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Statins - A Thriving New Era in Periodontal Therapy

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Abstract: ***It is a well-established fact today that many variants of periodontal disease are essentially infections to the periodontal structures. Numerous techniques have been tried to correct the periodontal attachment and bone loss caused due to the disease. Introduction of an agent for regenerative therapy that hampers tissue destruction and enhances the regenerative capacity of periodontal tissues is required. Statins are group of drugs that are known to exhibitantibone resorbing properties by up regulating the bone morphogenic proteins and blocking the intermediate metabolites of the mevalonate pathway. Hence, it has been widely accepted to increase the bone mineral density and effective for periodontal regeneration. This article reviews the role of statins as a therapeutic agent in the treatment of periodontal diseases.***

Keywords: Bone formation, Periodontal regeneration, Statins

1. Introduction

Statins are drugs that lower the level of cholesterol in the blood by reducing the production of cholesterol by the liver providing an important and effective approach for the treatment of hyperlipidemia by reducing the blood cholesterol levels. According to angiographic studies these drug reduces the progression and may induce the regression of artherosclerosis. Statins differ in terms of their chemical structures, pharmacokinetic profiles, and lipid-modifying efficacy. The absorption, distribution, metabolism and excretion is based on the chemical structures of statins, which in turn influences their absorption[1]. Statins are known to inhibit tumor cells growth and enhance intracellular calcium mobilization. Statins are believed to increase bone formation by stimulating the production of bone morphogenetic protein-2 which may play an important role in periodontal bone and ligament growth. So it could be possible that statins might be protective not only act as cardiovascular disease protector but also could be effective against chronic periodontal disease[2].

Periodontitis is an infectious disease with marked inflammatory response, leading to destruction of underlying tissue.The aim of the periodontal therapy is to arrest this destruction and restore periodontal tissues to their original structure and function. The need to achieve greater regeneration warrants the use of an agent, which not only inhibits resorption of the alveolar bone but also stimulates new bone formation. Statin has proved to have beneficial effects on periodontal regeneration.

Statins also have number of pleotropic effects. Besides, their antiboneresorptive property, they also exert anabolic effect on bone. Systemic administration of statin is found to be associated with a reduced risk of tooth loss in patients diagnosed with chronic periodontitis as observed by a retrospective analysis over a 7-year period. The anabolic effects on bone have been attributed mainly to an up-regulation of BMP-2 by statin[3].

Thus the use of statins both systemically and locally has gained wide acceptance by the periodontists to increase the bone mineral density and effective for periodontal regeneration by stimulation of regenerative factors.

2. Historical Background

In 1976, the Japanese biochemist Akira Endo while working at Sankyo Company first isolated a factor from the funguspencilliumcitrinum. This isolated factor was identified as a competitive inhibitor of 3 hydroxy-3-methyl glutaryl coenzyme A reductase. He named this substance as compactin or mevastatins, which was the first statin to be administered to humans[4, 5].

Alfered Alberts with his colleagues in 1978 at Merck Research Laboratories Laboratories found a potent inhibitor of HMG-CoA reductase in a fermentation broth of Aspergillusterreus. They named their discovery mevinolin; later, the official (USAN) name was established as lovastatin[6].

Researchers at Merck synthesized a side chain ester analog from lovastatin called simvastatins with a 2.5 fold better activity inhibiting 3 hydroxy-3-methyl glutaryl coenzyme A reductase activity.

Investigators at warner–lambert synthesized a substituted H pyrole compound known as atrovastatins. This drug was approximately 3-4 times more potent in rat models when compared to lovastatins.

In 1978 lovastatin became the first statins to be approved in the USA by the Food and Drug Administration smvastatins was approved for marketing in Sweden in 1988, followed by pravastatins in 1991, fluvastatins in 1994, atrovastatins in 1997, cerivastatins in 1998 and rosuvastatins in 2003.

Molecular Structure of Statins

The structures of statin can be broadly divided into three parts:

1) An analog of the target enzyme substrate, 3-hydroxy-3methyglutaryl coenzyme A (HMG-CoA)
2) A complex hydrophobic ring structure that is covalently linked to the substrate analogue and is involved in binding of the statin to the reductase enzyme;
3) Side groups which are present on the rings define the solubility properties of the drugs and therefore many of their pharmacokinetic properties[7].

