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Do Statins improve Periodontal Status? Plaque Index, Community Periodontal Index and Salivary Alpha-amylase Enzyme in A case- control study

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Running Heading

The effect of Statins on Plaque Index, Community Periodontal Index and Alpha-amylase Enzyme

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Abstract

Periodontal disease is a chronic inflammatory condition prevalent among adults. Given the anti-inflammatory properties of statins and their potential relation with periodontal disease, this study aims to investigate the effects of statins on the plaque index (PI), community periodontal index (CPI), and salivary alpha-amylase enzyme.

This case-control study included 140 patients into three major groups: a control group, a moderate-dose statin and a high-dose statin group (atorvastatin and rosuvastatin). PI and CPI indices were assessed for all participants. Saliva samples were collected to measure the activity of salivary alpha-amylase enzyme and total protein using a spectrophotometric method. Data were analyzed using SPSS version 27, applying Chi-square, Kruskal-Wallis and Univariate statistical tests.

Significant differences in PI, CPI and salivary enzyme alpha-amylase levels were observed among the groups ($P<0.05$). However, total protein levels did not differ significantly. No significant relationships were found between PI and CPI and salivary alpha-amylase enzyme and variables such as sex, age, oral health behaviors or duration of drug use.

The findings suggest that statins are capable of affecting periodontal indices and salivary enzyme activity. Further research is recommended to confirm these effects.
In Addition, no relationship between higher statin dose intakes and periodontal health improvement were observed.

Key words: Atorvastatin, Rosuvastatin, Alpha-amylase, Health Behavior, Plaque index, Periodontal disease.

1. Introduction

Periodontal disease refers to inflammatory conditions affecting the periodontal tissues; including the gum, cementum, periodontal ligament and alveolar bone. The prevalence of periodontal diseases is increased by aging among adults, which is a major cause of tooth loss [1,2]. Periodontitis, one of the most common forms of periodontal disease, is primarily caused by bacterial infection in subgingival plaque and exacerbated by the host's inflammatory response and environmental factors [3-5]. Plaque indices, such as the Loe & Silness Plaque Index (PI), and periodontal indices, such as the Community Periodontal Index (CPI), are used to assess oral health status [6-12]. Also, salivary enzymes like alpha-amylase and protease have garnered attention as potential biomarker for diagnosis of periodontal disease. Alpha-amylase, secreted by the parotid gland, facilitates starch digestion and plays a role in oral microbial interactions [13-16].

Statins are a class of medication introduced in 1987 [5]. They are prescribed to reduce the risk of cardiovascular events, which are common conditions among adults [17]. Statins are a group of cholesterol-lowering drugs that work by inhibiting the enzyme HMG-CoA reductase. There are different types of statins such as atorvastatin, rosuvastatin, simvastatin, fluvastatin, lovastatin, pitavastatin, and pravastatin [18]. Other proven effects of these drugs include anti-inflammatory and anti-cancer properties, prevention of growth, invasion, and metastasis, cell proliferation and differentiation. Also, they can regulate the cell cycle and induce apoptosis. Since statins have many benefits, they have received much attention. In addition to their effects on cardiovascular diseases, these drugs are also beneficial for oral health and wound healing and are also used in periodontal diseases due to their antibacterial properties. According to studies, the effects of statins on bone resorption, implant osteointegration, dental pulp cells, orthodontic movements, salivary gland function and wound healing have been proven. Thus, they have recently been considered in improving and enhancing oral health due to their cheapness, safety and availability [14].

The oral cavity is often referred to as a "mirror of systemic health," as the oral mucosa reflects the body's general health, and many systemic diseases frequently manifest in the mouth [19].

Saliva, a transparent fluid secreted by the major and minor salivary glands, contains electrolytes, immunoglobulins, proteins, and enzymes, playing a crucial role in oral health. Its primary functions include protecting the oral mucosa, maintaining teeth and tissues, and performing antibacterial, antiviral, taste, and digestive activities [20-22]. Saliva is composed primarily of water and a variety of proteins, including alpha-amylase, protease, lysozyme, and

lactoferrin [23,24]. Due to its ease of collection, non-invasive nature, and diagnostic potential comparable to blood samples, saliva has gained attention as a diagnostic tool for detecting biomarkers in systemic and oral diseases [25,26].

