ISSN: 0975-833X

Available online at http://www.journalcra.com

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

International Journal of Current Research
Vol. 13, Issue, 05, pp.17350-17354, May, 2021

DOI: https://doi.org/10.24941/ijcr.41322.05.2021

RESEARCH ARTICLE **OPEN ACCESS**

NON-CHOLESTEROL-DEPENDENT BIOLOGICAL EFFECTS OF STATINS: A NEW HORIZON IN PERIODONTAL THERAPY

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ARTICLE INFO

Article History:
Received 09th February, 2021
Received in revised form
14th March, 2021
Accepted 20th April, 2021
Published online 20th May, 2021

Key Words:
Periodontitis, Statins, Anti-inflammatory, Immunomodulatory, Osteomodulatory, Regenerative Periodontal therapy.

ABSTRACT

Periodontitis is an inflammatory process causing destruction of the periodontal tissues and alveolar bone. Various adjunctive treatment approaches are introduced along with scaling and root planing for treating periodontitis; Statins being one of them. Statins are considered as "Gold-standard" to treat hyperlipidemia and widely used to control cardiovascular and cerebrovascular diseases. Apart from the lipid-lowering properties, various non-cholesterol-dependent biological effects of statins are captivated. These include Antioxidative, Antibacterial, Antithrombotic, Anti-inflammatory, Immunomodulatory, and Osteomodulatory properties. Considering these effects, this group of drugs might play a potential role in regenerative periodontal therapy.

Citation: Rakesh Kumar Medhi, Nischal Das and Swarga Jyoti Das. "Non-cholesterol-dependent biological effects of statins: a new horizon in periodontal therapy*", 2021. International Journal of Current Research, 13, (05), 17350-17354.*

INTRODUCTION

Periodontitis are infectious diseases characterized by immune-mediated destruction of periodontal supporting tissues and tooth loss. The pathogenesis of periodontitis involves a complex interaction of immune and inflammatory cascades initiated by a specific microorganism or groups of specific microorganisms. The inflammatory cells especially the macrophages in response to the bacterial endotoxins, namely lipopolysaccharides (LPS) synthesize and secrete a wide array of molecules including the inflammatory cytokines, proinflammatory mediators, namely interleukin (IL) -1α and β, and tumour necrosis factor α (TNF-α), IL- 6, prostaglandins (PG), particularly PGE2 and hydrolytic enzymes (e.g. matrix metalloproteinases), which are responsible for the periodontal breakdown (Socransky and Haffajee, 1992; De Nardin 2001; Newman *et al*, 2011).

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However, these pro-inflammatory mediators are balanced by anti-inflammatory cytokines and lipoxins (Van Dyke and Serhan, 2003). Imbalance in between the activity of pro-inflammatory and anti-inflammatory mediators is a major determinant of periodontal destruction (Page, 1999). Thus, both pro-inflammatory and anti-inflammatory cytokines initiate, mediate and control the immune and inflammatory responses. Periodontal disease has been linked to an increased risk of various systemic diseases, namely cardiovascular disease, diabetes mellitus, respiratory diseases, etc., and causes increase in obstetric complications (Jeffcoat *et al*., 2001; Fowler *et al*., 2011; Newman *et al*., 2011).

The periodontal therapy is aimed at to arrest the inflammation by eliminating the causative bacterial plaque and regeneration of lost periodontal tissues as a consequence of disease process. Traditional therapy for periodontitis has involved elimination or suppression of subgingival microbial complexes by mechanical debridement such as scaling and root planing or surgical procedures. However, the pathogenic microbiota becomes more complex over time and they can invade periodontal tissues. Then the mechanical therapy alone is

sometimes ineffective in a sense that complete elimination of sub-gingival microflora is difficult from the areas inaccessible to periodontal instrumentation so systemic administration of antibiotics may be required as an adjunct in controlling bacterial infections (Saglie *et al*., 1982; Barca *et al*., 2015). Therefore, mechanical debridement is considered critical to disrupt the biofilm when using systemic antibiotics to treat periodontitis. The rationale for use of adjunctive systemic antimicrobials is to further reduce the bacterial load, enabling resolution of the inflammation in the periodontal pocket. Anti-microbial agents remain an important adjunctive therapy in the treatment of periodontal diseases. However, systemic anti-microbial agents should be used with caution considering the risk of adverse drug reactions, development of multiple antibiotic resistant microorganisms and uncertain patient compliance (Barca *et al*., 2015). In contrast to the traditional antibiotics, to achieve a greater predictability with regenerative therapy necessitates an introduction of agents which would interrupt tissue destruction and enhance regenerative capabilities of the periodontal tissues through modulation of both host cells and bacteria, as periodontitis is the result of host-microbial interaction (Newman *et al*, 2011).

