ISSN: 2581-5989
PubMed - National Library of Medicine - ID: 101738774

*International Journal of Dental Science and Innovative Research (IJDSIR)*
*IJDSIR : Dental Publication Service*
*Available Online at: www.ijdsir.com*
*Volume – 3, Issue – 4, August - 2020, Page No. : 463 - 480*

# The Effect of Locally Delivered Statins in the Treatment of Infrabony Defect in Chronic Periodontitis: A Literature Review

[1]Dr Ishita Kamal Jain, II Year MDS in Department of Periodontics, Mahatma Gandhi Mission's Dental College & Hospital, Navi Mumbai, Maharashtra, India.

[2] Dr. Sarika S Shetty, Reader in Department of Periodontics, Mahatma Gandhi Mission's Dental College & Hospital, Navi Mumbai, Maharashtra , India.

**Corresponding Author:** Dr Ishita Kamal Jain, II Year MDS in Department of Periodontics, Mahatma Gandhi Mission's Dental College & Hospital, Navi Mumbai, Maharashtra, India.

**Citation of this Article:** Dr Ishita Kamal Jain, Dr. Sarika S Shetty, "The Effect of Locally Delivered Statins in the Treatment of Infrabony Defect in Chronic Periodontitis: A Literature Review", IJDSIR- August - 2020, Vol. – 3, Issue -4, P. No. 463– 480.



**Type of Publication:** Review Article

**Conflicts of Interest:** Nil

## Abstract

**Background:** Periodontitis is an inflammatory disease of the supporting tissues of the teeth, caused by a group of specific microorganisms. Local drug delivery therapy targets on specific pathogenic microorganisms, many drugs have been studied using local drug delivery to improve the periodontal health and to achieve periodontal regeneration. Statins are lipid lowering drug and they also modulate the bone formation, thus providing a new direction in the field of periodontology. The aim of this literature review is to assess the effect of locally delivered statins in the treatment of infrabony defect in chronic periodontitis.

**Methods:** Literature search was performed through electronic bibliographic databases- the PubMed and MEDLINE and EBSCO DOSS database and Google scholar search engines. Manual search was also carried out to identify relevant scientific papers published from 2000 to 2019.

**Result:** This review of literature assessed the effect of locally delivered statins in the treatment of infrabony defect in chronic periodontitis and showed improvement in clinical and radiographic parameters.

**Conclusion:** The adjunctive use of locally delivered statins with non-surgical periodontal treatment in treating intrabony defects has shown promising results in bone fill, reduction of inflammation and bleeding, PD reduction as well as CAL gain.

**Keywords:** Chronic periodontitis, periodontal regeneration, infrabony defects, statins, local drug delivery.

## Introduction

Periodontitis is a common chronic infectious disease affecting the adult population and is characterized by

inflammation of the periodontal tissues, leading to tissue destruction, bone resorption, attachment loss, and, in some cases, tooth loss.[1] Studies have shown an association between periodontitis and systemic disorders with an inflammatory component such as cardiovascular disease (CVD).[2,3] In cardiovascular diseases the total cholesterol, low-density lipoprotein- cholesterol (LDL-C) and total triglycerides are elevated, whereas levels of high- density lipoprotein- cholesterol (HDL-C) are decreased.[4] A hyperlipidemia state precipitates a highly proinflammatory state i.e. characterized by an upregulation of interleukin-1b [IL-1b]) and proinflammatory cytokines (tumor necrosis factor-alpha [TNF-a] from monocytes/ polymorpho nuclear leukocytes (PMNs) as well as reduced growth factor production by macrophages.[5-8]

To correct the loss of periodontal attachment and alveolar bone resulting from this disease, various different treatment modalities have been tried. Regeneration of the lost periodontal tissue is the most desirable and ideal outcome that one would want to achieve. The need to achieve greater regeneration warrants the use of an agent, which not only stimulates new bone formation but also inhibits resorption of the alveolar bone. Topical delivery of biological molecules like fibroblast growth factor (FGF)[9] and bone morphogenetic protein-2(BMP-2)[10] have shown to enhance the growth of the bone. However, there are some drawbacks like degradation at the site of application and activation of a host immune response.[11]

Different types of pharmacologic compounds, have shown to affect bone growth and are used in periodontal diseases offering a wide range of benefits like sub-antimicrobial doses of doxycycline (mediated by inhibition of MMP synthesis).[12] Bisphosphonates are a commonly used group of drugs which inhibit bone resorption by blocking the mevalonate pathway. Some of the products of this pathway are involved in osteoclast maturation and activation and thus its blockade leads to inhibition of bone resorption.[13] However, bisphosphonates do not stimulate new bone formation.[14]

