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RESEARCH ARTICLE

Role of Statins in Periodontitis- An overview

Dr Shilpa Shetty [1] ,[*] Dr Mranali K Shetty[2]

1. Dept of Periodontology, AJ institute of dental science, Mangalore

2. [*]Dept of Periodontology, Manipal college of dental sciences , mangalore , Manipal University. (Corresponding Author)

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Corresponding Author
Dr Mranali K Shetty

Abstract

Periodontal disease is a chronic inflammatory disease which represents a primarily anaerobic Gram-negative oral infection that results in gingival inflammation, loss of attachment, bone destruction. Certain organisms within the microbial flora of dental plaque are the major etiologic agents of periodontitis which produce endotoxins in the form of lipopolysaccharides (LPS) that are instrumental in generating a host-mediated tissue destructive immune response by mobilizing their defensive cells and releasing cytokines like Interleukin-1□□(IL-1□), Tumor Necrosis Factor-□□(TNF-□), and Interleukin-6 (IL-6),which lead to tissue destruction by stimulating the production of the collagenolytic enzymes: Matrix metalloproteinases (MMPs). Statins, 3-hydroxy-3-methylglutarylcoenzyme A (HMG CoA) reductase inhibitors, besides having lipid-lowering abilities also have antioxidant, antithrombotic, anti-inflammatory, immunomodulatory and osteomodulatory properties. All of these pleiotropic effects of statins point out to it perhaps becoming the novel host modulation agent in periodontics.

Introduction

Periodontal disease is a chronic inflammatory disease which represents a primarily anaerobic Gram-negative oral infection that results in gingival inflammation, loss of attachment, bonedestruction**.(1)** Matrix metalloproteinases (MMPs) and tumour necrosis factor-a (TNF-a) may
play important roles in this process. (Golub et al.2001, Nishikawa et al. 2002).(2,3)

Statins (or hmg-coa reductase inhibitors) are a class of drugs used to lower cholesterol levels by inhibiting the enzyme HMG-CoA reductase, which plays a central role in the production of cholesterol in the liver, which produces about 70 percent of total cholesterol in the body. High cholesterol levels have been associated with cardiovascular disease (CVD). Statins have been found to prevent cardiovascular disease in those who are at high risk. The evidence is strong that statins are effective for treating CVD in the early stages of a disease (secondary prevention). The evidence is weaker that statins are effective for those with elevated cholesterol levels but without CVD (primary prevention) (4)

Statins differ in terms of their chemical structures,pharmacokinetic profiles, and lipid-modifying efficacy.The chemical structures of statins govern their watersolubility, which in turn influences their absorption,distribution, metabolism and excretion. Lovastatin,pravastatin and simvastatin are derived from fungal metabolites and have elimination half-lives of 1-3 h.Atorvastatin, fluvastatin and rosuvastatin are fullysynthetic compounds, with elimination half-livesranging from 1 h for fluvastatin to 19 h for rosuvastatin.Atorvastatin, simvastatin, lovastatin and fluvastatin arerelatively lipophilic compounds. Lipophilic statins are more susceptible to metabolism by the cytochromeP (450) system. Pravastatin and rosuvastatin are relatively hydrophilic and not significantly metabolizedby cytochrome P (450) enzymes. All statins are selective for effect in the liver, largely because

ofefficient first-pass uptake. The bioavailability of the statins differs greatly, from 5% for lovastatinand simvastatin to 60% or greater for cerivastatin.(4)
These structures can be broadly divided into three parts: An analogue of the target enzyme substrate, HMG-CoA; 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; side groups on the rings that define the solubility properties of the drugs and therefore many of their pharmacokinetic properties.Potential pleiotropic effects of statins involve immunomodulatory, antioxidant, antithrombotic and endothelium stabilization actions, as well as angiogenesis promotion and increase of osteoblastic differentiation, inducing bone formation. In addition,statins can inibit tumor cells growth and enhance intracellular calcium mobilization. It was observed that inhibitors of HMG-CoA reductase induce a reduction of the formation of osteoclasts in rodents.(4)
Human subjects treated with statins have shown a reduction in the number of bone fractures statins, lower cholesterol levels through inhibition of cholesterol biosynthesis. They reduce the risk of cardiovascular events, as do other drugs that lower serum cholesterol levels, but at least part of their protective cardiovascular effect seems to come from anti-inflammatory properties such as inhibition of MMP-9 and TNF-a (Wong et al. 2001)(5)

