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Evaluation of statins (Simvastatin and lovastatin) in reducing periodontal parameters in patients with chronic periodontitis

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Abstract

Introduction and objective: *Chronic periodontitis is the most common form of periodontal disease. Progression of the disease is due to high levels of pro-inflammatory cytokines. Statins are a class of lipid-lowering drugs that used for cardiovascular disease and stroke. Statins has potential anti-inflammatory effect by blocking intermediate metabolites of the mevalonate pathway. The aim of this study was to evaluate the influence of Lovastatin and Simvastatin in improve the parameters of chronic periodontitis in the population of Khorasan Razavi province.*
Methods and materials: *40 subjects with chronic periodontitis were selected and informed consent was obtained from participants. Participants were divided into control and experimental groups and we scaling for patients of both groups, then control group without high blood cholesterol and treatment of patients was done without statin drugs and in case groups, patients with blood cholesterol higher than 240 mg/dl with Lovastatin 20 mg/day during 3 month treated. Periodontal indices; such as probing pocket depth (PPD), GI, PI, CAL and bleeding on probing in patients with chronic periodontitis were measured by the examiner before and after treatment in the control group and the experimental group. Also this index were measured 3 months after treatment in both groups by the same person examiner as Blind and dataes were analyzed by statistical software.*
Results: *In this study, Mean ± SD of age was 7.93 ± 43.8 in the control group and the experimental group was 7.72 ± 47.8 and of the 40 patients in the study, 18 were males and 22 were females. Our study showed that the index of GI, CAL, BOP and probing depth were significantly different between the two groups after the intervention (P<0.05) and only after the intervention PI index was not significantly different between the two groups (P>0.05).*
Conclusion: *Our findings showed that statins may improve periodontal index in patient with periodontal disease. This is probably because that statins increase bone regeneration and reduced inflammatory parameters such as CRP, MMP-9, TNF-α and the intermediate products.*

Keywords: *Chronic periodontitis, Simvastatin, Lovastatin, Gingival Index, Plaque Index, Clinical Attachment Level, Bleeding on Probing*

Introduction

Periodontal disease is responsible for the majority of tooth loss after 35 years. (1) Chronic periodontitis is the most common form of periodontal disease and its prevalence in different societies varied and widespread (2). Progression of the disease is due to high levels of pro-inflammatory cytokines. It was recently demonstrated in patients with periodontitis 4 times more likely than healthy individuals may suffer from rheumatoid arthritis (3, 4). Chronic periodontitis is an infectious disease that leads to inflammation of the tissues supporting the teeth; loss of connections is progressive and lead to bone loss (5).

Clinical findings of chronic periodontitis are untreated: formation of subgingival and above gum plaque is often associated with the dental calculus, gingival inflammation, pocket formation, loss of alveolar bone resorption connections (6).

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In response to endotoxin that periodontal pathogens excreted, targeting a number of inflammatory mediators associated with osteoclasts, bony tissue and connective tissue around the teeth, including the periodontal ligament and destroys them. Scaling, root planning, antibiotics and mouthwash such treatments are also recommended in chronic periodontitis (7). Statins consumption reduces the possibility of periodontal criteria.

Sangwan *et al* (2016) performed a study aimed to evaluate the response to nonsurgical periodontal therapy among hyperlipidemic subjects and whether statin use by hyperlipidemic subjects influences the response. This study was conducted on 107 chronic periodontitis subjects 35 normolipidemic, 36 hyperlipidemics on nonpharmacological therapy and 36 hyperlipidemics on statins and periodontal index (GI, PD, CAL) and biochemical (plasma triglyceride, total cholesterol, LDL, and LDH) examination was done at baseline and 3 months after nonsurgical periodontal treatment. They found that the GI in the control groups and treatment with statins significantly improved and PD and LDL compared to the beginning of the study reduced and HDL increased. While higher baseline lipid levels were somewhat detrimental to the resolution of inflammation postperiodontal treatment, the inclusion of statin therapy among hyperlipidemic subjects seemed to improve clinical response as compared to those devoid of the drug. (8)

Estanislau *et al* (2015) in a systematic review evaluate the effect of statins on periodontal treatment. They reviewed all articles blind or double-blind, retrospective cohort or randomized controlled trials, published between the years 2004 and 2014 in English and Portuguese. They founded that statins have important anti-inflammatory and immune effects such as-reactive protein and matrix metalloproteinases and their intermediate product (such as TNF-α) and also able to inhibit the adhesion and extravasation of leukocytes, which block the co-stimulation of T cells.(9)

Haris *et al* (2015) examine the role of statins in the treatment of periodontitis. They found that many cardiovascular studies have suggested that statins have potential anti-inflammatory and antioxidant properties and also found that statins systemically and locally increased osteogenic differentiation and bone morphogenic protein and bone formation by upregulating the intermediate metabolites and also by blocking the mevalonate (10).

