Annals of R.S.C.B., ISSN: 1583-6258, Vol. 25, Issue 1, 2021, Pages. 6244 – 6249
Received 15 December 2020; Accepted 05 January 2021.

Periodontal Regeneration & Statins - A Review

Dr Mohammad Shoyab Khan,
Lecturer, Department of Preventive Dental Sciences, College of Dentistry, Prince Sattam Bin Abdulaziz University, Alkharj, Kingdom of Saudi Arabia.
E mail: drkhanmds@gmail.com

Abstract:

Periodontitis is an inflammatory process which causes gradual destruction of periodontal tissues and thereby loss of alveolar bone. Statins are the one among the various periodontal therapies that have been introduced in order to lower the periodontal destruction. Statins are the drugs which lower the cholesterol; however, they also promote bone formation, thereby they have been proven to be effective in the periodontal therapy. The present article reviews the effects of statins and describes its potential role in the periodontal regenerative therapy.

Keywords: Bone formation, periodontal disease, periodontal regeneration, statins

INTRODUCTION- The "statins" are cholesterol- lowering class of drugs that reduces the level of cholesterol in the blood by decreasing the cholesterol production by the liver. The statins act by blocking a enzyme in the liver which is responsible for making the cholesterol. Lately, the interest has been focused on the pleiotropic effects of statins which has been utilised in various periodontal therapies. Periodontitis is characterized by an inflammatory breakdown of tooth supporting structures. The objective of periodontal therapy is to arrest this inflammatory breakdown and thereby restoring the periodontal tissues to their original structure and function. The requirement is to achieve a greater regeneration, not just by reducing the alveolar bone resorption but also by stimulating the new bone formation. The statins have proved to have such a potential role in the periodontal regenerative therapy.

STATINS- MECHANISM OF ACTION- They block an enzyme in the liver, HMG-CoA reductase, which is linked to the liver's cholesterol production thereby, inhibiting the liver's ability to produce low-density lipoprotein (LDL). The statins have shown to reduce the LDL levels from 18% to 55% and increase the high-density lipoprotein levels from 5% to 15%. The reaction of conversion of HMG-CoA to a compound called mevalonate via an intermediate is being catalysed by HMG-CoA reductase enzyme and inhibited by simvastatin (SMV). Hence, statin is an inhibitor of the mevalonate pathway and thereby the cholesterol synthesis. Therefore, reduction in the mevalonate pathway intermediates with a subsequent inhibition of the prenylation by statins, is responsible for their various pleiotropic effects.

Pleiotropic actions of statin- Various effects have been observed with the statins, which are higher than expected. Besides the lipid lowering properties, this drug has additional non-lipidic effects that are responsible for its complicated pharmacological profile which have been demonstrated in the clinical trials. Likewise, the recent studies have shown the various

Annals of R.S.C.B., ISSN: 1583-6258, Vol. 25, Issue 1, 2021, Pages. 6244 – 6249
Received 15 December 2020; Accepted 05 January 2021.

non-lipidicbiological effects of statins which are known as "pleiotropic effects" of statins, that includes osteo-modulatory, anti-inflammatory, antioxidant, antithrombotic and immunomodulatory properties.[1]Perhaps, by the virtue of all these pleiotropic effects of the statins, these are one of the novel host modulation agent in the periodontics. Simvastatin has been shown to inhibit the ability of macrophages to oxidize LDLs.[2] It has been shown by various studies that statins reduce the plasma levels of inflammatory markers like C-reactive protein (CRP).[3] Moreover, the statins significantly decreased the production of interleukin-6 (IL-6) by these cells. It has also been observed that the decrease in CRP concentrations mediated by statins could be due to IL-6 inhibition. It has also been suggested that the statins also inhibit the production of nicotinamide adenine dinucleotide phosphate oxidase, which is a major source of oxidant production.[4] Thereby, the statins, including SMV, are believed to have biologically significant anti-inflammatory as well as antioxidant effects, which could prove to be beneficial for the treatment of periodontitis. Moreover, the various experiments have also shown that statins have immunomodulatory effects. They can inhibit the tumor cell growth and enhance the intracellular calcium mobilization. It was also observed in rodents that inhibitors of HMG-CoA reductase induce a reduction in the osteoclasts' formation.[5] Various other studies have also demonstrated the free radical scavenging activity of statins. The direct scavenging reactive oxygen species prevents its interaction with lipids, proteins, and deoxyribonucleic acid. In this aspect, simvastatin and atorvastatin are more active against hydroxyl radical while that fluvastatin is more active against peroxyl radical.[6]Thereby, various pleotropic effects of statin have proved that it is a potential host modulating agent for the therapy of periodontal diseases.