The most commonly prescribed cholesterol-lowering drugs in patients with hypercholesterolemia are Statins (e.g., atorvastatin [ATV], simvastatin [SMV], and rosuvastatin [RSV]). Statins inhibit the 3-hydroxy- 3-methylglutaryl coenzyme A reductase, which is the rate-limiting enzyme in the mevalonate pathway. They inhibit cholesterol synthesis and reduce the risk for cardiovascular diseases.[15-18]

Statins have pleotropic effects like anti-inflammatory, antiviral, antimicrobial, fungicidal, Anti-thrombotic, Plaque stability, Vascular cytoprotection, Anti-oxidant, increases Endothelial function and pro-osteogenic properties and to enhance the function of mesenchymal stromal cells and/or endothelial progenitor cells;[19-23] thus, statins play a role in periodontology, either in preventing disease or in periodontal therapy.

A retrospective analysis over a 7-year period by Cunha-Cruz J, Saver B et al 2006 found an association of systemic administration of simvastatin with a reduced risk of tooth loss in patients diagnosed with chronic periodontitis. The anabolic effects on bone are mainly due to up-regulation of BMP-2 by simvastatin and other statins. Local application of simvastatin has been shown to stimulate bone formation in rodents both in vitro and in vivo and in human periodontal ligament cells in vitro.[24]

Statins could play a significant role as therapeutic agents in the treatment of periodontal diseases because of their biologically significant antioxidant and anti-inflammatory properties of simvastatin are other pleiotropic effects.

This current literature review was performed with the aim to assess the effect of locally delivered statins in the treatment of infrabony defect in chronic periodontitis.

**History of statins**

In the cholesterol biosynthetic pathway, HMG-CoA reductase is the rate-limiting enzyme. Microbiologist Endo et al in 1970s, during a search for antimicrobial agents discovered natural products with a powerful inhibitory effect on HMGCoA reductase, including compactin in a fermentation broth of Penicillium citrinum.[27,28] In 1978, Albert's, Chen, and others at Merck Research Laboratories found a potent inhibitor of HMG-CoA reductase in a fermentation broth of Aspergillusterreus.[29] They named their discovery mevinolin; later, the official (USAN) name was established as lovastatin.

**Classification of statins**

Molecular structure of statins contains a hexahydronaphthalene ring with two major side chains, viz. dimethylbutyrate ester and a second one contains a hydroxyacid.

According to the structure the statins are classified into two groups:

Type I- Lovastatin, pravastatin, and simvastatin

Type II- Fluvastatin, cerivastatin, atorvastatin, and rosuvastatin

The replacement of the butyryl group of type 1 statins by the fluorophenyl group of type 2 statins is the main difference between type I and type II statins.

**Carriers Used**

To promote bone formation by successful use of statin depends on the local concentration, which requires an appropriate delivery system.[30] Advantages of an appropriate carrier are localization and retention of the molecule to the location of application, thus reducing the loading dose. Many studies have demonstrated the osteopromotive effect achieved by the local application of the drug with different carriers in various animal models.

• Gelatin sponge - bioresorbable and biocompatible, adapts easily to the shape of defects because of its sponge-like form.

• Polylactic acid/polyglycolic acid copolymer carriers.

• Methylcellulose is generally regarded as a non-toxic, nonallergic, and non-irritating material and is used as a sustained release vehicle for therapeutic drugs.[31]

**Methods**

The research question for this literature was **"**Is there an effect of locally delivered statins in the treatment of infrabony defects in chronic periodontitis?**"** The populations included in the review were the subjects diagnosed with infrabony defects and chronic periodontitis. Interventions studied in this review are locally delivered subgingival statin drugs as an adjunct to mechanical scaling and root planning/open flap debridement. Control selected was statin group compared to no treatment group or scaling and root planing alone/open flap debridement alone or placebo treatment group. The outcomes evaluated were changes in probing depth (PD) reduction, clinical attachment level (CAL), and defect depth.

The inclusion criteria for this literature review were articles written in English language, ≥ 3 months follow up, data on bleeding on probing, defect depth, probing pocket depth reduction, and clinical attachment level, human randomized controlled clinical trials, non-randomized clinical trials, retrospective studies and prospective studies. Exclusion criteria included cross-sectional studies, case reports and case series, animal studies**,** insufficient information on drug administration, no definite inclusion and exclusion criteria in the article.

The search for this review was performed from electronic bibliographic databases- the PubMed and MEDLINE and EBSCO DOSS database. The search strategy included the use of Controlled terms (MeSH) and keywords and their

combinations. The terms used for search strategy were “periodontitis”, “periodontal disease”, “chronic periodontitis”, "periodontal regeneration", “infrabony defects”, "bone defects", "statins", “atorvastatin”, “rosuvastatin”, “simvastatin”,” fluvastatin”, "local drug delivery". The literature search was also performed through hand search of peer-reviewed journals for relevant articles. The literature was searched from 2000 to 2019, from which 16 studies published in the last 19 years were selected.