It leads to the concept of 'Host Modulation Therapy', which is aimed at to restore the balance of pro-inflammatory and anti-inflammatory mediators to that seen in healthy individuals. The use of modulating agents, including inhibition of matrix metalloproteinases (MMPs) with antiproteinases, blocking production of pro-inflammatory cytokines and prostaglandins with anti-inflammatory drugs, and inhibiting activation of osteoclasts with bone-sparing agents, has been postulated to be of therapeutic value as an adjunctive therapy (Reddy *et al.*, 2015). These therapies may provide the next wave of disease-specific chemotherapeutics to manage chronic periodontitis. Although these drugs offer great potential to modulate a variety of mammalian cells, a notable and consequential limitation of these agents is a lack of specificity (Elavarasu *et al*., 2012). Statins, a widely prescribed group of drugs and considered as the "Gold-standard" to treat hyperlipidemia (Tripathy, 2018) has been explored recently in periodontal treatment considering their non-cholesterol-dependent biological effects (Estanislau *et al*., 2015).

MECHANISM OF ACTION OF STATIN

'Statins' is a group of drugs that lowers the cholesterol level in blood by reducing its production by liver. They are the inhibitors of 3-hydroxy-3-methylglutaryl Coenzyme A reductase (HMG- CoA reductase), the enzyme that plays a central role in cholesterol production. Since statins are similar in structure to HMG-CoA on a molecular level, they fit into the enzyme's active site and compete with the native substrate (HMG-CoA). This competition reduces the rate by which HMG-CoA reductase is able to produce mevalonate, the next molecule in the cascade that eventually produces cholesterol. Thus, this group of drugs blocks the pathway of synthesizing cholesterol in the liver (Tripathy, 2018). This is significant because most circulating cholesterol comes from the internal manufacture rather than the diet. When the liver can no longer produce cholesterol, levels of cholesterol in the blood will fall concurrently. By blocking HMG-CoA reductase, Statin inhibits the liver's ability to produce low-density lipoprotein (LDL). This further causes 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.

There are various forms of statin. They differ mainly in their ring structure, and these structural differences modify their pharmacological properties including hydrophilicity and lipophilicity. The lactone ring is present either in an active form (already hydrolyzed) or become activated (hydrolyzed) in the liver. The lactone ring of the statins enables their transport, metabolism, and clearance. These distinct characteristics of hydrophilic (e.g. pravastatin, rosuvastatin, and fluvastatin) and lipophilic statins (e.g. simvastatin, lovastatin, pitavastatin, and atorvastatin) may lead to differential effects of statins in terms of efficacy as well as the adverse effects. Based on the way of manufacturing, Statins are of micro-organisms derivative (fermentation-derived or Type 1) and synthesize chemically (synthetic or Type 2) (Tripathy, 2018).

PLEIOTROPIC EFFECTS OF STATINS

Apart from the lipid-lowering properties, various non-cholesterol-dependent biological effects of statins are captivated, referred to as "PLEIOTROPIC EFFECTS". These include Antioxidative, Antibacterial, Antithrombotic, Anti-inflammatory, Immunomodulatory, and Osteomodulatory properties (Bonetti *et al.*, 2003) (Figure 1). These wide ranges of pleiotropic effects occur through the production of mevalonate and isoprenoids (other intermediates of cholesterol synthesis) that regulate diverse cellular functions during the inhibition of HMG-CoA reductase (Estanislau *et al.*, 2015).

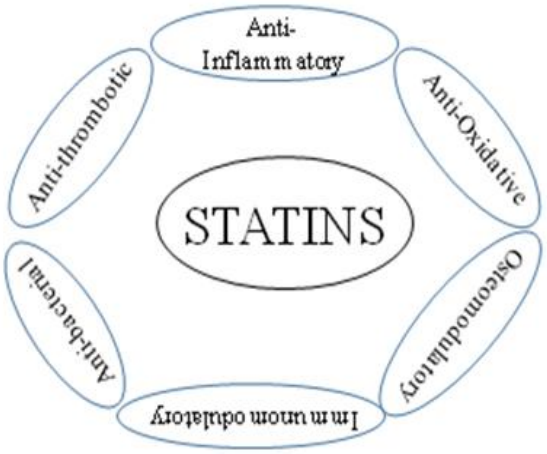

Figure 1. Non-Cholesterol-Dependent Biological Effects of Statins

ANTI-OXIDATIVE EFFECTS

Statins, which are primarily used to reduce the concentration of low-density lipoprotein cholesterol, have also been shown to reduce oxidative stress that plays an important role in the development of atherosclerosis and cardiovascular diseases, diabetic complications and of fatty liver. Statins reduce oxidative stress by modulating redox system, namely blocking the generation of ROS, inhibiting the production of nicotinamide adenine dinucleotide phosphate oxidase, myeloperoxidase and up-regulating the activity of antioxidant enzymes such as catalase and paraoxonase. However, possible adverse effects of statins on glucose homeostasis may be related to the redox system. These drugs also have effects on nitric oxide synthase, lipid peroxidation and the adiponectin levels.