Chen Xu *et al* (2014) examined the effects of simvastatin prevents alveolar bone loss in an experimental rat model of periodontitis after ovariectomy. Their study included 36 female rats Sprague Dawley during 4 months in 6 research group. This study found that local simvastatin increase height of alveolar bone and reduce alveolar localized bone resorption without systemic symptoms of bone resorption (11).

Meisel *et al* (2014) in a study evaluate the effect of statins on periodontitis and tooth loss. In this study, 134 patients with a history of follow up 5 years treated with statins. They founded that statins significantly reduced the teeth loss due to the reduced plasma LDL-c. (12)

Subramanian *et al* (2013) examined the effect of high dose statins on reducing periodontal inflammation. For this study, 83 patients with atherosclerosis were enrolled in the study and atorvastatin for treatment was prescribed and CAL and PD parameters evaluated. They concluded that high-dose atorvastatin reduces gingivitis, which recently the effect of statins recognized (13)

Rao *et al* (2013) in RCT study aimed to investigates the effects of simvastatin in smokers with chronic periodontitis. In this study, 50 patients in the two treatment groups SRP with simvastatin and SRP with placebo were divided and indicators BOP, PD and CAL at the time of the baseline, 3, 6 and 9 months after treatment was measured. It concluded that a significant reduction in the BOP and PD and a significant increase in the CAL in smokers with chronic periodontitis were treated with SRP plus local simvastatin observed. (14)

Suresh *et al* (2013) evaluated anti-inflammatory effect of statins in chronic periodontitis. In this study, 30 patients aged 40 to 60 years in both groups treated with statin and non-statin therapy were divided and the level of IL-1β gingival crevicular fluid (GCF) was evaluated. The study concluded that the reduced levels of IL-1β in GCF in group treated by statins, show anti-inflammatory effect of statins in periodontitis. (15)

Materials and methods

After extensive library survey on the issue and determine variables, this study on 40 subjects with chronic periodontitis were selected and informed consent was obtained from participants.

Participants in the study were those who were admitted to the School of Dentistry, Mashhad University of Medical Sciences. Participants were divided into control and experimental groups and we scaling for patients of both groups, then control group without high blood cholesterol and treatment of patients was done without statin drugs and in case groups, patients with blood cholesterol higher than 240 mg/dl with Lovastatin 20 mg/day during 3 month treated. Periodontal indices; such as probing pocket depth (PPD), GI, PI, CAL and bleeding on probing in patients with chronic periodontitis were measured by the examiner before and after treatment in the control group and the experimental group. Also this index were measured 3 months after treatment in both groups by the same person examiner as Blind and dataes were analyzed by statistical software.

Results

In this section the results of statistical data collection in the form of tables and graphs are presented. Mean ± SD

of age was 7.93 ± 43.8 in the control group and the experimental group was 7.72 ± 47.8. T-student test was not observed a significant difference between the two groups in terms of mean age (t=1.61, P=0.115) of the 40 patients studied, 18 (0.45%) were male and 22 (0.55%) were female. The results showed that the two groups were similar in terms of gender (Chi - square=1.61, P=0.20) (Table 1)

Table 1: Frequency of subjects according to gender and group

Total	Experimental group	Control group	
(Percentage) number	(Percentage) number	(Percentage) number	
(45.0)18	(35.0)7	(55.0)11	Male
(55.0)22	(65.0)13	(45.0)9	Female
(100.0)40	(100.0)20	(100.0)20	Total

However the results of the interventions described above.