**Result**

As per the current search strategy for literature review the following literature has compared the intervention scaling and rootplaning (SRP)/open flap debridement (OFD) alone or open flap debridement with placebo or open flap debridement with bone grafts and locally delivered subgingival statin drug and open flap debridement with locally delivered subgingival statin drugs as an adjunct to open flap debridement (OFD/SRP or OFD + placebo or OFD + bone graft + Statin or OFD + Statin), open flap debridement with PRF and locally delivered subgingival statin drug and open flap debridement with locally delivered subgingival statin drugs as an adjunct to open flap debridement (OFD/SRP or OFD + placebo or OFD + PRF + Statin or OFD + Statin). The locally delivered subgingival statin drugs which came under the purview of this literature are locally delivered subgingival statin drugs in the form of gel, locally delivered subgingival statin drugs used in the treatment of infrabony defects. The parameters studied in these studies included in this literature review are - modified sulcus bleeding index (mSBI), reduction in probing depth (PD) and clinical attachment level (CAL) and radiographic defect fill or bone fill. The individual study outcomes are highlighted with the above mentioned parameters in the reference annexure (Table no.1- Individual study outcomes of included randomized clinical control trials and Table no. 2- Individual study outcomes of included retrospective and prospective studies).

**Discussion**

The aim of the literature review was to compare the healing outcomes using locally delivered statin drugs along with intervention scaling and rootplaning (SRP)/open flap debridement (OFD) alone or open flap debridement with placebo or open flap debridement with bone grafts and locally delivered subgingival statin drug and open flap debridement with locally delivered subgingival statin drugs as an adjunct to open flap debridement (OFD/SRP or OFD + placebo or OFD + bone graft + Statin or OFD + Statin), open flap debridement with PRF and locally delivered subgingival statin drug and open flap debridement with locally delivered subgingival statin drugs as an adjunct to open flap debridement (OFD/SRP or OFD + placebo or OFD + PRF + Statin or OFD + Statin), outcomes measured were reduction in probing pocket depth, gain in clinical attachment level, defect fill , bone fill. Outcomes were assessed at 3, 6 months and 9 months. The search strategy, inclusion and exclusion criteria included patients suffering from chronic periodontitis. However all these studies showed that open flap debridement along with locally delivered statin drugs, statin drugs studied were in the form of locally delivered in situ gel has shown additional beneficial effects in reduction of probing pocket depth, gain in clinical attachment level and defect fill.

As mentioned in the above studies the healing outcomes were better in OFD+statin group which could be attributed to its anti-bone resorbing properties by upregulating the bone morphogenic proteins and blocking the intermediate metabolites of the mevalonate pathway, isoprenoids leads to disruption of vesicular fusion and ruffled border formation of osteoclasts, which are essential for their bone

resorbing activity. As a result, osteoclast inactivation occurs and bone resorption is inhibited.[15] Local stimulation of a major bone growth regulatory factor, BMP-2, can lead to new bone formation. In addition to their anti-resorptive actions, they have been found to exert anabolic effects on bone.

Statins have number of pleiotropic effects as well. They have shown to reduce the plasma levels of inflammatory marker like C-reactive protein, [21] this could be due to inhibition of IL-6 in the vascular tissues. Thus, statins are believed to have biologically significant antioxidant and anti-inflammatory effects, which could prove beneficial in the treatment of periodontitis.[48,49]

Periodontal therapy necessitates a focused effect in specific defects, suggesting the importance of local application of this drug. It has been observed that application of this agent to a culture of human periodontal ligament cells enhances their proliferation and metabolism.[50] Therefore; Statins could play a significant role as a therapeutic agent in the treatment of periodontal disease.

Several limitations were noted in the current literature review; there might be a selection bias as maximum included studies were from the same study group (Pradeep et al., Rao et al. 2013), sample sizes noted in the included studies were small, ranging 15-35 participants per test/control group. Accuracy of measurements was not calibrated in most of the studies, which might contribute to geometric errors in IBD fill on the conventional radiographs. The search criteria involved only English-written articles.

