymal stromal cells and endothelial progenitor cells. Statins have a positive effect on differentiation of osteoblasts, bone morphogenetic protein and vascular endothelial growth factor expression and it hinders with resorption of bone and the process of osteoclastogenesis.[40] In a systematic review of randomized controlled clinical trials, including meta-analyses, the administration of local statin as an addition to phase I periodontal treatment resulted in sufficient clinical and radiographic enhancement compared to SRP alone. There was a positive impact of intra-surgical statin administration, whereas there was no positive impact with systemic statin administration with addition to non-surgical periodontal treatment.[41] The introduction of local drug delivery help in stimulating alveolar bone regeneration. Large- scale studies have been carried out to state these findings such as the efficacy of statins as potential inhibitors of bone resorption and their anabolic effects on bone to further regeneration.[42]

Conclusions

Analysis of the available scientific evidence demonstrates that statin administration may represent a new approach and a valuable tool as an addition to periodontal treatment. Local delivery proved to be ideal by providing high concentrations at target site and decreases the disadvantages of systemic delivery, such as adverse reactions and low patient compliance. We can consider topically delivered statins as an adjunct treatment for the hindrance of periodontal disease in high-risk patients because it enhances the resolution of periodontitis, reverses the associated defects, and represents a form of periodontal maintenance. This drug can accomplish the objective of regeneration without any intrusive methods, thereby producing minimal distress to the patients. It is proved that the antioxidant and anti-inflammatory effects of this agent could promote healing of osseous deformity. Studies conclude that statins have potential effect on alveolar bone present in both preclinical and clinical field and some have opposing results of SMV effects. Nevertheless, long-duration clinical research in human patients are necessary to demonstrate the mode of application, optimum therapeutic threshold and the effectiveness in humans for regeneration of bone and assess the capable benefits of statin in periodontal regeneration.

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Nil.

Conflicts of Interest Statement

No conflicts of interest

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