In addition to direct antioxidant effects, statins reduce the circulating oxidized low-density lipoproteins (oxLDL) and inhibit their uptake by macrophages. The HDL-raising effects of statins may also relieve oxidative stress (Lim and Barter, 2014). Statins interfere with oxidation in several ways that contribute in reducing the atherogenic process. Thus, it is possible that the antioxidant properties of statins contribute to their protective cardiovascular effects, independent of the lipid-lowering actions of these agents.

ANTI-BACTERIAL EFFECTS

Cholesterol is an integral component needed by bacteria for maintaining their membrane integrity. Statins kill bacteria directly by inhibiting the intermediate in the isoprenoid biosynthesis pathway necessary for membrane stability and by lowering accessible host cholesterol content for bacterial growth and protection. Such effects may be due to the disruption of teichoic acid structures reducing biofilm formation (Jerwood and Cohen, 2008). Statins display antibacterial activity towards anaerobic bacteria, including periodontal pathogens such as *Actinobacilus actinomycetemcomitans* and *Porphyromonus gingivalis*. However, not all statins exhibit antibacterial activity. It also reduces the severity of an infection by enhancing bacterial clearance at the site of infection through production of several endogenous chemical and proresolving lipid mediators such as the lipoxin, resolvins, protectins, and maresins (Chaudhry *et al*., 2008; Spite and Serhan, 2010).

ANTITHROMBOTIC EFFECTS

The antithrombotic activity of statins is peculiar because it differs from that of commonly used anticoagulants or antiplatelet drugs. The anticoagulant property of statins occurs via downregulation of tissue factor, a glycoprotein that converts factor X to factor Xa and/or upregulation of thrombomodulin, which results in impaired thrombin generation. With respect to the antiplatelet activity, the peculiarity of statins lies in their ability to inhibit the platelet thromboxane A2 and isoprostane formation, thus enhances fibrinolysis (Violi *et al.,* 2013). Oxidized LDL resides the inner lining (endothelium) of the body's arteries, namely carotid and coronary arteries and promotes atherosclerosis. Statins have been shown to inhibit the ability of macrophages to oxidize LDL-mediated CD36 and Toll-like receptor 4/6 (TLR4/6) activation (Giroux *et al*., 1993). Thus, statins possess a potentially unique antithrombotic mechanism that alters both coagulation and platelet activation, which may offer a new therapeutic strategy to improve antithrombotic treatment and likely to contribute in reduction of the incidence of cardiovascular death.

ANTI-INFLAMMATOTY EFFECTS

The effects of lowering LDL cholesterol with statins may lead to anti-inflammatory actions because LDL cholesterol itself strongly promotes inflammation. Statins reduce the plasma levels of inflammatory markers like C-reactive protein, cytokines such as IL-1, IL-6 and tumor necrosis factor- (TNF-). and adhesion molecules such as ICAM-1, lymphocyte function associated antigen-1and monocyte chemotactic protein-1. ICAM-1 inhibits the adhesion and trans-endothelial migration of leukocytes at the sites of inflammation (Chow, 2009). Statins further slowing down the inflammatory process by modulation of T cell activity particularly Th1- type chemokine receptors on T cells and inhibiting chemokine release which could be due to inhibition of IL-6 in the vascular tissues. The entire anti-inflammatory pleiotropic effects are supposed to result from the inhibition of isoprene modification of signal transducers of inflammation (Corsonello, 2010).

IMMUNOMODULATORY EFFECT

Inhibition of T cell activation and proliferation by statins *in vitro* has prompted speculations that immunomodulatory effects of statins may be beneficial in recipients of organ transplants. Major histocompatibility complex class II (MHC-II) molecules, which affect the immune response and organ rejection after transplantation, may be induced by the pro-inflammatory cytokine interferon gamma (IFN-γ). Statins were found to repress the induction of MHC-II by IFN-γ (Petit *et al*., 2019). This may explain the immunosuppressive effects of statins and suggest a potential role for statins as immunosuppressive agents.