Classification of Statins

Statins are divided into two groups, according to their structure:

Type I- Lovastatin, pravastatin, and simvastatin

Type II- Fluvastatin, cerivastatin, atorvastatin, and rosuvastatin

The difference between type 1 and type 2 statins is the replacement of the butyryl group of type 1statins by the fluorophenyl group of type 2 statins[7].

Statins can also be classified by the way they are manufactured. Some are derived from micro-organisms through biotechnology. These are called as fermentation-derived or Type 1. Eg.Lovastatin, pravastatin, and simvastatin.

Others are made through chemical synthesis (no living organisms involved). These are synthetic or Type 2 statins. It is common for pharmaceuticals to be made through fermentation or through chemical synthesis. Eg. Fluvastatin, cerivastatin, atorvastatin, and rosuvastatin. Statins are soluble in both aqueous environments and oily environments. The solubility levels differ enough for it to be possible to classify some as hydrophilic (better solubility in water) egparavastatin, rosuvastatins or lipophilic (better solubility in fats) eg atorvastatin, fluvastatin, simvastatins.

Mechanism of Action of Statins

Statins conduct their action by blocking a step in the body's production of cholesterol. Cholesterol is a natural product of the liver; sometimes the liver produces excess of cholesterol. These drugs block the enzyme linked to the liver's cholesterol production, HMG-CoA reductase, hence, inhibiting the liver's ability to produce low-density lipoprotein (LDL). This leads to an increase in the number of the LDL receptors on the surface of liver cells, resulting in more cholesterol being removed from the bloodstream and a reduction in risk for high cholesterol-related diseases. Statins have been proved to lower LDL levels from 18% to 55% and to raise high-density lipoprotein levels from 5% to 15%. The reaction catalyzed by HMG-CoA reductase and inhibited by statin is the conversion of HMG-CoA to a compound called mevalonate via an intermediate. Thus, statin inhibits the mevalonate pathway and consequently cholesterol synthesis. This reduction in mevalonate pathway intermediates with a subsequent inhibition of prenylation by statins, is responsible for a large proportion of the pleiotropic effects of these drugs[8].

Effects on Bone Meatbolism

Inhibition of the enzyme HMG-CoA reductase and the subsequent blockade of the mevalonate pathway is the major mechanism of inhibition of bone resorption by statins. Statins increases the bone formation by stimulating the production of BMP, which play a significant role in periodontal bone and ligament growth/healing[9].

It has also been proved that use of statin is associated with decreased tooth loss in chronic periodontitis patients. Statins have been found to prevent periodontal tissue breakdown and to have beneficial effects on alveolar bone recovery after ligature-induced alveolar bone resorption, in various animal models[10].

Another study evaluated effect of atorvastatin on osteoblastic production of osteoprotegerin (OPG) and receptor activator of the nuclear factor êB ligand (RANKL), essential cytokines for osteoclast cell biology. Atorvastatin could able to increase OPG mRNA levels and protein secretion in human osteoblasts, and enhanced expression of osteoblastic differentiation markers likeosteocalcin and alkaline phosphatase[11].

Inhibition of Bone Resorption-

Inhibition of the enzyme HMG-CoA reductase and the subsequent blockade of the mevalonate pathway remains the main mechanism of action of statns[12].

Compounds called isoprenoids are primarily responsible for the prenylation of GTP-binding proteins and are involved in cytoskeletal function and vesicular trafficking[13]. Thus, interference with the generation of isoprenoids could leads to disruption of vesicular fusion and ruffled border formation of osteoclasts, which are necessary for their bone resorbing activity. As a result, osteoclast inactivation occurs and bone resorption is inhibited.

Local stimulation of BMP-2 is a major bone growth regulatory factor. Its local stimulation can lead to new bone formation. According to Mundy et al., lovastatin, simvastatin, mevastatin, and fluvastatin increases gene expression for BMP-2 in osteoblasts. There was also a striking increase after statin application a marked increasein osteoblast cell numbers was also observed.