Considering the antibacterial and anti-inflammatory effect of statins, and the lack of sufficient evidence of their efficiency in prevention and treatment of periodontal disease, this study aims to compare the effects of different types of statins on PI, CPI, salivary alpha-amylase and total protein in patients who receive these medications.

2. Material and Methods

2.1 Study Design and Ethical Approval

This case-control study was conducted to evaluate the effect of statins on plaque index (PI), community periodontal index (CPI), and salivary enzyme activity in patients in 2023. Ethical approval was obtained from the Research Ethics Committee of Alborz University of Medical Sciences (identifier: IR.ABZUMS.REC.1402.102) and all methods and experiments were performed in accordance with relevant guidelines and regulations. Also, Written informed consent was obtained from all participants before their inclusion in the study.

2.2 Participants and Data Collection

The study included 140 participants, collected among Alborz dental faculty's patients, accidentally divided into three groups: two case groups and one control group. Each case group was further categorized into two subgroups based on the name of their participants statin intake:

- **Case Group 1**: High-intensity statin intake (atorvastatin 80/40 mg or rosuvastatin 40/20 mg).
- **Case Group 2**: Moderate-intensity statin intake (atorvastatin 20/10 mg or rosuvastatin 10/5 mg).
- **Control Group**: Participants who were not taking statin medications. Patients with low-intensity statin intakes were excluded due to their infrequent use of these medicine.

In total, the study consists of five groups (one control and four subgroups) with 28 participants in each category.

A demographic checklist was prepared to record participants'demographic features including age, gender, type and duration of statin use, and oral hygiene behaviors, including the use of a toothbrush and dental floss.

2.3 Saliva Collection and Laboratory Analysis

Non-stimulated saliva samples were collected from all participants using the spitting method. One code was assigned for each sample (based on the patient dental file number) to preserve their identification. Samples were sent to the laboratory for analysis of alpha-amylase and total protein activity using the spectrophotometric method.

2.3.1 Clinical Assessments

The PI and CPI were measured for all participants using standard codes and procedures. The plaque index was scored on four surfaces of six selected teeth, and the CPI was assessed based on sextant-specific periodontal pocket depth and clinical signs of disease.

2.3.2 Saliva collection

To collect 5 cc of unstimulated saliva, the participants in the study were asked to collect their saliva in sterile glass tubes. After preparing the saliva samples, they were immediately placed at a temperature of minus 18 degrees to prevent bacterial growth and enzymatic changes, and then the samples were centrifuged in the laboratory at a speed of 4000 rpm for 10 minutes to separate the debris and finally stored in a refrigerator at 4 degrees [27].

2.3.3 PI and CPI Measurement Procedure

To assess plaque and periodontal health, the following steps were undertaken:

- **Plaque Index (PI)**:
    - After drying the teeth and gingiva, four surfaces of six preselected teeth (upper right first molar, upper right lateral incisor, upper left first premolar, lower left first molar, lower left lateral incisor, and lower right first premolar) were examined.
    - Plaque coverage was scored on a scale of 0–3:
        - **0**: No plaque.

        - **1**: A thin layer of plaque at the gingival margin.
        - **2**: Moderate plaque visible to the naked eye.
        - **3**: Heavy plaque accumulation.
- **Community Periodontal Index (CPI)**:
    - Periodontal pockets were probed using a WHO periodontal probe.
    - Each sextant was scored as follows:
        - **Code 0**: Healthy periodontal tissues.
        - **Code 1**: Gingival bleeding on probing.
        - **Code 2**: Subgingival calculus or other retentive deposits.
        - **Code 3**: Pocket depth of 4–5 mm.
        - **Code 4**: Pocket depth ≥6 mm (Silness & Löe, 1964).

2.3.4 Alpha amylase measurement

This examination was performed colorimetrically using a kit (Sigma-Aldrich, Zwijndrecht, The Netherlands) and the compound 2-chloro-4-nitrophenyl-α-d-maltotrioside for absorption at a wavelength of 405 nm [28].

2.3.5 Normalization Process

Total Protein Measurement: First, the total protein content in each saliva sample was determined, typically using assays like the Bradford assay, BCA (bicinchoninic acid) assay, or Lowry assay. This step quantifies the overall protein concentration present in the saliva sample. The measured alpha-amylase activity (e.g., in units per mL) was then normalized by dividing it by the total protein concentration (e.g., micrograms of protein). This normalization step adjusts for variations in the protein content between different samples. This ensures that any observed differences in alpha-amylase activity are due to changes in enzyme activity rather than differences in sample volume or protein concentration [29].