EFFECT OF STATINS ON MATRIX METALLOPROTEINASES (MMPs)

MMPs regulate cell proliferation, adhesion, migration, growth factor bioavailability, chemotaxis, and signaling; and they are crucial for angiogenesis, vasodilation, tumorogenesis, metastasis immunity, inflammation, and wound healing. In addition, MMPs have been proposed as master regulators of inflammation, through proteolysis of chemokines, growth factors, receptors and their binding proteins, proteases, protease inhibitors, as well as intracellular multifunctional proteins, resulting in pro- or anti-inflammatory functions leading to either tissue homeostasis or pathology (Franco *et al.*, 2017). Most statins have been reported to potently inhibit the expression of MMP-1, MMP-8, and MMP-9 upregulated by LPS both *in vitro* (Poston *et al,* 2016) and *in vivo* (Balli *et al*., 2014).

OSTEOMODULATORY EFFECT

Statins influences bone metabolism through increase of osteogenesis, decrease of apoptosis of osteoblast and osteoclastogenesis. It allows periodontal regeneration either enhancing bone formation through augmenting BMP-S mad signal or by osteoclastic differentiation through antagonizing TNF-*α*. Both of the situations involve Ras/Rho/mitogen-activated protein kinase (MAPK). Moreover, they significantly enhance alkaline phosphatase activity and mineralization, as well as increase the expression of bone sialoprotein (BSP), osteocalcin, and Type 1 collagen, BMP-2, osteopontin (OPN), and vascular endothelial growth factor (VEGF) (Zhang *et al*, 2014). Statin interferes the generation of isoprenoid, which is associated in cytoskeletal function and vesicular dealing. Thus, it leads to disruption of vesicular fusion and formation of ruffled borders in osteoclasts, which are fundamental for their bone resorbing activity. As a result, osteoclast inactivation occurs and bone resorption is inhibited (Petit *et al*., 2019).

DISCUSSION

The biological properties of Statins might be of interest for the management of periodontitis as they act on each tissue compartment of periodontium through several pathways to

modulate inflammation, immune response, bone metabolism, and bacterial clearance. Statins control periodontal inflammation through inhibition of pro-inflammatory cytokines and promotion of release of anti-inflammatory molecule, mainly through the ERK, MAPK, PI3-Akt, and NF-κB pathways. Periodontal wound healing and regeneration is promoted through the modulation of inflammatory-immune crosstalk, bone regeneration, and antibacterial activity of Statins (Petit *et al.,* 2019). Despite its infectious etiology, the loss of periodontal supporting tissues during periodontitis is considered as an ultimate consequence of the host's immune response. Matrix metalloproteinases (MMPs) are key proteases involved in destructive periodontal diseases through degradation of extracellular matrix proteins, especially collagen thereby, contributes to destruction of periodontal tissues including alveolar bone (Franco *et al*., 2017). Since statins have been reported to potently inhibit the expression of lipopolysaccharide (LPS)-induced MMP-1, 8, and 9 in monocytes and osteoblastic cells, it may prevent the destruction of periodontal tissue and alveolar bone by inhibiting the release of MMPs (Balli *et al*., 2014; Poston *et al*, 2016). In clinical trials, the local application of statins with surgical periodontal treatment has shown significant improvements in periodontal parameters (Martande *et al*., 2016), while a contradictory result is seen *in vivo* which could be explained by the limitations of animal models to simulate conditions identical to human periodontal disease (Morris *et al*., 2008). However, some conflicting results on the effect of statins is also available, which is probably due to a range of factors, such as the method of administration, duration of exposure, experimental animal model, and bioavailability (Morris *et al*., 2008). In addition, efficacy and action of Statins on the pathogens are determined by the hydrophobic or hydrophilic nature of it (Tripathy, 2018) and the response to it appears to be largely cell- and tissue-dependent (Shitara and Sugiyama, 2006). In addition, the efficacy, safety, and cost-effectiveness of the long-term use of Statins are unknown. Inflammation, bone metabolism, and connective tissue metabolism are necessary for the homeostasis of the tissue, but they are also involved in the pathologic destruction. Thus, they are two-edges of a sword. Henceforth, drugs that inhibit destruction of the connective tissue in one site of the periodontium also interfere with wound healing at another. Notably, Statins has the ability to control inflammation, stimulates osteogenesis and enhances bacterial clearance from the site of infection. Considering the pleotropic effects of Statins, it may be incorporated with antimicrobial agents, growth factors, pro-regenerative molecules or other drugs in an efficient carrier system to enhance the periodontal treatment outcomes as an adjunct to mechanical debridement.

CONCLUSION

The studies on the applicability of statins in chronic periodontitis indicate that statins possesses beneficial effects. It is of antioxidant and anti-inflammatory in nature and stimulates bone formation. It is also safe, non-invasive and cost effective, though it cannot be substitute the conventional periodontal treatment of removal of causative microorganisms. The pleiotropic effects of statins indicate that it might have a great potential to improve the therapeutic effect in the treatment of periodontitis, thereby it will be a new horizon worldwide in near future.

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