APPLICATION OF STATINS IN PERIODONTAL DISEASES-

A. **Periodontal regeneration-** The periodontal disease is a major oral health problem. The inflammatory mediators and cytokines liberated by the deep periodontal pockets affect the remote tissues. [7] Moreover, the chronic periodontitis affects the patient's systemic condition. It further deteriorates the diabetic condition,[9]and also causes increase in obstetric complications.[8] Over the years, various treatment modalities have been tried with varying success to correct the periodontal attachment and alveolar bone loss resulting from this disease. The objective of periodontal therapy is to restore the tissues destroyed by the disease. However, in order to achieve greater outcome with the regenerative therapy requires the introduction of an agent which not only reduces the tissue destruction but also increase the regenerative capabilities of the periodontal tissues. It has been observed that statins have anti-inflammatory as well as the bone stimulating properties that may positively affect the chronic periodontitis. Simvastatin is not well absorbed, and only <5% of an oral dose reaches the systemic circulation. Thereby, in the bone marrow, concentrations of statins have not been well established yet, but the osteoblasts and osteoclasts may be exposed to a very low concentrations of statin with the existing oral regimens.

B. **Osteogenic properties in periodontal therapy -** Simvastatin has been reported to promote the osteoblastic activity and also inhibit the osteoclastic activity. The

Annals of R.S.C.B., ISSN: 1583-6258, Vol. 25, Issue 1, 2021, Pages. 6244 – 6249
Received 15 December 2020; Accepted 05 January 2021.

transient exposure of bone to the statins was enough in order to initiate a cascade of the bone formation, which is probably induced by the locally produced bone morphogenic protein-2 (BMP-2). BMP-induced osteoblast differentiation occurs through antagonizing tumor necrosis factor (TNF)-α-to-Ras/Rho/mitogen activated protein kinase and also augmenting the BMP-S mad signaling.[10] It has been demonstrated that Simvastatin has reverse the suppressive effects of TNF and also prevents the inhibition of BMP-2 mediated by Smad 1, 5, and 8 phosphorylation. It has been observed that an oral administration of Simvastatin, lowered activity of serum tartrate-resistant acid phosphatase 5b, indicating the decreased osteoclast activity.[11]Simvastatin enhances the alkaline phosphatase activity and mineralization and also increases the expression of bone sialoprotein, Type I collagen and osteocalcin, and it is shown to have anti-inflammatory effect by decreasing the production of IL-6 and IL-8.[12]

Topical Application/Delivery- It has been observed that the local delivery of chemotherapeutic agents into the pockets through a syringe or an irrigating device have an effect on subgingival flora. The local tissue concentration of a drug can be enhanced by incorporating an active agent into the controlled release delivery systems which must be placed directly into the periodontal pocket or in the defect area. The periodontal therapy requires a focused effect in the specific defects, thereby suggesting the importance of the local application of statin. The attempts have been made in order to deliver the statins to the peripheral tissue by subcutaneous injection or transdermal patch and to escape its accumulation in the liver.[13]When delivered or applied locally, the statins also seem to have increased the expression of the bone morphogenetic protein-2 and thereby modulate the bone formation,[14]which assists in the regeneration of bone as well as has the anti-inflammatory effect. It has also been reported that simvastatin stimulates the release of vascular endothelial growth factor (VEGF) in the dose-dependent manner and many authors have suggested that statins may also promote the osteoblast differentiation and bone nodule formation by stimulating the VEGF expression in bone tissue.[15, 16] When statin administered in the prodrug form, it is more lipophilic than the active beta-hydroxyacid form, because of this the simvastatin molecule can effectively cross the cellular membrane barriers by passive diffusion.[17] Moreover, it can also be implied that incorporating it into hydrophobic delivery vehicles can lead to local sustained release in order to achieve the bone formation in periodontal defects. Hence, as a therapeutic agent, simvastatin plays a significant role in the treatment of periodontal disease.[18, 19]

Topical Application of Statin- Human Model Studies: Tin 2003, the studies conducted by Low and Al-Qawasmi showed that the relationship between osteoprotegerin (OPG) and the receptor activator of nuclear factor-kappaB ligand (RANKL) will affect the resorption of root. By the given fact that simvastatin increases OPG to RANKL ratio in the periodontal tissues, it can be a factor in preventing root resorption.[20]In 2005, Yazawa*et al*. analyzed that the effect of simvastatin on the cell proliferation as well as the osteoblastic differentiation in