2.3.6 Inclusion criteria

- Consent of the patients to participate in the study
- Age above 18
- History of statin therapy for a minimum of 3 months
- Absence of any systemic disease (control group only)
- Absence of oral diseases, including Oral Candidiasis or congenital conditions with oral manifestations

2.3.7 Exclusion Criteria

- Refusal or withdrawal of consent to participate in the study
- Presence of systemic disease unrelated to statin therapy
- Pregnancy or breastfeeding

3. Results

The Data was analyzed by SPSS software, version 27.

The results of the chi-square test and the p-value, which was greater than 0.05, indicate that there is no significant difference between genders across the different groups. The results of this test and the p-value, which was less than 0.05, show a significant difference in age across the groups. The number and percentage values reveal that there are more people over 60 years of age in the statin user group (both medium and high doses) than in the control group.

Additionally, the results of this test and the p-value, which was less than 0.05, show a significant difference in health behavior across the groups. The number and percentage values indicate that in the statin user groups (both moderate and high doses), more individuals have average oral health behaviors compared to the control group.

The results indicated a significant difference in the Plaque Index (PI) levels among the three investigated groups. Using the Kruskal-Wallis test, a p-value of 0.035 was obtained ($p < 0.05$), suggesting a statistically significant variation in PI levels across the groups (Figure 1).

The mean values demonstrate that PI levels are higher in the group of high-intensity statin users compared to the other groups. In the pairwise analysis, a significant difference was observed between the medium and high-dose statin user groups, with the high-dose statin user group showing a higher PI level on average.

However, the results of the Mann-Whitney test showed that there is no significant difference between PI and the type of statin drugs used in moderate and high dose groups.

In addition, the results based on the Kruskal-Wallis test, revealed a p-value of 0.048 (less than 0.05); indicating a significant difference in CPI levels among the three investigated groups. The average values suggest that CPI is higher in the high-intensity statin user group. Pairwise analysis of the groups shows significant differences in CPI between the moderate and high-dose statin user groups, as well as between the high-dose statin user group and the control group. The average values further indicate that the CPI level is highest in the high-dose statin user group, with a significant difference from the other two groups (Figure2).

The results of the Mann-Whitney test showed a significant difference between CPI and the type of drugs consumed at an average dose. The average of CPI value in atorvastatin users is higher than the rosuvastatin users.

Also, based on the Kruskal-Wallis test, revealing a p-value of 0.073, which is greater than 0.05, results indicated that there is no significant difference in the concentration of total protein among the three investigated groups (Figure3).

The results shown in Figure 4, based on the Kruskal-Wallis test, revealed a p-value of 0.002, which is less than 0.05, indicating a significant difference in the amount of alpha-amylase enzyme among the three investigated groups. The value was higher in the moderate-dose statin group compared to the other groups (Figure4).

Pairwise analysis of the groups indicates a significant difference in alpha-amylase enzyme levels between the moderate-dose statin user group and both the high-dose statin and control groups (Table 1).

The results of the Mann-Whitney test indicated that there is no significant difference in alpha-amylase enzyme levels based on the type of drugs used at moderate and high doses (Table 2).

The results of the Kruskal-Wallis test revealed a p-value of 0.076, which is greater than 0.05, indicating that there is no significant difference in the ratio of amylase to total protein among the three investigated groups (Table 3).

The results of the univariate test showed a p-value greater than 0.05, indicating that there is no significant difference between PI and CPI with respect to gender, age, oral hygiene behavior, and duration of drug use in the studied groups.

Also, The results of the univariate test showed a p-value greater than 0.05, indicating that there is no significant difference in salivary alpha-amylase enzyme with respect to gender, age, oral hygiene behavior, and duration of drug use in the studied groups (The demographic data is presented with details in the supplementary file document).
(Figure5)

4 Discussion

Periodontal disease is a chronic inflammatory condition affecting the periodontal tissues. Despite the advances in understanding the pathogenesis of periodontitis and promising developments in other diseases, the treatment of periodontitis has remained mainly unchanged for decades. Cardiovascular disease, a common condition in adults, is treated with various medications, including statins [17]. Given the pleiotropic effects of statins and their role in disease prevention and the management of complications, further research on this class of drugs is warranted [30]. Considering the anti-inflammatory effect of statins and the need to explore their potential in the prevention and treatment of periodontal diseases, this study aims to compare the effects of different types of statins on the plaque index (PI), community periodontal index (CPI), and salivary alpha-amylase and total protein in patients on statin therapy.