Compactin, a known inhibitor of HMG-CoA reductase could able to 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 also induce this promoter activity and found to be more potent than compactin[14]. Statins like simvastatin, atorvastatin, and cerivastatin also significantly 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.

Antioxidant and Anti-Inflammatory Properties

Statins have been proved to inhibit the ability of macrophages to oxidize low-density lipoproteins[15]. Various studies have shown the ability of statins to reduce the plasma levels of inflammatory markers like C-reactive protein. Ikeda et al., conducted a study to evaluate the effects of statins on the production of interleukin-6 (IL-6) by cultured human monocytes and smooth-muscle cells. The addition of statins remarkably decreased IL-6 production by these cells[16]. It has also been observed that the statin mediated decrease in CRP concentrations could be due to an inhibition of IL-6 in the vascular tissues. Thus, statins are believed to have biologically significant antioxidant and anti-inflammatory effects, which could show favourable outcome, in the treatment of periodontitis.

Immunomodulatory

Under various animal and human studies statins have shown to have immunomodulatory effects. Statins mainly inhibits the major histocompatibility complex II expression. The antigen presenting cells such as endothelial cells and monocytes requiresco-stimulation by interferon gamma and this is achivedby inhibition of promoter IV of class II transcription activator which is an important regulator in this pathway. Another effect on immune system is mediated by binding of statins to leucocyte function associated antigen and preventing its binding to ICAM1. This leads to inhibition of its function in leucocyte adhesion and extravasation[17].

Statins−Enhancement of Periodontal Regeneration

Simvastatin has been shown to inhibit bone resorption. However, this effect appears minor in comparison to its anabolic action on new bone formation and osteoblast maturation[18]. It also possesses anti-inflammatory and antioxidant properties. It could, therefore, have a potential role in regenerative therapy.

It is administered in the prodrug form, which is much more lipophilic than the active beta-hydroxyacid form. As a result, the simvastatin molecule can easily cross cellular membrane barriers by passive diffusion[19]. It also implies that it can be incorporated into hydrophobic delivery vehicles for local sustained release to achieve bone formation in periodontal defects. Moreover, simvastatin solution in optimal concentrations could be combined with bone grafts to enhance their regenerative potential. The low cost and impressive long-term safety profile of this compound makes it a favourable agent in periodontal therapy[20].

Studies on Statins Use in Periodontal Disease

Animal Studies-Systemic Administration of Statins

Mundy et al. first reported that statins stimulate in vivo bone formation in rodents and increase new bone volume in mouse calvaria cell cultures. He identified that simvastatin may help in periodontal regeneration by inducing BMP-2 and TGF beta in osteoblasts[18].

Goes et.al. found that Atrovastatin (ATV) reduced alveolar bone loss by over 47% ($p<0.05$), when compared to the group of untreated rats and concluded that ATV was able to prevent alveolar bone loss seen on a ligature-induced periodontitis model[21].

Human Studies-Systemic Administration Of Statins

Lindy et. al. examined the association of statin use and clinical markers of chronic periodontitis and concluded that patients on statin medication exhibit fewer signs of periodontal inflammatory injury than subjects without the statin regimen[22].

Fajardo et. al. studied the effect of Atrovastatin (ATV) treatment on bone loss prevention in subjects with chronic periodontitis and reported that ATV have beneficial effects on alveolar bone loss and tooth mobility in subjects with periodontal disease[23].

Sangwan et. al. reported that relative to the general population, hyperlipidemic subjects are more prone to periodontal disease and also stated that statins have a positive impact on periodontal health[24].

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[25].

Animal Studies- on Locally Delivered Statins

Jeon et al, conducted a study in which sustained or intermittent release of simvastatin hydroxyacid were formed using a blend of cellulose acetate phthalate and a poly (ethylene oxide) and poly (propylene oxide) block copolymer, and they were implanted directly over the calvarium of young male rats. Drug-free devices were used as controls. After 9, 18, or 28 days, specimens were histologically evaluated for new bone formation. Intermittent delivery of simvastatin hydroxyacid in rats calvarium resulted in localized osteogenesis[26].

