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Original Article

Evaluation of periodontal health in patients taking Atorvastatin

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Abstract

Introduction: Periodontal disease as a chronic inflammatory condition is more prevalent in adults. Considering the anti-inflammatory effect of statins and the need to find out the effects of these drugs on the prevention and treatment of periodontal diseases, this study was conducted to investigate the role of atorvastatin in periodontal health.

Material & Methods: In this cross sectional study the effect of atorvastatin on plaque index, probing pocket depth (PPD), gingival index (GI) and bleeding on probing (BOP) index were examined. Patients with plaque index between 1 and 2 were included in the study, and those who had taken atorvastatin for at least 3 months were selected as the case group and those who had not taken atorvastatin were considered as the control group.

Results: A total of 138 patients (50 patients for the atorvastatin group and 88 patients for the control group) were included. The mean probing pocket depth in the atorvastatin group was 2.03±0.35 mm and that in the control group was 2.8±0.31 mm (p=0.335). The mean bleeding index in the atorvastatin group was 0.20±0.14 and compared to the control group was 0.20±0.17 (p<0.001). The GI index in the atorvastatin group was 1.29±0.33, compared to the control group was 1.20±0.40 (p=0.218).

Conclusion: The results of this study indicate the positive effect of the use of atorvastatin on reducing the bleeding on probing index in patients taking this drug. The probing pocket depth index and gingival index were not significantly different between the atorvastatin group and the group not taking this drug.

Keywords: Atorvastatin, Periodontitis, Hyperlipidemias

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بررسی سلامت پریودنتال در بیماران مصرف کننده داروی آتورواستاتین

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چکیده

مقدمه: بیماری پریودنتال بیماری مزمن التهابی است که در بزرگسالان شایع تر است. با توجه به اثر ضد التهابی استاتین ها و نیاز به پیدا کردن اثرات این داروها در پیشگیری و درمان بیماری های پریودنتال، این مطالعه به منظور بررسی اثر آتورواستاتین در سلامت پریودنتال انجام شد.

مواد و روش ها: در این مطالعه اثر آتورواستاتین بر سلامت پریودنتال با ارزیابی شاخص پلاک، عمق پاکت (PPD)، شاخص لثه (GI) و خونریزی حین پروبینگ (BOP) مورد بررسی قرار گرفت. بیماران با شاخص پلاک بین ۱ تا ۲ در مطالعه قرار گرفتند و افرادی که آتورواستاتین را برای حداقل ۳ ماه مصرف کرده بودند به عنوان گروه مورد و افرادی که آتورواستاتین را مصرف نکرده بودند به عنوان گروه شاهد در نظر گرفته شدند.

یافته ها: در مجموع ۱۳۸ بیمار (۵۰ بیمار در گروه آتورواستاتین و ۸۸ بیمار در گروه شاهد) شامل می شدند. میانگین عمق پاکت در گروه آتورواستاتین ۰/۳۵±۲/۰۳ میلی متر و در گروه شاهد ۰/۳۱±۲/۸ میلیمتر بود ($p = 0.335$). میانگین شاخص خونریزی در گروه آتورواستاتین ۰/۱۴±۰/۲۰ و در مقایسه با گروه شاهد ۰/۱۷±۰/۲۰ بود، ($p< 0.001$) شاخص GI در گروه اتورواستاتین ۰/۳۳±۱/۲۹ بود در مقایسه با گروه شاهد ۰/۴۰±۱/۲۰ ($p = 0.218$).

نتیجه گیری: نتایج این مطالعه نشان دهنده تاثیر استفاده از آتورواستاتین بر کاهش خونریزی حین پروبینگ در بیماران مصرف کننده این دارو است. عمق پاکت و شاخص لثه ای بین گروه آتورواستاتین و گروهی که این دارو را مصرف نمی‌کردند تفاوت معنی داری نداشت.