The limitations of this study include:

1. Obtaining informed consent from patients was challenging.
2. Recruitment of patients across different medication groups and doses, especially those on moderate and high-dose intake of rosuvastatin, was difficult.
3. Reduced salivation in elderly patients, due to physiological factors, made saliva collection challenging.
4. Lack of access to baseline periodontal data before statin therapy, which could have significantly influenced the results.
5. This study focused on a limited set of salivary enzymes. Given the complex composition of saliva, this approach provided only a partial view salivary components.

4.1 Investigation of the Effect of Statin Use on PI and CPI Indices

The results of this study demonstrated a significant difference in the PI and CPI indices amongst the three groups (control, Group1 and Group2). Notably, the PI index was higher in Group1 compared to the other groups. Our goal was to assess the potential positive effects of statins on periodontal health. While it was hypothesized that higher statin doses would lead to improvements in periodontal health, this was not observed in our study. Since the patients in this group were elder and generally in poorer health than the control group, the higher PI observed in Group1 could be attributed to these factors. This was evident from both self-reported data and clinical examinations. Although, no prior studies have specifically investigated the effects of different intake of statin doses on periodontal status our findings are in contrast with previous studies. Greenthurst et al. [31] evaluated the effects of statins as a supplementary treatment in periodontal disease. They reported that there was a PI decrease in patients who consume these medications. Moreover, Pradeep et al. and Vemanaradhya et al. [32,33] examined statins as a topical medicine for treating chronic periodontitis and both studies have shown positive results for PI index. This contradiction might be duo to differences in methods and participants.

There are other studies in which, other periodontal indices are evaluated. Carvalho de Parolina et al. [34] examined Simvastatin as an effective medicine for controlling periodontal disease and they have reported positive results. Also, Hasan Faiza et al. [35] evaluated Simvastatin mouthwash as a supplementary treatment in cooperation with scaling and the results have shown significant decrease in periodontal parameters.

4.2 Investigation of the Effect of Statin Use on Alpha-Amylase Enzyme

The results of our study indicated a significant difference in salivary alpha-amylase enzyme levels among the three groups. Specifically, the alpha-amylase enzyme levels were higher in statin users, with medium-dose users showing higher levels than those on high-dose statins, compared to the control group. Moreover, Raluca-Paula Vacaru et al. [28] assessed the relationship between salivary enzymatic activity and carious experience in children. Thus, it can be concluded that alpha-amylase enzyme levels are capable to be considered as oral health indicators. Also, Kaminska Marta et al. [30] examined the effects of statins on multispecies oral biofilm and stated that simvastatin can be considered as a promising drug to control periodontal dysbiosis. They also mentioned an increase in alpha-amylase enzyme levels which

is in consistency with present study's results. In addition, Christiansen et al. [19] examined local simvastatin effects on inflammation during periodontal mini-flap wound healing.

4.3 Investigation of the Effect of Statins on Total Protein

The results of this study indicated that there was no significant difference in salivary total protein levels among the three groups. A similar conclusion was attained from Varacu Raluca-Paula et al. [28] study in which, no relationship was observed between total protein levels and caries index.

5 Conclusion

This study aimed to investigate the effect of statins on plaque index (PI), community periodontal index (CPI), and salivary enzymes in patients. The results showed that the levels of PI, CPI, and the salivary enzyme alpha-amylase were significantly different among the studied groups suggesting no positive effect for Statins on periodontal health. On the other hand, no significant difference was observed in the level of total protein among them. Additionally, no significant relationship was found between the levels of PI and CPI and salivary alpha-amylase enzyme in the case (statin user) and control groups based on sex, age, oral health behaviors, or the duration of drug use.

Availability of data and material

The data that support the findings of this study are not openly available due to the reasons of sensitivity. They are available from the corresponding author upon reasonable request.

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Declarations

Conflict of interest

The authors have no conflict of interests to declare that are relevant to the content of this article.