PI Index

The results showed that mean PI index significantly reduced in the experimental group and control group (p <0.001). The independent t-test showed a reduction in both groups were not significantly different (P = 0.41). (Table 2)

Table 2: Mean and standard deviation PI before and after treatment in both study groups

Paired t-test result	difference before and after	After intervention	Before intervention	Groups
	Mean ± SD	Mean ± SD	Mean ± SD	
T=10.37 P<0.001	0.36±-0.85	0.696±1.2	0.686±2.05	Control group
T=10.78 P<0.001	0.39±-0.95	0.587±0.85	0.696±1.8	Experimental group
	T=0.83 P=0.41	T=1.71 P=0.94	T=1.14 P=0.26	Paired t-test result

Analysis of covariance to control age and gender variables was used (Table 3). According to the table, the control of age and gender variables and PI before intervention has significant differences in reducing PI in two groups. So that in the control group the average value of PI is 0.27.

Table 3 Shows the results of covariance analysis on the effect of intervention on PI changes according to the control age and gender variables

Variable	**Coefficient**	Standard error	**t**	**p-value**
Control group	0.274	0.385	2.68	**0.01**
Experimental group	0	-	-	**-**
Male	-0.131	0.117	1.118	**0.271**
Female	0	-	-	**-**
Age	0.016	0.009	1.75	**0.089**
Before PI	0.658	0.097	6.79	**<0.001**

a) is base

GI Index

The results showed that mean GI index significantly reduced in the experimental group and control group (p <0.001). The independent t-test showed a reduction in both groups were significantly different (P = 0.25). (Table 4)

Table 4: Mean and standard deviation GI before and after treatment in both study groups

Groups	Before intervention	After intervention	Difference before and after	Independent t test result
	Mean ± SD	Mean ± SD	Mean ± SD	
Control group	0.47±2.30	0.510±1.45	0.366±-0.85	T=10.37 , p<0.001
Experimental group	0.605±1.95	0.587±0.85	0.307±-1.1	T=15.98, P<0.001
Independent t test result	T=2.043 , P=0.048	T=3.44, P=0.001	T=2.33, P=0.025	

Analysis of covariance to control age and gender variables was used (Table 5). According to the table, the control of age and gender variables and GI before intervention has significant differences in reducing GI in two groups. So that in the control group the average value of GI is 0.33.

Table 5 Shows the results of covariance analysis on the effect of intervention on GI changes according to the control age and gender variables

Variable	**Coefficient**	Standard error	**t**	**p-value**
Control group	.337	.132	2.559	**.015**
Experimental group	.0[a]	.	.	**-**
Male	.078	.116	.671	**.506**
Female	0[a]	.	.	**-**
Age	.006	.010	.673	**.505**
Before GI	.780	.134	5.813	**<0.001**

a) is base

CAL Index

The results showed that mean CAL index significantly reduced in the experimental group and control group (p <0.001). The independent t-test showed a reduction in both groups were significantly different (P = 0.019). (Table 6)

Table 6: Mean and standard deviation CAL before and after treatment in both study groups

Groups	Before intervention	After intervention	Difference before and after	Independent t test result
	Mean ± SD	Mean ± SD	Mean ± SD	
Control group	0.686±3.05	0.444±2.25	0.410±-0.80	T=8.71 p<0.001
Experimental group	0.510±2.95	0.410±1.80	0.489±-1.15	T= 10.51 p<0.001
Independent t test result	T= 0.52 p=0.060	T= 3.32 p= 0.002	T=2.45 p=0.019	

Analysis of covariance to control age and gender variables was used (Table 7). According to the table, the control of age and gender variables and CAL before intervention has significant differences in reducing CAL in two groups. So that in the control group the average value of CAL is 0.46.

Table 7 Shows the results of covariance analysis on the effect of intervention on CAL changes according to the control age and gender variables

Variable	**Coefficient**	Standard error	**t**	**p-value**
Control group	.460	.108	4.255	**<0.001**
Experimental group	0[a]	.	.	**.**
Male	-.029	.112	-.261	**.796**
Female	0[a]	.	.	**.**
Age	.011	.008	1.370	**.179**
Before CAL	.399	.099	4.044	**<0.001**

a) is base

BOP Index

The results showed that mean BOP index significantly reduced in the experimental group and control group (p <0.001). The independent t-test showed a reduction in both groups were significantly different (P = 0.001). (Table 8)

Table 8: Mean and standard deviation BOP before and after treatment in both study groups

