Statins: A Major Breakthrough In Periodontal Regeneration

Dr. Shanam Kansil, Dr. Faizan Sharif

Periodontology and Oral Implantology, Chandigarh[2]

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Introduction

The discovery of 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase inhibitors, called statins, was a breakthrough in the prevention of hypercholesterolemia and related diseases. Which are considered to be one of the major risk factors for atherosclerosis that leads to cardiovascular, cerebrovascular and peripheral vascular diseases.[1] The statins inhibit cholesterol synthesis in the body and leads to reduction in blood cholesterol levels, which is thought to reduce the risk of atherosclerosis and diseases caused by it. The primary goal was to inhibit the enzyme 3-hydroxy-3-methylglutaryl-CoA reductase (HMGR) responsible for cholesterol biosynthesis in the body. In 1970s the Japanese microbiologist Akira Endo first discovered natural products with a powerful inhibitory effect on HMGR in a fermentation broth of Penicillium citrinum, which was named as compactin (mevastatin). Various animal trials showed very good inhibitory effect, however in dogs it produced toxic effects at higher doses. In 1978, Alfred Alberts and colleagues at Merck Research Laboratories discovered a new natural product in a fermentation broth of Aspergillus terreus, their product showed good HMGR inhibition and they named the product mevinolin, which later became known as lovastatin.[2] The most widely used oral statins in day to day use are simvastatin (20/30 mg)and atorvastatin (40/80 mg).

Periodontal diseases result in destruction of the supporting structures of the teeth. The primary goal of periodontal therapy is the regeneration of lost attachment apparatus. Search for the cost effective and efficient agents to promote periodontal regeneration continues till date. One of the agents which have the potential in periodontal regeneration is the statins. Statins have pleiotropic effects like anti inflammatory, antioxidant and anabolic effects on bone apart from lipid lowering action. The statin family reportedly increased bone mineral density in humans and decreases the risk of fractures in osteoporotic and elderly patients. Horiuchi and Maidea pointed out that statins may be useful for treating periodontal disease in patients with osteoporosis.[3] Also it was found that the systemic administration of simvastatin is associated with a reduced risk of tooth loss in patients diagnosed with chronic periodontitis as observed by a retrospective analysis over a seven year period. Many studies have been carried out by the use of locally delivered statins in chronic periodontitis patients and showed good results.[4] The present review focuses on the role of statins in bone metabolism and their applications in periodontal regeneration.

Molecular Structure of Statins

Statin contains a hexahydronaphthalene ring with two major side chains, viz. dimethylbutyrate ester and a second one, which contains a hydroxyacid. The hydroxyacid of the second chain forms a six-membered analog of the intermediate compound in the HMG-CoA reductase reaction, which is the rate-limiting step in the mevalonate pathway. As a result of its similarity to the compound HMG-CoA, statin is a reversible competitive inhibitor of the enzyme HMG-CoA reductase. The reaction catalyzed by HMG-CoA reductase and inhibited by simvastatin is the conversion of HMG-CoA to a compound called mevalonate via an intermediate. Thus they consequently inhibits cholesterol synthesis.[5]

Classification of Statins

Statins have been grouped into two groups according to their structure:

Type I- Lovastatin, pravastatin, and simvastatin

Type II- Fluvastatin, cerivastatin, atorvastatin, and rosuvastatin

The main difference between the type 1 and type 2 statins is the replacement of the butyryl group of type 1 statins by the fluorophenyl group of type 2 statins. This group is responsible for additional polar interactions that cause tighter binding to the HMGR enzyme.