Table 1: Individual study outcomes of included randomized clinical control trials

| Sn. | Author and year | Study design and sample size | Study outcomes | Type of Periodontal defect | Treatment comparison | Material used | Follow up | Results | Conclusion |
|---|---|---|---|---|---|---|---|---|---|
| 1 | A R. Pradeep and M S. Thorat 2010 [32] | RCT 64 | mSBI, PD and CAL, intrabony defect fill. | Intrabony defect (IBD) | Test group - SRP plus SMV 1.2% Control group-SRP plus placebo | 1.2% simvastatin | 1,2,4,6 months | Both therapies resulted in significant improvements. The decrease in mSBI, reduction in PD, and gain in CAL was more in test | There was a greater decrease in gingival index and PD and more CAL gain with significant IBD fill at sites treated with SRP plus locally delivered SMV in |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | group. | patients with chronic periodontitis. |
| 2 | A.R. Pradeep, N. Priyanka Nitish Kalra,Savitha B. Naik, Sonender P. Singh, and Santosh Martande 2012 [33] | RCT 72 | mSBI, PD and RVAL and RHAL, bone defect fill | class II furcation defects | Test group - SRP plus SMV 1.2% Control group-SRP plus placebo | 1.2% simvastatin | 3 and 6 months | The decrease in mSBI score and mean decrease in PD at 6 months was greater in group 2.A significantly greater gain in mean RVAL and RHAL and greater mean percentage of bone fill was found in group 2 than in group 1. | Locally delivered SMV provides a comfortable and flexible method to improve clinical parameters and also to enhance bone formation. |
| 3 | Rao NS, Pradeep AR, Bajaj P, Kumari M, Naik SB 2013 [34] | RCT 40 | mSBI, PD and CAL | Intrabony defect (IBD) | Test group - SRP plus SMV 1.2% Control group-SRP plus placebo | 1.2% simvastatin | 3,6 and 9 months | Statistically significant results were obtained in 1.2% simvastatin group for clinical and radiographic parameter. | There was a greater decrease in mSBI and PD and more CAL gain with significant IBD fill at sites treated with SRP plus locally |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | delivered SMV in patients with chronic periodontitis. |
| 4 | A.R. Pradeep, Nishanth S. Rao, Pavan Bajaj, and Minal Kumari 2013 [35] | RCT 38 | mSBI, PD and CAL | Intrabony defect (IBD) | Test group - SRP plus SMV 1.2% Control group-SRP plus placebo | 1.2% simvastatin | 3,6 and 9 months | Statistically significant results were obtained in 1.2% simvastatin group for clinical and radiographic parameter. | There was a greater decrease in mSBI and PD and more CAL gain with significant IBD fill at sites treated with SRP plus locally delivered SMV in patients with type 2 diabetes and CP. |
| 5 | A.R. Pradeep, Minal Kumari, Nishanth S. Rao, Santosh S. Martande, and Savitha B. Naik 2013 [36] | RCT 67 | mSBI, PD and CAL,IBD fill | Intrabony defect (IBD) | test group-SRP plus 1.2% ATV control group-SRP plus placebo gel | 1.2 % Atorvastatin | 3,6 and 9 months | Mean PD reduction and mean CAL gain were greater in the ATV group at 3, 6 and 9 months. A significantly greater mean percentage of | ATV as an adjunct to SRP can provide a new direction in the management of IBDs. |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | radiographic bone fill was found in the ATV group. | |
| 6 | A R Pradeep , Shruti Karvekar ,Kanika Nagpal, Kaushik Patnaik, C. N.Guruprasad, K M Kumaraswamy 2015 [37] | RCT 70 | mSBI, PD and CAL | Intrabony defect (IBD) | Test Group - SRP plus RSV, 1.2 mg Control Group -SRP plus placebo. | 1.2mg rosuvastatin | 1, 3, 4, and 6 months | There was significant improvement in both the study groups. There was greater decrease in mean IBD in test group compared to control group | 1.2% Rosuvastatin in situ gel, when delivered locally into intrabony pockets/defect sites showed a greater reduction in probing depth and gingival index along with increased gain in clinical attachment level. |
| 7 | Shruti Garg, A R Pradeep 2016 [38] | RCT 90 | mSBI, full-mouth plaque index (PI) score, PD, RVCAL, and RHCAL | class II furcation defects | SRP with placebo gel (group 1), SRP with 1.2% RSV gel (group 2) and SRP with 1.2% ATV gel (group3) | 1.2% RSV Gel and 1.2% ATV gel | 6 and 9 months | Significant results were seen in the RSV group than ATV group at 6 and 9 months. A significantly greater mean percentage of defect depth reduction | RSV group showed significant improvement in all clinical parameters along with significantly greater defect depth reduction as compared to ATV group in treatment of mandibular |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | was found in the RSV group than ATV group at 6 and 9 months, respectively. | class II furcation defects as an adjunct to SRP. |