periodontal ligament cells. The result observed in this study suggested that a low concentration (10-8 M) of simvastatin demonstrated a positive effect on proliferation and also the osteoblastic differentiation of human periodontal ligament cells and these effects were caused by inhibiting the mevalonate pathway.[21]A study done in 2006 by Yoshinari*et al.* showed that the immobilization of simvastatin onto the titanium implants is advised to promote the osteogenesis in bone tissue surrounding the implants via its topical application.[22] In 2009,Okamoto *et al*. did a study on simvastatin, describing that it increases the dentin sialophosphoprotein gene expression and osteocalcin; both of these result in the differentiation of odontoblasts and thereby in the production of hard dental tissues.[23] In 2010, Pradeep and Thorat investigated the effectiveness of locally delivered 1.2 mg simvastatin in order to improve the clinical parameters and also to enhance the bone formation. This study showed a greater decrease in the gingival index as well as the probing depth and more clinical attachment level gain with the significant bone fill at sites treated with the scaling and root planning and locally delivered simvastatin in the patients with chronic periodontitis.[24]

DOSAGE OF STATIN -BONE GROWTH PROMOTION- Simvastatin possesses the topical and systemic anti-inflammatory properties, but this property alters at the high-dose local applications. The effective dosage range to treat the hypercholesterol in humans by oral administration is up to 1.0 mg/kg/day. The animal testing has indicated that the high-dose simvastatin i.e., 20 mg/kg/day increases the bone formation, while the low-dose simvastatin ie., 1 mg/kg/day decreases the bone formation and increases the bone resorption.[25] In rats, a dose of 10 mg/kg/day about equivalent to 70 mg/day for humans has also taken into account that metabolic process in rodents are 10 times faster than in humans.[26] A number of studies demonstrated that the long-term systemic administration of simvastatin for decreasing the plasma cholesterol levels in humans has beneficial effects on the skeleton. In 2000, Chan *et al*. carried out a case–control study of women aged 60 years or older and observed that the regular statin use among them was associated with more than 50% reduction in the risk of the pathologic fracture.[27] Similar findings were observed in the study of Wang *et al*. whichsupported an association between the statin use and reduction in the risk of hip fracture in the elderly patients. The doses should be chosen with caution considering the benefits and risks, and thereby further studies are required in order to confirm the optimal dosage for the therapeutic effects.[28]

CONCLUSION-The conclusion can be made within the limits of various studies that were conducted, that SMV shows the protective features against the impact of periodontitis on the attachment apparatus and also on the alveolar bone. Statin is able to achieve the goal of regeneration without any invasive procedures and thereby causing less discomfort to the patients. It has been observed that the patients on statin medication exhibit fewer clinical signs of the periodontal inflammatory injury than the subjects without the statin. It has been proved that the anti-inflammatory and antioxidant properties of this compound could facilitate the healing of osseous defects. However, long-term clinical studies in human subjects are required to determine the effectiveness in humans for bone regeneration and also to evaluate the potential benefits of statin in periodontal regenerative therapy.

Annals of R.S.C.B., ISSN: 1583-6258, Vol. 25, Issue 1, 2021, Pages. 6244 – 6249
Received 15 December 2020; Accepted 05 January 2021.