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Ethical approval statement

Ethical approval was obtained from the Research Ethics Committee of Alborz University of Medical Sciences (identifier: IR.ABZUMS.REC.1402.102) on 8th July. 2023.

Consent to participate

Written informed consent was obtained from all participants before their inclusion in the study.

Author contributions

Arezoo Aghakouchakzadeh, Maryam Aghakouchakzadeh and Hessam Kakavand have made contributions to the concept and design of the study. Arezoo Aghakouchakzadeh, Bahareh Abdolali and Azadeh Babaei have been involved in the acquisition, analysis and interpretation of data for the work. Ali Lotfi, Khashayar Ghazanfari and Mina Teymori BadlehDareh have also been involved in interpretation of the data. All of the authors have been involved in initial drafting of the work to ensure the accuracy of its important intellectual content and also, they have been involved in drafting the later versions of the manuscript and approved the final version to be published.

Acknowledgement

We appreciate the Clinical Research Developmental Unit of the Dental school, Alborz University of Medical Sciences, for its support.

Tables:

p-value	Groups
0/002	Control and moderate dose
0/7	Control and high dose
0/005	High and moderate dose

Table 1. Determination and pairwise comparison of alpha-amylase enzyme levels among the studied groups.

P- value	Standard deviation	Mean	Drug	Dose

0/22	679/88	7343/84	Atorvastatin	Moderate
	744/3	6099/75	Rosuvastatin	
0/86	744/63	4809/61	Atorvastatin	High
	799/6	5098/47	Rosuvastatin	

Table 2. Determination and comparison of alpha-amylase enzyme levels in users of different drugs with two doses studied.

P- value	Standard deviation	Mean	Group
0/076	12	78/38	Control
	16/3	124/9	Moderate
	11/3	107/9	High

Table 3. Determination and comparison of amylase/total protein ratio in case and control groups.

Figures:

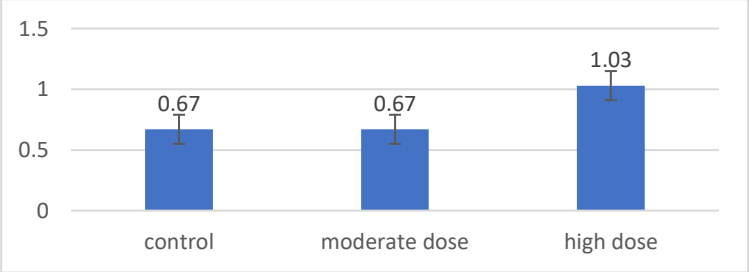


Fig1 Average PI level in case and control groups

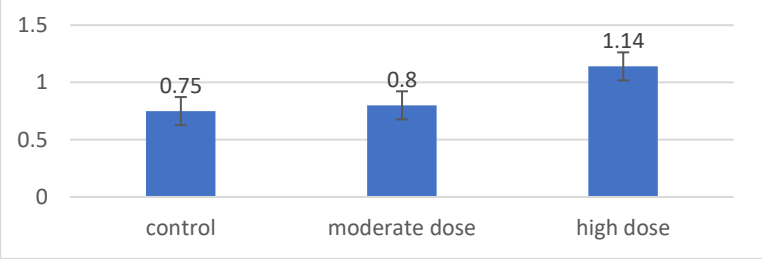


Fig2 Average CPI level in case and control groups

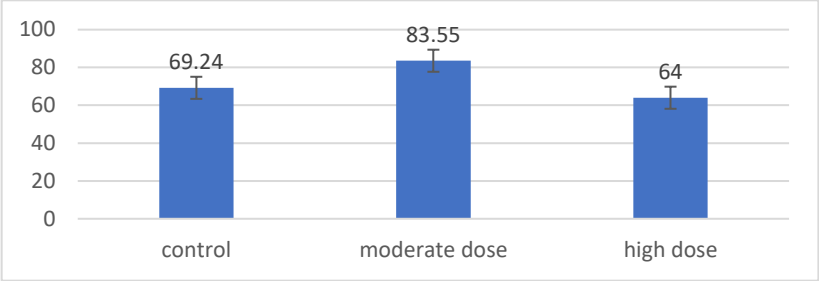


Fig3 Average Total Protein level in case and control groups

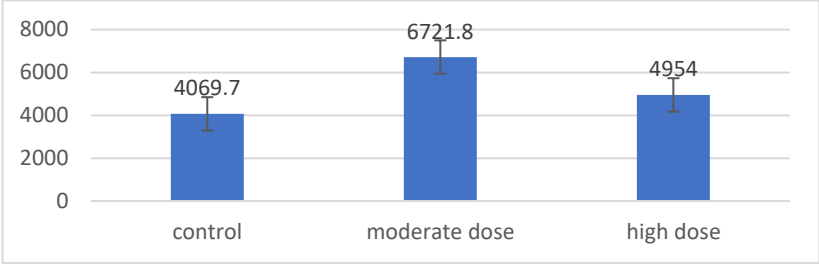


Fig4 Average Alpha-amylase level in case and control groups

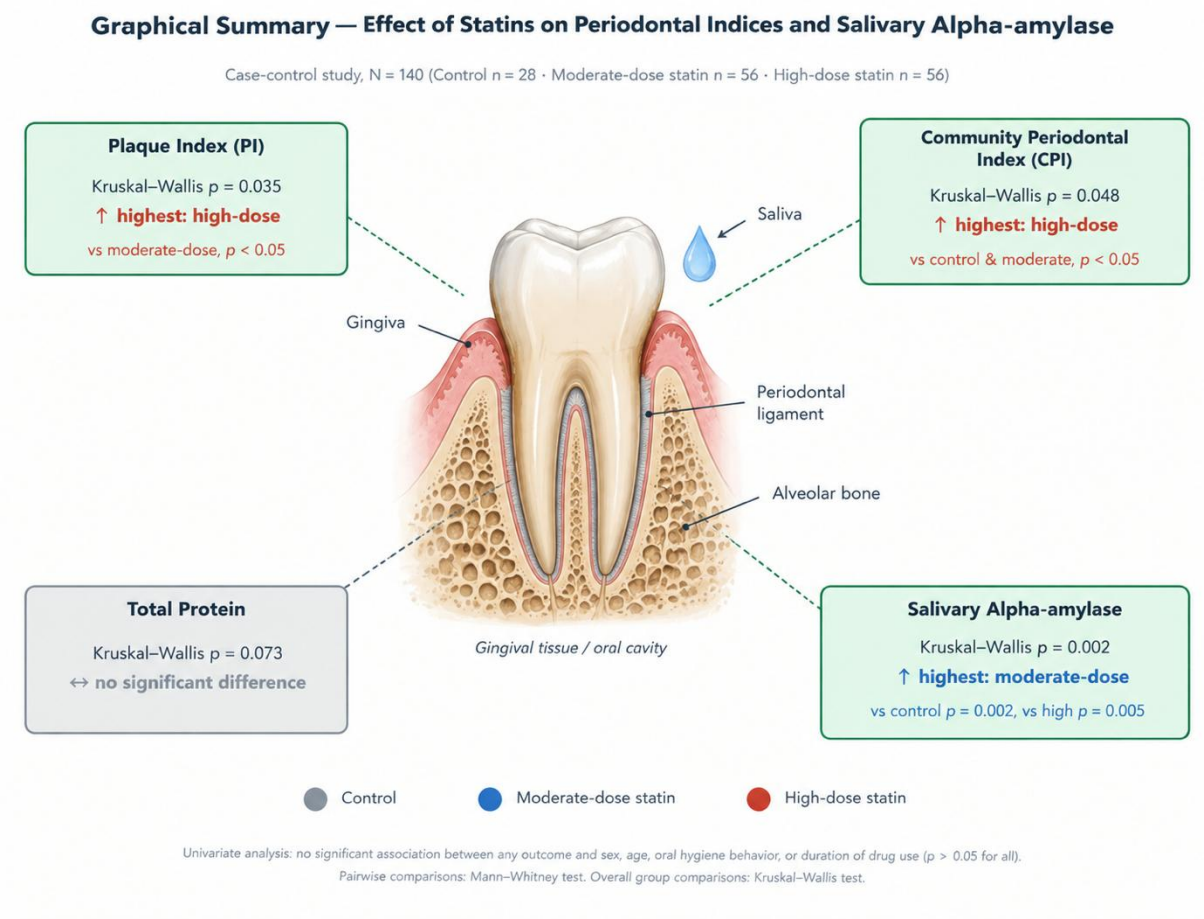


Figure5: Graphical summary of the results

Supplementary Files

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- Supplementarydocument.docx