| 8 | Minal Kumari, Santosh S. Martande, A R Pradeep, Savitha B. Naik 2016 [39] | RCT 75 | mSBI, PD and CAL, bone defect fill | intrabony defects | Test group- SRP plus 1.2% ATV control group- SRP plus Placebo | 1.2% ATV | 6,9 months | Mean PD reduction and mean RAL gain was found to greater in ATV group than placebo group, at 3, 6 and 9 months. Furthermore, ATV group sites presented with a significantly greater percentage | Locally delivered ATV in was found to be effective in treatment of intrabony defects in CP in subjects with type 2 diabetes |
| 9 | Minal Kumari, Santosh S. Martande & Avani R. Pradeep 2016 [40] | RCT 71 | mSBI, PD and CAL, radiographic defect depth | Infrabony defects | Test group- SRP + 1.2% ATV gel control group- SRP + placebo gel. | 1.2% ATV gel | 3, 6, and 9 months | The mean probing depth reduction and mean clinical attachment level gain were found to be greater in | The ATV local drug delivery as an adjunct to SRP can be used in the treatment of IBD in CP among smokers. |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | the ATV group than the placebo group at 3, 6, and 9 months. A significantly greater mean percentage of radiographic defect depth reduction was found in the ATV group. | |
| 10 | A R Pradeep, Vibhuti Garg, Dharmendra Kanoriya, Sandeep Singhal 2016 [41] | RCT 90 | Plaque index (PI), mSBI, PD and CAL and IBD depth | infrabony defects | SRP followed by LDD of 1.2% RSV, 1.2% ATV or placebo gel | 1.2% RSV, 1.2% ATV | 6 ,9 months | All the three groups showed significant reduction in PI and mSBI at all intervals. The mean mSBI and PD reductions, CAL gain and intrabony defect depth reduction with statin drugs were | LDD of 1.2% RSV results in significantly greater clinico-radiographic improvement compared to 1.2% ATV or placebo gels as adjuncts to mechanical periodontal therapy. |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | significantly greater. Improvements in these parameters were significantly greater with RSV LDD than ATV or placebo gels at 6 and 9 months. | |
| 11 | Swati Agarwal, Krishna Kumar Chaubey, Abhinav Chaubey, Vikas Agarwal, Ellora Madan, Manvi Chandra Agarwal 2016 [42] | RCT 60 | plaque index, gingival index, PD ,CAL , radiographically vertical and angle of defect | Intrabony defects | test group-SRP + SMV Control group-SRP + placebo | 1.2% simvastatin | 1,3,6 months | The treatment improved the periodontal condition in both the groups but significant reductions in PPD, along with gain in CAL were observed in test group. | Local drug delivery of SMV enhanced the beneficial effect of SRP, in pocket reduction, gain in CAL and bone fill. |
| 12 | A R Pradeep, Vibhuti Garg, Dharmendra Kanoriya | RCT 90 | Plaque index (PI), mSBI, PD , CAL and IBD depth | Intrabony defects | 1) OFD alone, 2) OFD + PRF and 3) OFD + PRF + 1.2% RSV gel | 1.2% RSV gel and PRF | 9 months | Significant PI and mSBI reductions were observed in all the 3 | 1.2% RSV with PRF results in significantly greater periodontal benefits |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | , Sandeep Singhal 2016 [43] | | | | placement. | | | groups. PRF placement significantly enhanced the improvements in periodontal parameters. Addition of 1.2% RSV gel to PRF resulted in significantly greater CA level gain and PD and IBD depth reductions over 9 months | compared to OFD alone or with PRF. |
| 13 | Santosh S. Martande, Minal Kumari, A. R. Pradeep, Sonender Pal Singh, Deepak Kumar Suke 2017 [44] | RCT 96 | full-mouth plaque index (PI), mSBI, PD and relative attachment level (RAL), radiographic defect depth | Intra bony defect | SRP plus 1.2% ATV, SRP plus 1.2% SMV and SRP plus placebo. | 1.2% ATV, 1.2% SMV | 6 and 9 months | Both ATV and SMV showed significant PD reduction and RAL gain than placebo. ATV group showed greater mean PD reduction and mean RAL gain | ATV resulted in greater improvements in clinical parameters with higher percentage of radiographic defect depth reduction as compared to SMV in the treatment of intrabony defects in CP subjects |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | as compared to SMV group at 3, 6 and 9 months. Furthermore, ATV group sites exhibited a significantly greater percentage of radiographic defect depth reduction. | |