Independent t test result	Before intervention	After intervention	Difference before and after	Independent t test result
	Mean ± SD	Mean ± SD	Mean ± SD	
Independent t test result	7.50±36.66	7.29±33.65	2.11±-2.95	T=6.23 p<0.001
Independent t test result	11.52±34.50	7.62±23.85	7.81±-11.05	T=6.32 p<0.001
Independent t test result	T=0.553 p=0.58	T= 4.15 p<0.001	T= 4.47 , p=<0.001	

Analysis of covariance to control age and gender variables was used (Table 9). According to the table, the control of age and gender variables and BOP before intervention has significant differences in reducing BOP in two groups. So that in the control group the average value of BOP is 9.72.

Table 9 Shows the results of covariance analysis on the effect of intervention on BOP changes according to the control age and gender variables

Variable	**Coefficient**	Standard error	**t**	**p-value**
Control group	9.721	1.489	6.527	**<0.001**
Experimental group	0[a]	.	.	**.**
Male	-3.121	1.488	-2.098	**.043**
Female	0[a]	.	.	**.**
Age	.062	.140	.442	**.661**
Before BOP	.559	.106	5.264	**<0.001**

a) is base

PD Index

The results showed that mean PD index significantly reduced in the experimental group and control group (p <0.001). The independent t-test showed a reduction in both groups were significantly different (P = 0.001). (Table 10)

Table 10: Mean and standard deviation PD before and after treatment in both study groups

Groups	Before intervention	After intervention	Difference before and after	Paired t-test result
	Mean ± SD	Mean ± SD	Mean ± SD	
Control group	0.461±3.65	0.433±3.35	0.299±-0.30	T=4.48 p<0.001
Experimental group	0.500±3.75	0.412±2.77	0.379±-0.975	T=11.48 p<0.001
Paired t-test result	T= 0.657 p=0.515	T=4.32 p<0.001	T=6.24 p<0.001	

Discussion

Periodontal disease is responsible for the majority of tooth loss after 35 years. (1) Chronic periodontitis is the most common form of periodontal disease and its prevalence in different societies varied and widespread (2). Progression of the disease is due to high levels of pro-inflammatory cytokines. It was recently demonstrated in patients with periodontitis 4 times more likely than healthy individuals may suffer from rheumatoid arthritis (3, 4). Chronic periodontitis is an infectious disease that leads to inflammation of the tissues supporting the teeth; loss of connections is progressive and lead to bone loss (5).

Clinical findings of chronic periodontitis are untreated: formation of subgingival and above gum plaque is often associated with the dental calculus, gingival inflammation, pocket formation, loss of alveolar bone resorption connections (6).

In response to endotoxin that periodontal pathogens excreted, targeting a number of inflammatory mediators associated with osteoclasts, bony tissue and connective tissue around the teeth, including the periodontal ligament and destroys them. Scaling, root planning, antibiotics and mouthwash such treatments are also recommended in chronic periodontitis (7). Statins is one of the drugs consumption and the possibility of reducing periodontal criteria is not expected.

Statins consumption reduces the possibility of periodontal criteria. The aim of this study was evaluation of statins (Simvastatin and lovastatin) in reducing periodontal parameters in patients with chronic periodontitis. Gingival biofilm plaque includes a large number of different bacteria feeds from bleeding gums, saliva and GCF. In general, it is believed that the biofilm contains inflammatory response to neutralizing bacterial challenge. The accumulated plaque gets worse via inflammation (16). Various reports described the impact

of dental plaque on the systemic inflammatory response and lipid-cycle levels including cholesterol (17, 18). The joint effect of bacterial biofilm and infection, mirror image of the relationship between systemic reactions and periodontal inflammation include increased phospholipid, cytokines and markers of inflammation such as fibrinogen, CRP and the potential relationship seen between periodontal and cardiovascular disease (19). Periodontitis is a type of inflamed tissue wound is because of an microbiological injury and can be used with conventional mechanical harvesting plaque above and below the gums, causing inflammation and increased control it and restore its clinical remission (20).