واژگان کلیدی: آتورواستاتین، پریودنتیت، هیپرلیپیدمی

Introduction

Statin drugs (HMG-COA inhibitors) inhibit 3-Hydroxy-3-methylglutaryl–coenzyme A (HMG-CoA) reductase in the mevalonate (MVA) pathway. [1] The pathway of MVA is a very important metabolic one in eukaryotes and many bacteria, which ultimately leads to the production of many important compounds such as cholesterol and isoprenoids (terpenes such as lycopene and carotene). In the human liver, the conversion of HMG-CoA to mevalonic acid is influenced by HMG-CoA reductase enzyme in the initial stages of cholesterol production. Therefore, the competitive inhibition of this enzyme by static drugs reduces blood cholesterol levels. [2] Statins have been developed to lower serum cholesterol levels [3] and successfully used to control and treat coronary artery diseases. [4-6]

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Recently, cholesterol-independent or "pleiotropic" effects of statins have attracted the most attention and it is expected that the anti-inflammatory pleiotropic effects result from the inhibition of isoprene modulation from an inflammatory signal transducer. [7, 8] Much attention has been paid to these potential effects including antithrombotic, antioxidant, anti-inflammatory, anti-proliferative and immune modulatory effects. In addition, statins enhance the expression of the bone morphogenic protein-2 (BMP-2) and stimulate the proliferation of osteoblasts. [1] Furthermore, the decrease in LDL-C level, which is a pleiotropic characteristic of statins, indicates their anti-inflammatory properties. [7, 9-13] Periodontal disease is caused by the function of certain microorganisms. Microorganisms and their products stimulate the inflammatory cells, produce cytokines, release proteolytic enzymes and activate osteoclasts. Although some studies have focused on the topical and systemic use of statins in the treatment of periodontal disease, many aspects of this disease still require further investigation. [5] Gingivitis is one of the most common topical inflammatory diseases in adults [14, 15], leading to periodontitis as a continuous inflammatory process that results in the destruction of periodontal tissue if left untreated. [16] This moderate inflammation can impose significant loads on the cardiovascular system, is involved in cardiovascular disease [16-19] and has been shown to be associated with systemic inflammation. [20]

Since cardiovascular disease is also a common disease among adults, and various drugs including statins are administered for the prevention and treatment of their disease as well as considering the anti-inflammatory effect of statins and the need to find out the effects of these drugs on the prevention and treatment of periodontal diseases, this cross-sectional study was performed to investigate the relationship between the use of atorvastatin and clinical symptoms of chronic periodontitis.

Materials & Methods

After ethical approval was given by Babol University of Medical Sciences (Mubabol.REC.1395.170). A total of 138 patients were selected from the patients admitted to Shahid Beheshti and Rouhani Hospitals of Babol University of Medical Sciences (Babol, Iran) and entered into the study. Patients were informed about the study process. To determine the anti-inflammatory pleiotropic effect of atorvastatin, the patients were divided into two groups, the first group included those who used 10 or 20 mg/daily of atorvastatin for at least 3 months and the second group was those who did not use this drug with almost identical conditions. The patients were similar in terms of oral hygiene, and all of them regularly used toothbrushes.

The patients' plaque index was examined and those with equal plaque indices (between 1 and 2) were compared in the current study. The two groups were equal in terms of age, ranging from 40 to 60 years and the exclusion criteria were smokers and patients with systemic diseases which affect periodontium, with the history of periodontal therapy for 6 months and with the history of antibiotic therapy since 1 month ago. The selected subjects in the atorvastatin group did not differ significantly in terms of the duration of this drug use.

The indices were tested via examination on Ramfjord teeth using a periodontal probe, catheter and mirror. These teeth were the maxillary right first molar, maxillary left first incisor, maxillary left first premolar, mandibular left first molar, mandibular right first incisor and mandibular right first premolar .[21] All of the patients were examined in the hospitals using a steady flashlight. Information such as age, gender, smoking and statin use were collected from the patients' records before they were examined. The patients' history of other diseases including diabetes mellitus and rheumatoid arthritis as well as history of the use of other medications were recorded.