mSBI- modified sulcus bleeding index, PD-pocket depth, CAL-clinical attachment level, IBD-infrabony defect, SRP-scaling and planning, SMV-simvastatin, RCT-randomized clinical trial, RVAL- relative vertical attachment level, RHAL-relative horizontal attachment level, CP-chronic periodontitis, RSV-rosuvastatin, ATV-atorvastatin, PI-plaque index, RVCAL-relative vertical clinical attachment level, RHCAL-relative horizontal clinical attachment level, LDD-local drug delivery, DDR-defect depth reduction, PRF- Platelet derived factor, OFD- open flap debridement.

Table 2: Individual study outcomes of included retrospective and prospective studies

| Sn. | Author and year | Study design and sample size | Study outcomes | Type of Periodontal defect | Treatment comparison | Material used | Follow up | Results | Conclusion |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Otso Lindy, Kimmo Suomalainen, Marja Mäkelä ,Seppo Lindy | retrospective 97 | visible plaque index, bleeding index, PD, Periodontal Inflamm | - | statin user and non-statin user | SMV and ATV | - | Periodontitis patients taking statins had a 37% lower number of pathological periodontal pockets than | Patients on statin medication exhibit fewer signs of periodontal inflammatory injury than subjects |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 2008 [45] | | atory Burden Index or PIBI | | | | | those without statin medication. | without the statin regimen. |
| 2 | Kinra P, Gupta H, Khan S., Moham mad Sami Ahmad P 2010 [46] | prospect ive 15 | PD , CAL and Infrabon y defect fill | 2-walled or 3-walled infrabon y defects | test group - DFDBA + simvastatin control group- DFDBA alone | SMV | 12 weeks and 24 weeks | DFDBA alone as well as the combination of DFDBA and simvastatin resulted in a highly significant mean reduction in clinical parameters, and linear defect fill. The values of mean changes in parameters were significantly greater with the drug-graft combination in comparison with the graft alone. | Combination of DFDBA with a solution of simvastatin leads to significantly greater reduction in clinical parameters and linear defect fill than when graft is used alone. |
| 3 | Sai M. Surve, Anirudh B. Acharya | prospect ive 45 | plaque index (PI), sulcus bleeding | infrabon y defects | group 1 - SRP only (control), group 2 - SRP with | SMV and ATV | 1, 3, 6 months | All three groups showed significant reductions in | Subgingivally delivered atorvastatin and simvastatin as |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | and Srinath L. Thakur 2015 [47] | | index (SBI), and PD, relative attachment level and defect depth and IL-1 levels | | subgingival delivery of 1.2% simvastatin, group 3, receiving SRP with subgingival delivery of 1.2% atorvastatin | | | clinical parameters and IL-1α levels in the GCF ($p < 0.05$). | an adjunct to SRP is efficacious but did not demonstrate any added benefit as compared with SRP alone. |

PD-pocket depth, CAL-clinical attachment level, IBD-infrabony defect, SRP-scaling and planning, SMV-simvastatin, ATV-atorvastatin, DFDBA-demineralized freeze dried bone allograft, GCF-gingival crevicular fluid, IL- interleukin.

**Conclusion**

Effect of statin on bone metabolism, its anti-inflammatory and antioxidant properties facilitate healing of periodontal intrabony defects. The adjunctive use of locally delivered statins with non-surgical periodontal treatment in treating intrabony defects has shown promising results in bone fill, reduction of inflammation and bleeding, PD reduction as well as CAL gain.

**Reference**


1. 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 Clin Periodontol 2007;34:931-937.
2. Kim J, Amar S. Periodontal disease and systemic conditions: A bidirectional relationship. Odontology 2006;94:10-21.
3. Dave´ S, Van Dyke T. The link between periodontal disease and cardiovascular disease is probably inflammation. Oral Dis 2008;14:95-101.
4. Castelli WP. Lipids, risk factors and ischaemic heart disease. Atherosclerosis 1996;124(Suppl.):S1-S9.
5. Stapleton PA, Goodwill AG, James ME, Brock RW, Frisbee JC. Hypercholesterolemia and microvascular dysfunction: Interventional strategies. J Inflamm (Lond) 2010;7:54.
6. Niemann-Jo¨nsson A, Dimayuga P, Jovinge S, et al. Accumulation of LDL in rat arteries is associated with activation of tumor necrosis factor-alpha expression. Arterioscler Thromb Vasc Biol 2000;20:2205-2211.
7. Thomas CE, Jackson RL, Ohlweiler DF, Ku G. Multiple lipid oxidation products in low density lipoproteins induce interleukin-1 beta release from human blood mononuclear cells. J Lipid Res 1994;35:417-427.
8. Chu X, Newman J, Park B, Nares S, Ordonez G, Iacopino AM. In vitro alteration of macrophage phenotype and function by serum lipids. Cell Tissue Res 1999;296:331-337.
9. Sangwan A, Tewari S, Singh H, Sharma RK, Narula SC. Periodontal status and hyperlipidemia: Statin users versus non-users. Journal of periodontology. 2013 Jan 1;84(1):3-12.
10. Kataria P, Kaur J, Parvez E, Maurya RP. Statins: The paradigm shift in periodontal regeneration. SRM

Journal of Research in Dental Sciences. 2014 Jan 1;5(1):26.