Proper wound healing depends on various cytokines and growth factor that is the primary source of macrophages as well. Factors help wound healing, including platelet and growth factor and TGF-β which reduced lipid (21) as strong proven that fat causes increased levels of cooperation will be delayed wound healing. It has been reported that increased fat levels increase inflammatory cytokine production (eg, TNF-α and IL-1β), which are produced by monocyte and PMN (22, 23). According to the results, we found that the PI parameter was significantly decreased in both groups (P <0.001), but there is no significant difference between the two groups (P> 0.05). We also noticed parameters GI, CAL, PD and BOP were significantly decreased in both groups (P <0.001) the indexes was significantly different between the two groups (P <0.001) in such a way that these measures had a greater reduction in the statin group.

Saver (24) showed that, unlike our study, statin group does not have any significant difference between the control group, also in the study Saxline (25) observed that not only improves periodontal disease but also has led to increase the disease, but in studies Lindy (26), Pradeep & Thorat (27), Fajardo (28), Meisel (12, 29), Pradeep (30, 31) and Sangwan (32) as our study parameters PD, GI and CAL significantly reduced in the statin group compared to the control group (P <0.001).

In Invivo and Invitro studies the mechanism of protection and treatment of periodontal disease has been described. In Invitro studies conducted, it reported that different statins are able to stimulate osteogenic differentiation and simultaneously inhibit idiopathic differentiation of bone marrow mesenchymal cells (33-34). Animal studies have shown that the effect of statins in oral and maxillofacial bone tissue as well as its effect on the rest of the bone tissue like tibia and skull bones (35, 36-38). Also, recent studies in humans have shown that statins have positive effects on the reduction of alveolar bone defect (13, 27, 31, and 32) that we can see its effects on periodontal health (12, 23). Its use can reduce periodontal pocket depth and reduce the symptoms of inflammation in periodontal disease (13, 25, 30). After using simvastatin with different carriers such as calcium sulfate (28), methyl cellulose gel (27, 30, 31, 39, 40), bovine bone matrix (38), collagen sponge (41) and bisphosphonate alendronate (42) reported positive results during the regenerated bone Defect (27, 30, 31).
Lovastatin and simvastatin increase bone density by stimulating the bone morphogenetic protein (BMP-2) in Invitro and in mice (43, 44). Statins also have anti-inflammatory and immunologic effect by reducing levels of protein C-reactive (CRP), matrix metalloproteinase -9 (MMP-9), intermediate products and TNFα (45, 46). High activity of MMPs and TNFα increased periodontal diseases by the tissue destruction (47). So that it is biologically plausible reasons of positive impact of statins on periodontal disease. Also the pharmacology effect of statins can justify our findings (48).

Conclusion

In this study, Mean ± SD of age was 7.93 ± 43.8 in the control group and the experimental group was 7.72 ± 47.8 and of the 40 patients in the study, 18 were males and 22 were females. Our study showed that the index of GI, CAL, BOP and probing depth were significantly different between the two groups after the intervention (P<0.05) and only after the intervention PI index was not significantly different between the two groups (P>0.05).
Our findings showed that statins may improve periodontal index in patient with periodontal disease. This is probably because that statins increase bone regeneration and reduced inflammatory parameters. One limitation of our study was small sample size, which was recommended in future studies inflammatory factors such as MMP-9, IL-8, TNF-α and CRP examined.

References

[1]. Carranza FA, Newman MG. Clinical periodontology: WB Saunders Company; 1996.
[2]. Novak M, Novak K. Chronic periodontitis. Newman M, Takei H, Klokkevold R Carranzas Clinical Periodontology 9th ed Philadelphia: WB Saunders Co. 2006:134-5.
[3]. Mercado F, Marshall R, Klestov A, Bartold P. Relationship between rheumatoid arthritis and periodontitis. Journal of periodontology. 2001;72(6):779-87.
[4]. Berthelot J-M, Le Goff B. Rheumatoid arthritis and periodontal disease. Joint Bone Spine. 2010;77(6):537-41.
[5]. Flemmig TF. Periodontitis. Annals of Periodontology. 1999;4(1):32-7.
[6]. Newman MG, Takei H, Klokkevold PR, Carranza FA. Carranza's clinical periodontology: Elsevier health sciences; 2011.
[7]. Lang NP, Lindhe J. Clinical periodontology and implant dentistry: John Wiley & Sons; 2015.
[8]. Sangwan A, Tewari S, Singh H, Sharma RK, Narula SC. Effect of hyperlipidemia on response to nonsurgical periodontal therapy: Statin users versus nonusers. European journal of dentistry. 2016;10(1):69.
[9]. Estanislau IMG, Terceiro IRC, Lisboa MRP, Teles PdB, Carvalho RdS, Martins RS, *et al*. Pleiotropic effects of statins on the treatment of chronic periodontitis–a systematic review. British journal of clinical pharmacology. 2015;79(6):877-85.