Role of Statins In Periodontal Regeneration

The normal architecture of the alveolar bone is dependent on the balance between bone resorption and formation. The successful management of periodontal bone loss with a pharmacologic compound should preferably involve inhibition of resorption as well as an upregulation of formation of bone. Inhibition of the enzyme HMG-CoA reductase and the subsequent blockade of the mevalonate pathway is probably the most important mechanism of inhibition of bone resorption by statins. Statins increase bone formation by stimulating the production of BMP, which plays an important role in alveolar bone and periodontal ligament growth as well as healing.[6] Mundy et al. identified that lovastatin, simvastatin, mevastatin, and fluvastatin increased gene expression for BMP-2 in osteoblasts. The findings of their study were comparable to those seen in similar conditions after direct application of BMP-2 and FGF-1. There was also an increase in osteoblast cell numbers after statin application.[7] In another study, it was found that compactin, a known inhibitor of HMG-CoA reductase-induced BMP-2 promoter activity in a concentration-dependent manner in transfected human osteosarcoma cells. The induction by compactin seemed to be specific for BMP-2 gene. Simvastatin was also found to induce this promoter activity and appeared to be more potent than compactin (Sugiyama et al., 2000). BMP-2 and BMP-3 have been shown to enhance collagen synthesis by 60%-70%. In addition, only BMP-2 induces a significant increase in cellular alkaline phosphatase activity at doses ranging between 20 and 200 ng/mL (Takuwa et al., 1991). These findings suggest that stimulation of bone formation by simvastatin is mediated by BMP-2. This association is further substantiated by the observation that noggin, a natural antagonist of BMP-2, inhibits bone formation stimulated by simvastatin (Garrett et al.).[8] Additionally, it has been observed that statins like simvastatin, atorvastatin, and cerivastatin markedly enhance gene expression for vascular endothelial growth factor, which is involved in the process of endochondral bone formation and stimulates osteoblastic differentiation leading to new bone formation.

Simvastatin has been shown to inhibit the ability of macrophages to oxidize low-density lipoproteins.[9] Various studies have shown that statins reduce the plasma levels of inflammatory markers like C-reactive protein (CRP). Ikeda et al. studied the effects of statins on the production of interleukin-6 (IL-6) by cultured human monocytes and smooth-muscle cells. The addition of statins significantly decreased IL-6 production by these cells. It has also been suggested that the statin mediated decrease in CRP concentrations could be due to an inhibition of IL-6 in the vascular tissues. Thus, statins, including simvastatin, are believed to have biologically significant antioxidant and anti-inflammatory effects, which could prove

beneficial in the treatment of periodontitis.[10] Cells derived from the periodontal ligament are believed to play an important role in the healing of alveolar bone. In vitro studies have demonstrated that they exhibit osteoblast-like properties and are responsible not only for osteogenesis and osteoclasis, but also for fibrogenesis and fibroclasis, and cementogenesis and cementoclasis.[11] Yazawa et al. carried out an in vitro study using periodontal ligament cells obtained from human teeth. It was observed that simvastatin enhanced cell proliferation and metabolism dose dependently after 24 h. It also promoted cell proliferation significantly. The maximum effect was seen at simvastatin concentrations of 10^{-8} and 10^{-7} M. After 7 days, alkaline phosphatase activity was promoted dose dependently and the maximum effect was seen at a concentration of 10^{-8} M.[12]

Pradeep and Thorat[13] recently reported a greater decrease in gingival index and probing depth at sites treated with scaling and root planning and locally delivered simvastatin as compared to scaling and root planning plus placebo in human subjects with chronic periodontitis. In addition, more clinical attachment level gain as well as significant intrabony defect fill was seen in the simvastatin-treated individuals. Pradeep et al conducted a randomized, controlled longitudinal trial of 6 months duration in patients having chronic periodontitis alongwith diabetes mellitus to investigate the effectiveness of simvastatin (1.2 mg) as local drug delivery in conjunction with scaling and root planing and found significant improvement in plaque index, gingival index and more clinical attachment gain was seen.[14]

Conclusion

Statins have been suggested to have anti-inflammatory and bone anabolic effects. Thus, statins have a broad therapeutic effect beyond that of cardio-protection and potentially show great promise in regenerative therapies. Many studies have suggested that statin medication may also have beneficial effects on the periodontium. Statins may have therapeutic effect in the management of periodontal disease due to their effect on bone metabolism. This may lead to the identification of other potential molecular targets for drug discovery as well as other novel therapeutic approaches to enhance periodontal regeneration, if confirmed by consecutive prospective studies.

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