REFERENCES-

1. Landmesser U, Bahlmann F, Mueller M, Spiekermann S, Kirchhoff N, Schulz S, *et al.* Simvastatin versus ezetimibe: Pleiotropic and lipidlowering effects on endothelial function in humans. Circulation 2005;111:2356-63.
2. Giroux LM, Davignon J, Naruszewicz M. Simvastatin inhibits the oxidation of low-density lipoproteins by activated human monocytederived macrophages. BiochimBiophysActa 1993;1165:335-8.
3. Davignon J, Laaksonen R. Low-density lipoprotein-independent effects of statins. CurrOpinLipidol 1999;10:543-59.
4. Jeon SM, Bok SH, Jang MK, Lee MK, Nam KT, Park YB, *et al.* Antioxidative activity of naringin and lovastatin in high cholesterolfed rabbits. Life Sci 2001;69:2855-66.
5. Bellosta S, Ferri N, Bernini F, Paoletti R, Corsini A. Non-lipid-related effects of statins. Ann Med 2000;32:164-76.
6. Suzumura K, Yasuhara M, Tanaka K, Odawara A, Narita H, Suzuki T. An *in vitro* study of the hydroxyl radical scavenging property of fluvastatin, and HMG-CoA reductase inhibitor. Chem Pharm Bull (Tokyo) 1999;47:1010-2.
7. Nibali L, D'Aiuto F, Griffiths G, Patel K, Suvan J, Tonetti MS. Severe periodontitis is associated with systemic inflammation and a dysmetabolic status: A case-control study. J ClinPeriodontol 2007;34:931-7.
8. Paunio K, Impivaara O, Tiekso J, Mäki J. Missing teeth and ischaemic heart disease in men aged 45-64 years. Eur Heart J 1993;14Suppl K: 54-6.
9. Offenbacher S, Boggess KA, Murtha AP, Jared HL, Lieff S, McKaig RG, *et al.* Progressive periodontal disease and risk of very preterm delivery. ObstetGynecol 2006;107:29-36.
10. Yamashita M, Otsuka F, Mukai T, Otani H, Inagaki K, Miyoshi T, *et al.*Simvastatin antagonizes tumor necrosis factor-alpha inhibition of bone morphogenetic proteins-2-induced osteoblast differentiation by regulating Smadsignaling and Ras/Rho-mitogen-activated protein kinase pathway. J Endocrinol 2008;196:601-13.
11. Mundy G, Garrett R, Harris S, Chan J, Chen D, Rossini G, *et al.* Stimulation of bone formation *in vitro* and in rodents by statins. Science 1999;286:1946-9.
12. Sakoda K, Yamamoto M, Negishi Y, Liao JK, Node K, Izumi Y. Simvastatin decreases IL-6 and IL-8 production in epithelial cells. J Dent Res 2006;85:520-3.
13. Gutierrez GE, Lalka D, Garrett IR, Rossini G, Mundy GR. Transdermal application of lovastatin to rats causes profound increases in bone formation and plasma concentrations. OsteoporosInt 2006;17: 1033-42.
14. Cochran DL, Schenk R, Buser D, Wozney JM, Jones AA. Recombinant human bone morphogenetic protein-2 stimulation of bone formation around endosseous dental implants. J Periodontol 1999;70:139-50.
15. Takenaka M, Hirade K, Tanabe K, Akamatsu S, Dohi S, Matsuno H, *et al.* Simvastatin stimulates VEGF release via p44/p42 MAP kinase in vascular smooth muscle cells. BiochemBiophys Res Commun 2003;301:198-203.
16. Rath A, Mahenra J, Thomas L, Sandhu M, Namasi A, Ramakrishna T. A clinical,

radiological and IL-6 evaluation of subgingivally delivered simvastatin in the treatment of chronic periodontitis. Int J Drug Deliv 2012;4:70-81.
17. Goes P, Lima AP, Melo IM, Rego RO, Lima V. Effect of atorvastatin in radiographic density on alveolar bone loss in Wistar rats. Braz Dent J 2010;21:193-8.
18. Lee Y, Liu X, Nawshad A, Marx DB, Wang D, Reinhardt RA. Role of prostaglandin pathway and alendronate-based carriers to enhance statin-induced bone. Mol Pharm 2011;8:1035-42.
19. Sangwan A, Tewari S, Singh H, Sharma RK, Narula SC. Periodontal status and hyperlipidemia: Statin users vs. non-users. J Periodontol 2013;77:1061-6.
20. Al-Qawasmi RA, Hartsfield JK Jr, Everett ET, Flury L, Liu L, Foroud TM, *et al.* Genetic predisposition to external apical root resorption in orthodontic patients: Linkage of chromosome-18 marker. J Dent Res 2003;82:356-60.
21. Yazawa H, Zimmermann B, Asami Y, Bernimoulin JP. Simvastatin promotes cell metabolism, proliferation, and osteoblastic differentiation in human periodontal ligament cells. J Periodontol 2005;76:295-302.
22. Yoshinari M, Hayakawa T, Matsuzaka K, Inoue T, Oda Y, Shimono M, *et al.* Oxygen plasma surface modification enhances immobilization of simvastatin acid. Biomed Res 2006;27:29-36.
23. Okamoto Y, Sonoyama W, Ono M, Akiyama K, Fujisawa T, Oshima M, *et al.* Simvastatin induces the odontogenic differentiation of human dental pulp stem cells *in vitro* and *in vivo*. J Endod 2009;35:367-72.
24. Pradeep AR, Thorat MS. Clinical effect of subgingivally delivered simvastatin in the treatment of patients with chronic periodontitis: A randomized clinical trial. J Periodontol 2010;81:214-22.
25. Maritz FJ, Conradie MM, Hulley PA, Gopal R, Hough S. Effect of statins on bone mineral density and bone histomorphometry in rodents. ArteriosclerThrombVascBiol 2001;21:1636-41
26. Wang JW, Xu SW, Yang DS, Lv RK. Locally applied simvastatin promotes fracture healing in ovariectomized rat. OsteoporosInt 2007;18:1641-50.
27. Chan KA, Andrade SE, Boles M, Buist DS, Chase GA, Donahue JG, *et al.* Inhibitors of hydroxymethylglutaryl-coenzyme A reductase and risk of fracture among older women. Lancet 2000;355:2185-8.
28. Wang PS, Solomon DH, Mogun H, Avorn J. HMG-CoA reductase inhibitors and the risk of hip fractures in elderly patients. JAMA 2000;283:3211-6.