[10]. PM MH, Narayanan M, Arjun M. Statins in periodontal regenerative therapy-A Review. Proteomics soon to revolutionize diagnosis–A short review 49.89.

[11]. Xu X-c, Chen H, Zhang X, Zhai Z-j, Liu X-q, Qin A, *et al*. Simvastatin prevents alveolar bone loss in an experimental rat model of periodontitis after ovariectomy. Journal of translational medicine. 2014;12(1):1.

[12]. Meisel P, Kroemer HK, Nauck M, Holtfreter B, Kocher T. Tooth loss, periodontitis, and statins in a population-based follow-up study. Journal of periodontology. 2014;85(6):e160-e8.

[13]. Subramanian S, Emami H, Vucic E, Singh P, Vijayakumar J, Fifer KM, *et al*. Simvastatin prevents alveolar bone loss in an experimental rat model of periodontitis after ovariectomy. Journal of the American College of Cardiology. 2013;62(25):2382-91.

[14]. Rao N, Pradeep A, Bajaj P, Kumari M, Naik S. Simvastatin local drug delivery in smokers with chronic periodontitis: a randomized controlled clinical trial. Australian dental journal. 2013;58(2):156-62.

[15]. Suresh S, Narayana S, Jayakumar P, Sudhakar U, Pramod V. Evaluation of anti-inflammatory effect of statins in chronic periodontitis. Indian journal of pharmacology. 2013;45(4):391.

[16]. U. van der Velden, "The significance of supragingival plaque accumulation in periodontal disease," International Journal of Dental Hygiene, vol. 4, pp. 11–14, 2006.

[17]. K. J.Mattila, P. J. Pussinen, and S. Paju, "Dental infections and cardiovascular diseases: a review," Journal of Periodontology, vol. 76, no. 11, pp. 2085–2088, 2005.

[18]. B. S¨oder, "Dental plaque as a possible risk factor for general disease–results from longitudinal studies," International Journal of Dental Hygiene, vol. 4, supplement 1, pp. 22–25, 2006.

[19]. K. J. Joshipura, H. C. Wand, A. T. Merchant, and E. B. Rimm, "Periodontal disease and biomarkers related to cardiovascular disease," Journal of Dental Research, vol. 83, no. 2, pp. 151–155, 2004.

[20]. Drisko CH. Nonsurgical periodontal therapy. Periodontol 2000. 2001;25:77–88.

[21]. 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;296:331–7.

[22]. Niemann-Jönsson A, Dimayuga P, Jovinge S, Calara F, Ares MP, Fredrikson GN, *et al.* Accumulation of LDL in rat arteries is associated with activation of tumor necrosis factor-alpha expression. Arterioscler Thromb Vasc Biol. 2000;20:2205–11.

[23]. 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;35:417–27.

[24]. Saver BG, Hujoel PP, Cunha-Cruz J, Maupome G. Are statins associated with decreased tooth loss in chronic periodontitis? J Clin Periodontol 2007; 34: 214–219.

[25]. Saxlin T, Suominen-Taipale L, Knuuttila M, Alha P, Ylostalo P. Dual effect of statin medication on the periodontium. J Clin Periodontol 2009; 36: 997–1003.

[26]. Lindy O, Suomalainen K, Makela M, Lindy S. Statin use is associated with fewer periodontal lesions: a retrospective study. BMC Oral Health 2008; 8: 16.

[27]. 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: 214–222.

[28]. Fajardo ME, Rocha ML, Sanchez-Marin FJ, Espinosa-Chavez EJ. Effect of atorvastatin on chronic periodontitis: a randomized pilot study. J Clin Periodontol 2010; 37: 1016–1022.

[29]. Meisel P, Kohlmann T, Wallaschofski H, Kroemer HK, Kocher T. Cholesterol, C-reactive protein, and periodontitis: HMG-CoA-reductase inhibitors (statins) as effect modifiers. ISRN Dent 2011; 2011: 125168.