Sub-antimicrobial doses of doxycycline have positive short-term effects on surrogate markers of chronic periodontitis and this is thought to be mediated by inhibition of MMP synthesis(Golub et al.2001). (3)MMP-9 and TNF-a appear to be involved in the tissue destruction of chronic periodontitis . Furthermore, statins [with the possible exception of pravastatin) are believed to increase bone formation by stimulating the production of bone morphogenetic protein-2 (which may play an important role inperiodontal bone and ligament growth/. Hence, itseems possible that statins might be protective not only against cardiovasculardisease but also against chronic periodontal disease. (6)

MECHANISM OF PLEIOTROPIC ACTION OF STATINS

Anti-inflammatory

Continuously growing evidences have recognized inflammation as a major component of atherosclerosis.When atherosclerotic process is at work, each characteristic lesion of atherosclerosis represents a different stage in a chronic inflammatory process in the artery; if unabated and excessive, this process will result in an advanced, complicated lesion. Certain cell and cytokine mediated markers likeC-reactive protein (CRP) are associated both with atherosclerosis and periodontal disease, proving a link between cardiovascular disease and periodontaldisease.(4)
Kleemann and colleagues have shown that atorvastatin at doses higher than those required for cholesterol lowering, decrease basal and IL-1β-induced plasma human C-Reactive Protein (huCRP) levels.[13] Statins also inhibits Intercellular Adhesion Molecule-1 (ICAM-1) upregulation and chemotaxis in adherent human monocytes.[14]Simvastatin lowers high sensitivity (hsCRP) by 14 days, independent of its effect on LDL cholesterol.[15] This rapid impact of a statin on hsCRP has potential implications in the management of acute coronary syndromes. JUPITER trail showed that statins could be beneficial in the primary prevention of cardiovascular diseasein patients with elevated hs CRP, but relatively low cholesterol levels and other cardiovascular risks.

Effect of statin on bone

Statins have been found to be a potent activator of bone morphogenetic protein (BMP-2) which accounts for major osteoinductive potential of bone.Simvastatin, mevastatin and atorvastatin stimulates BMP-2 transcription.Mechanism of action involves reduction in mevalonate pathway intermediates and inhibition of prenylationby statins is responsible for a large proportion of thepleiotropic effects of these drugs. Mevalonate, farnesyl pyrophosphate and geranyl-geranyl pyrophosphate allinhibited statin-stimulated bone formation. Furthermore,because geranylgeranyl pyrophosphate inhibited statin stimulated bone formation, inhibition of prenylation due to geranylgeranylation must play a major role in the stimulation of bone formation by these drugs.(7) Also statins influence the production of Receptor activator of nuclear factor kappa-B ligand (RANKL) and Osteoprotegrin by human gingival fibroblaststo favor bone catabolism under non-inflammatory conditions.

Immunomodulatory

Various experiments have shown statins to have immunomodulatory effects. Primary effects of statins include inhibition of major histocompatibility complex II expression. Antigen presenting cells such as endothelial cells and monocytes requiresco‑stimulation by Interferon gamma. This is done by 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.(8)

Antioxidant effects of statins

Antioxidant effect of statins is proposed as mechanism of its various pleiotropic effects. Many studies done to assess the antioxidant potential of statins have concluded favorably. Various mechanisms of its antioxidant activity are being proposed. Production of Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, a major source of oxidant production is inhibited by statins. Simvastatin has been reported most effective in this regard.[9)

CONCLUSION

Thus multiple effects of statins have been demonstrated in various experiments. The ultimate effect of statins on host is a combination of all these effects. Immunomodulation, anti‑inflammatory effects antioxidants effects are thought to contribute most towards its beneficial effects. Its effect on promotion of osteogenesis makes it a potential blockbuster in periodontics. Other systemic diseases whererole of statins are being studied are Alzheimers, multiple sclerosis, vitiligo, osteoporosis, pulmonary hypertension and many more.

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