The plaque index was performed based on the Loe and Silness method. [22] The total score of each tooth was divided into 4 and the plaque index of each subject was obtained by adding the plaque index of all examined teeth and dividing it into the number of the examined teeth. The plaque index was between 0 and 3. It was evaluated in patients and was equal in both case and control groups, and finally, only those who had the plaque index between 1 and 2 were included in the present study. The probing pocket depth (PPD) or the distance from the gingival margin to the most coronal level of the junctional epithelium was measured using a probe on the Ramfjord teeth in the six areas of Mesiobuccal, Midbuccal, Distobuccal, Distolingual, Midlingual, and Mesiolingual. [21]

The gingival index (GI) was performed based on the Loe and Silness method. [22] The total score of each tooth is divided into 4 and the gingival index of each

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subject is obtained by adding the gingival index of all examined teeth and dividing it into the number of the examined teeth. In this index, based the average of the obtained numbers, the status of the gingivitis is classified into three mild, moderate and severe degrees.

The bleeding on probing (BOP) index was performed based on Barnett's proposed method. In this method, the periodontal probe slowly moved in the gingival sulcus at the buccal and lingual surfaces, the duration needed for bleeding was measured, the sum of the indicators of the 4 surfaces of the 6 teeth examined is divided into 24 and the obtained bleeding index of each patient was a number between 0 and 3. [23]

Independent-sample t-test and paired-sample t-test were used to compare the data of the two groups using SPSS 21. P<0.05 was statistically considered as a significant difference.

Results

A total of 138 patients were entered into the present study. The atorvastatin group included 50 patients with an average age of 49.12±4.58 years and the control group was 88 patients with an average age of 48.95±3.55 years.

Table 1 shows the mean periodontal pocket depth in teeth 1, 4 and 6 for both atorvastatin and control groups. In general, the mean periodontal pocket depth in the atorvastatin group was 2.33±0.35 mm, whereas it was 2.8±0.31 mm in the control group, which was not significant between the two groups (p=0.335).

There was no significant difference between two groups in pocket depth according to the Mann-Whitney test.

Table 1. The mean (±SD) periodontal pocket depth for atorvastatin and control groups

Mean periodontal pocket depth and standard deviation per millimeters	Atorvastatin Group	control group	Pvalue
Tooth 1	0.32±1.56	0.29±1.59	0.555
Tooth 4	0.45±2.01	0.40±2.05	0.556
Tooth 6	0.58±2.54	0.53±2.62	0.472
Total	0.35±2.03	0.31±2.08	0.335

The mean scores of the bleeding on probing index for tooth 6 in the atorvastatin group and control group were 0.24±0.24 and 0.26±0.30, respectively. This mean score according to the Mann-Whitney test two groups was not statistically significant (p=0.718).

The bleeding index for tooth 4 in the atorvastatin group was 0.15±0.17, while it was 0.28±0.25 in the control group, which was statistically significant (p=0.003). The results suggested that the mean score of the bleeding index was higher in control group than atorvastatin group. The mean (±SD) of bleeding index for tooth 1 in the atorvastatin group was 0.21±0.24, but it was 0.35±0.32 in the control group (p=0.014). The mean bleeding index in the atorvastatin group was 0.20±0.14, whereas it was 0.20±0.17 in the control group (p<0.001).

The mean GI index was 1.29±0.33 and 1.20±1.40 in the atorvastatin and control groups, respectively, indicating no statistically significant difference (p=0.132). Frequency and percentage of the GI index in both groups are presented in table 2.

Table 2. Frequency and percentage of the GI index in both groups

			Atorvastatin Group	control group
GI index	mild	frequency	43	65
		percentage	87.8%	79.3%
	moderate	frequency	12.2%	17
		percentage		20.7%

Discussion

Periodontal disease is a chronic inflammatory disease characterized by the release of cytokines such as TNF-α and IL-1β. [24-27] Several studies have been conducted to investigate the possible association between serum lipid profile and periodontitis. [20, 27-33] Nevertheless, investigations on the optimal role of statin drugs in periodontal tissues have led to controversial reports in some studies. [27, 32, 33] A retrospective study conducted by Lindy et al. [34] illustrated that the use of statin drugs was significantly associated with fewer symptoms of periodontal inflammatory injuries. Other studies have indicated that the serum pre-inflammatory cytokines and tissue fluid may be responsible for the relationship between periodontal disease and hyperlipidemia. [35-37]

The present study aimed at evaluating the periodontal health in patients taking atorvastatin and pocket depth index between the two groups. The results indicated no significant difference between the mean pocket depth in the atorvastatin group and control

group. Lindy et al. and Sangwan et al. compared the pocket depth between patients taking and patients not taking statins .[34, 38] Both studies demonstrated a significant difference between the two groups in terms of this index, which is inconsistent with the findings of the present study.