11. Kimoto T, Hosokawa R, Kubo T, Maeda M, Sano A, Akagawa Y. Continuous administration of basic fibroblast growth factor (FGF-2) accelerates bone induction on rat calvaria — an application of a new drug delivery system. J Dent Res 1998;77:1965-9.
12. 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.
13. Garrett IR, Gutierrez G, Mundy GR. Statins and bone formation. Curr Pharm Des 2001;7:715-36
14. Ryan ME, Golub LM. Modulation of matrix metalloproteinase activities in periodontitis as a treatment strategy. Periodontol 2000 2000;24:226-38.
15. Fisher JE, Rogers MJ, Halasy JM, Luckman SP, Hughes DE, Masarachia PJ, *et al*. Alendronate mechanism of action: Geranylgeraniol, an intermediate in the mevalonate pathway, prevents inhibition of osteoclast formation, bone resorption, and kinase activation *in vitro*. Proc Natl Acad Sci U S A 1999;96:133-8.
16. Kinra P, Khan S. Simvastatin: Its potential new role in periodontal regeneration. Biol Med 2011;3:215-21
17. Delahoy PJ, Magliano DJ, Webb K, Grobler M, Liew D. The relationship between reduction in low-density lipoprotein cholesterol by statins and reduction in risk of cardiovascular outcomes: an updated meta-analysis. Clin Ther. 2009;31:236-244.
18. Edwards JE, Moore RA. Statins in hypercholesterolaemia: a dosespecific meta-analysis of lipid changes in randomised, double blind trials. BMC Fam Pract. 2003;4:18.
19. Endo A. A historical perspective on the discovery of statins. Proc Jpn Acad Ser B Phys Biol Sci. 2010;86:484-493.
20. Weng TC, Yang YH, Lin SJ, Tai SH. A systematic review and metaanalysis on the therapeutic equivalence of statins. J Clin Pharm Ther. 2010;35:139-151.
21. Davignon J, Laaksonen R. Low-density lipoprotein-independent effects of statins. Curr Opin Lipidol. 1999;10:543-559.
22. Mundy G, Garrett R, Harris S, et al. Stimulation of bone formation in vitro and in rodents by statins. Science. 1999;286:1946-1949.
23. Park A, Barrera-Ramirez J, Ranasinghe I, et al. Use of statins to augment progenitor cell function in preclinical and clinical studies of regenerative therapy: a systematic review. Stem Cell Rev. 2016;12:327-339.
24. Shah SR, Werlang CA, Kasper FK, Mikos AG. Novel applications of statins for bone regeneration. Natl Sci Rev. 2015;2:85-99.
25. Ting M, Whitaker EJ, Albandar JM. Systematic review of the in vitro effects of statins on oral and perioral microorganisms. Eur J Oral Sci. 2016;124:4-10
26. Cunha-Cruz J, Saver B, Maupome G, Hujoel PP. Statin use and tooth loss in chronic periodontitis patients. J Periodontol 2006;77:1061-6.
27. Endo A, Kuroda M, Tsujita Y. ML-236A, ML-236B, and ML-236C, new inhibitors of cholesterogenesis produced by Penicillium citrinium.J Antibiot (Tokyo) 1976;29:1346-8.
28. Endo A, Tsujita Y, Kuroda M, Tanzawa K. Inhibition of cholesterol synthesis *in vitro* and *in vivo* by ML-236A and ML-236B, competitive inhibitors of 3-