[30]. 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. J Periodontol 2013; 84: 871–879.

[31]. 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. J Periodontol 2013; 84: 24–31.

[32]. Sangwan A, Tewari S, Singh H, Sharma RK, Narula SC. Periodontal status and hyperlipidemia: statin users versus non-users. J Periodontol 2013; 84: 3–12.

[33]. Li X, Cui Q, Kao C, Wang GJ, Balian G. Lovastatin inhibits adipogenic and stimulates osteogenic differentiation by suppressing PPARgamma2 and increasing Cbfa1/Runx2 expression in bone marrow mesenchymal cell cultures. Bone 2003; 33: 652–659.

[34]. Maeda T, Matsunuma A, Kurahashi I, Yanagawa T, Yoshida H, Horiuchi N. Induction of osteoblast differentiation indices by statins in MC3T3-E1 cells. J Cell Biochem 2004; 92: 458–471.

[35]. Houshmand B, Hassanizade R, Eslami B, Amouei S, Dashti G, Morad G, Khojasteh A. Simvastatin and lovastatin induce ectopic bone formation in rat subcutaneous tissue. J Periodontol Implant Dent 2010; 2: 5.

[36]. Ferreira-Júnior DB, Pinto AS, Del Carlo RJ, Fonseca CC, Oliveira TT, Cardoso CA, Amaral GG, Lima LRP. Efeitos de bifosfonatos e estatinas na reparação de fraturas em tíbias de ratas com osteoporose induzida com dexametasona. Rev Ciênc Farm Básica Apl 2008; 29: 7.

[37]. Nyan M, Sato D, Oda M, Machida T, Kobayashi H, Nakamura T, Kasugai S. Bone formation with the combination of simvastatin and calcium sulfate in critical-sized rat calvarial defect. J Pharmacol Sci 2007; 104: 384–386.

[38]. Lima LL, Goncalves PF, Sallum EA, Casati MZ, Nociti FH, Jr. Guided tissue regeneration may modulate gene expression in periodontal intrabony defects: a human study. J Periodontal Res 2008; 43: 459–464.

[39]. Bradley JD, Cleverly DG, Burns AM, Helm NB, Schmid MJ, Marx DB, Cullen DM, Reinhardt RA. Cyclooxygenase-2 inhibitor reduces simvastatin-induced bone morphogenetic protein-2 and bone formation in vivo. J Periodontal Res 2007; 42: 267–273.

[40]. Rutledge J, Schieber MD, Chamberlain JM, Byarlay M, Killeen AC, Giannini PJ, Marx DB, Reinhardt RA. Simvastatin application to augment facial jaw bone in a dog model: pilot study. J Periodontol 2011; 82: 597–605.

[41]. Liu S, Bertl K, Sun H, Liu ZH, Andrukhov O, Rausch-Fan X. Effect of simvastatin on the osteogenetic behavior of alveolar osteoblasts and periodontal ligament cells. Hum Cell 2012; 25: 29–35.

[42]. 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: 1035–1042.

[43]. Mundy G, Garrett R, Harris S, *et al*. Stimulfation of bone formation in vitro and in rodents by statins. Science 1999;286:1946-1949.

[44]. Thylin MR, McConnell JC, Schmid MJ, *et al*. Effects of simvastatin gels on murine calvarial bone. J Periodontol 2002;73:1141-1148.

[45]. Koh KK, Son JW, Ahn JY, *et al*. Comparative effects of diet and statin on NO bioactivity and matrix metalloproteinases in hypercholesterolemic patients with coronary artery disease. Arterioscler Thromb Vasc Biol 2002;22:e19-e23.

[46]. Youssef S, Stuve O, Patarroyo JC, *et al*. The HMGCoA reductase inhibitor, atorvastatin, promotes a Th2 bias and reverses paralysis in central nervous system autoimmune disease. Nature 2002;420:78-84.

[47]. Garlet GP, Martins W Jr., Fonseca BA, Ferreira BR, Silva JS. Matrix metalloproteinases, their physiological inhibitors and osteoclast factors are differentially regulated by the cytokine profile in human periodontal disease. J Clin Periodontol 2004;31:671-679.

[48]. Hujoel PP. Does chronic periodontitis cause coronary heart disease? A review of the literature. J Am Dent Assoc 2002;133(Suppl.):31S-36S.