This cross sectional study also showed that the difference of bleeding index between the atorvastatin group and the control group was significant so that the bleeding index was significantly higher in the control group than atorvastatin group. Moreover, a study conducted by Sayar et al. [39] illustrated that the hyperlipidemia patients treated with statin drugs for at least 3 months had a better periodontal status compared to those in the control group in terms of periodontal clinical parameters such as the bleeding on probing index. This positive effect of statin on the bleeding index and other clinical parameters of periodontal disease was similarly indicated in other studies. [34, 38-44] A comparison of the GI parameter between the two groups showed that the difference in this parameter is not statistically significant, which is consistent with the result of Sangwan et al. [38] Since statins have anti-inflammatory effects, it can be construed that this lack of difference between the two groups is indicative of the positive effect of atorvastatin on maintaining the inflammatory status of the gingiva in the group taking this drug. However, the level of inflammatory proteins or other inflammatory markers has not been measured in the current study and this suggestion is based on previous studies conducted on the effect of statins on inflammation through measurement of inflammatory markers, histological analysis and genetic evaluation. [45, 46] Several known biological characteristics of lipids may be responsible for the periodontal changes observed and in some cases, may explain the role of periodontal protection by statins in this study. The first explanation is that the improved serum lipid levels as a result of using the atorvastatin can be useful for periodontal tissues, because higher levels of lipid lead to relatively weaker situation of the periodontal status. [20, 28-31] The hyperlipidemia status accelerates the pre-inflammatory status and the decreased lipid levels of serum as a result of using the atorvastatin can by itself be effective in modulating inflammation. [47-50] The second explanation is that the direct pleiotropic effect of atorvastatin can lead to apparent benefits of periodontal health.

This hypothesis is supported by previous studies, representing that the statins reduce the matrix metalloproteinase stimulated release [51], tumor necrosis factor (TNF-α) and C-reactive protein (CRP). [52] The pharmacokinetic analysis of statins has estimated plasma accumulation of about 10^{-9} and 10^{-7} mol in recipients of oral systemic doses [53] and shown that the drug level in the tissue fluid of the gum is nearly 10-100 times as much as plasma. [54] As a result, the topical anti-inflammatory effects on the oral tissue can be expected after oral administration of clinical doses. Although both of the described mechanisms can synergistically lead to the observed effects, the direct interpretation of the information obtained from this study cannot be linked to any of these mechanisms precisely, because the patients' serum lipid levels as well as inflammatory factors have not been measured due to the existing limitations. The results of the present study should be interpreted based on the limitations that the researchers encountered. The first limitation was the cross-sectional type of this research, explaining the cause-effect relationship.

Another limitation was related to the lack of access to the baseline periodontal status data before the patients started taking atorvastatin. Despite the fact that all patients had a clear range of atorvastatin treatment duration, the exact period of each patient treated with this drug was not statistically analyzed for the interpretation of the results. In addition, periodontal indicators were evaluated only on four surfaces of Ramfjord teeth.

Conclusion

The results of this study indicate that the use of atorvastatin can be effective in reducing the bleeding on probing index in patients who use this medication. The pocket depth index and GI were not significantly different between atorvastatin users and non-users. Since statins have anti-inflammatory effects, this lack of difference between the two groups can be interpreted to indicate the beneficial effect of atorvastatin on maintaining the gingivitis in the group using this medication.

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Conflict of interest: We declare no conflict of interest.

Authors' Contributions

The study was designed by Babak Amoian, and Kosar Rezaei defined the conceptual content of the research. The study data were collected by Kosar Rezaei. Statistical analysis and interpretation of data were accomplished by Soraya Khafri. Preparation of manuscript was performed by Kosar Rezaei,its editing and revision were done by Babak Amoian and Ali Akbar Moghadamnia contributed to the design and implementation of the research.

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