hydroxy-3- methylglutaryl-coenzyme A reductase. Eur J Biochem 1977;77:31-6

29. Alberts AW, Chen J, Kuron G, Hunt V, Huff J, Hoffman C, *et al*. Mevinolin: A highly potent competitive inhibitor of hydroxymethylglutaryl-coenzyme A reductase and a cholesterollowering agent. Proc Natl Acad Sci U S A 1980;77:3957-61.
30. Kishida Y, Naito A, Iwado S, Terahara A, Tsujita Y. Research and development of pravastatin. Yakugaku Zasshi 1991;111:469-87.
31. Elavarasu S, Suthanthiran TK, Naveen D. Statins: A new era in local drug delivery. Journal of pharmacy & bioallied sciences. 2012 Aug;4(Suppl 2):S248.
32. Pradeep AR, Thorat MS. Clinical effect of subgingivally delivered simvastatin in the treatment of patients with chronic periodontitis: a randomized clinical trial. Journal of periodontology. 2010 Feb 1;81(2):214-22.
33. Pradeep AR, Priyanka N, Kalra N, Naik SB, Singh SP, Martande S. Clinical efficacy of subgingivally delivered 1.2-mg simvastatin in the treatment of individuals with Class II furcation defects: a randomized controlled clinical trial. Journal of periodontology. 2012 Dec 1;83(12):1472-9.
34. Pradeep AR, Kumari M, Rao NS, Martande SS, Naik SB. Clinical efficacy of subgingivally delivered 1.2% atorvastatin in chronic periodontitis: A randomized controlled clinical trial. Journal of periodontology. 2013 Jul 1;84(7):871-9.
35. Pradeep AR, Rao NS, Bajaj P, Kumari M. Efficacy of subgingivally delivered simvastatin in the treatment of patients with type 2 diabetes and chronic periodontitis: A randomized double-masked controlled clinical trial. Journal of periodontology. 2013 Jan 1;84(1):24-31.
36. Rao NS, Pradeep AR, Bajaj P, Kumari M, Naik SB. Simvastatin local drug delivery in smokers with chronic periodontitis: a randomized controlled clinical trial. Australian dental journal. 2013 Jun;58(2):156-62.
37. Pradeep AR, Karvekar S, Nagpal K, Patnaik K, Guruprasad CN, Kumaraswamy KM. Efficacy of locally delivered 1.2% rosuvastatin gel to non-surgical treatment of patients with chronic periodontitis: a randomized, placebo-controlled clinical trial. Journal of periodontology. 2015 Jun 1;86(6):738-45.
38. Pradeep AR, Garg V, Kanoriya D, Singhal S. 1.2% rosuvastatin versus 1.2% atorvastatin gel local drug delivery and redelivery in treatment of intrabony defects in chronic periodontitis: a randomized placebo-controlled clinical trial. Journal of periodontology. 2016 Jul 1;87(7):756-62.
39. Agarwal S, Chaubey KK, Chaubey A, Agarwal V, Madan E, Agarwal MC. Clinical efficacy of subgingivally delivered simvastatin gel in chronic periodontitis patients. Journal of Indian Society of Periodontology. 2016 Jul;20(4):409
40. Kumari M, Martande SS, Pradeep AR, Naik SB. Efficacy of subgingivally delivered 1.2% atorvastatin in the treatment of chronic periodontitis in patients with type 2 diabetes mellitus: a randomized controlled clinical trial. Journal of periodontology. 2016 Nov;87(11):1278-85
41. Kumari M, Martande SS, Pradeep AR. Subgingivally delivered 1.2% atorvastatin in the treatment of chronic periodontitis among smokers: a randomized, controlled clinical trial. Journal of investigative and clinical dentistry. 2017 May;8(2):e12213.
42. Pradeep AR, Garg V, Kanoriya D, Singhal S. 1.2% rosuvastatin versus 1.2% atorvastatin gel local drug delivery and redelivery in treatment of intrabony defects in chronic periodontitis: a randomized

placebo-controlled clinical trial. Journal of periodontology. 2016 Jul 1;87(7):756-62.

43. Pradeep AR, Garg V, Kanoriya D, Singhal S. Platelet-Rich Fibrin With 1.2% Rosuvastatin for Treatment of Intrabony Defects in Chronic Periodontitis: A Randomized Controlled Clinical Trial. Journal of periodontology. 2016 Dec;87(12):1468-73.
44. Martande SS, Kumari M, Pradeep AR, Singh SP, Suke DK. Comparative evaluation of efficacy of subgingivally delivered 1.2% Atorvastatin and 1.2% Simvastatin in the treatment of intrabony defects in chronic periodontitis: a randomized controlled trial. Journal of dental research, dental clinics, dental prospects. 2017;11(1):18.
45. Lindy O, Suomalainen K, Mäkelä M, Lindy S. Statin use is associated with fewer periodontal lesions: A retrospective study. BMC oral health. 2008 Dec;8(1):16.
46. Kinra P, Gupta H, Khan S, Ahmad MS. Evaluation of the Relative Efficacy of an Allograft used alone and that in Combination with Simvastatin in the Treatment of Human Periodontal Infrabony Defects–A Clinical and Radiological Study. Journal of Taibah University Medical Sciences. 2010 Jan 1;5(2):75-88
47. Surve SM, Acharya AB, Thakur SL. Efficacy of subgingivally delivered atorvastatin and simvastatin as an adjunct to scaling and root planing. Drug metabolism and personalized therapy. 2015 Dec 1;30(4):263-9.
48. Muniz FW, Taminski K, Cavagni J, Celeste RK, Weidlich P, Rösing CK. The effect of statins on periodontal treatment—a systematic review with meta-analyses and meta-regression. Clinical oral investigations. 2018 Mar 1;22(2):671-87.
49. Elavarasu S, Suthanthiran TK, Naveen D. Statins: A new era in local drug delivery. Journal of pharmacy & bioallied sciences. 2012 Aug;4(Suppl 2):S248.
50. 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.