Messora MR et al local application Rosuvastatins promotes a protective effect against alveolar bone and connective tissue attachment losses attributable to periodontitis in hypertensive rats through inflammatory gene profile modulation[27].

Human Studies- on Locally Delivered Statins

Pradeep et.al. investigated the effectiveness of Simvastatin (SMV), 1.2 mg, in a Locally delivered SMV provides a comfortable and flexible method not only to improve clinical parameters but also enhances bone formation. indigenously prepared biodegradable controlled-release gel as an adjunct to scaling and root planning (SRP) in the treatment of chronic periodontitis and reported that there was a greater decrease in gingival index and probing depth and more CAL gain with significant bone fill at sites treated with SRP plus locally delivered SMV in patients with chronic periodontitis[28].

According to Kinra et al. when allograft is used in combination with a solution of simvastatin showed significantly greater reduction in probing depth, gain in clinical attachment level, and linear defect fill than when the graft is used alone in the treatment of human periodontal infrabony defects[29].

Pradeep et al showed the effectiveness of simvastatin (SMV), 1.2% on indigenously prepared biodegradable controlled release gel as an adjunct[30].

Pradeep AR et al evaluated the effect of rosuvastatins in situ gel (1.2%), when delivered locally into periodontal pockets or intrabony defects, showed a greater reduction than

placebo in periodontal and gingival index, along with increased gain in clinical attachment loss[31].

From the study conducted by Subramanian S et al concluded that the high doses of atrovastatins reduces periodontal inflammation as assessed by 18 f – fluorodeoxyglucosepositrom emission tomography/ computed tomography[32].

Statins in Implants

According to Ayukawa, et al., the application of simvastatin locally promotes osteogenesis around titanium implants. After the administration of statin, mesh-like structure of bone was found around the implant, this resulted in an improved implant fixation and that the bone. Topical application of statin also affects bone healing around implants[33].

Wen Fang et al, in their research study showed the influence of Simvastatins-loaded implant on osseointegration in an ovariectomized animal model. The results showed the Simvastatins coating improved the bone-implant contact and new bone formation around implant in the osteoporotic rats[34].

Adverse Effects of Statin

The most common adverse effects of statin therapy includes myalgias and muscle cramps. The increased risk of myopathy is associated with SLCO1B1 gene, which participates in the absorption of statins[35]. Pravastatin and fluvastatin showed lowest risk for myopathy as they are more hydrophilic and as a result have less muscle penetration.

Occasionally, statin use could cause an increase in the level of hepatic transaminases enzyme that signals the liver inflammation[36].Rarely statins can also cause rhabdomyolysis which attributes to severe muscle pain, liver damage, kidney failure and death[37].

Cruz, et al., in his study described the oral adverse effects of statins which are often underestimated. According to the study dry mouth, itching or paresthesia in tongue, lips or throat, bitterness and cough are the most common side effects and all of them subsided with interruption of statin therapy. Insomnia also found to be associated with above mentioned symptoms and94% of patients with insomnia reported better rest after interruption of the treatment[38].

Touomas Saxlin et al., conducted a study to investigate the association between statins medication and periodontal infection in an adult population. They found a weak negative association between statin medication and periodontal infection among subjects with dental plaque or gingival bleeding. Among subjects with no gingival bleeding, statin medication was found to be associated with an increased likelihood of having deepened periodontal pockets[39].

3. Conclusion

Recently statins have emerged as the paramount class of lipid lowering drugs. There is increasing evidences from various studies that the use of statins may have therapeutic effect in the management of periodontal disease due to their effect on bone metabolism. Its immunomodulation, anti-inflammatory effects, antioxidants effects and effects on promotion of osteogenesis are the reason, it has become a formidable drug in periodontal regenerative therapy. This may help to identify other potential molecular targets for drug discovery as well as other novel therapeutic approaches to enhance periodontal regeneration, if confirmed by consecutive prospective studies. Other systemic diseases where role of statins is being studied are Alzheimers, multiple sclerosis, vitiligo, osteoporosis, pulmonary hypertension and many more.

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