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Effect of Non-surgical Periodontal Therapy on Interleukin 17 in Gingival Crevicular Fluid and Serum of Coronary Artery Disease Patients with Periodontitis

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ABSTRACT

Objective: The role of proinflammatory cytokines in chronic periodontitis (P) and coronary artery diseases (CAD) is currently under investigation. Interleukin 17 (IL 17) may play a role in the bidirectional pathogenesis of both conditions. The aim of the study is to explore the effect of non-surgical periodontal therapy on the gingival crevicular fluid (GCF) and serum levels of IL 17 in stable CAD patients with P.

Methods: Sixty-one individuals were enrolled in the study including 32 chronic periodontitis [16 periodontitis (CAD-P+), 16 coronary artery disease with periodontitis (CAD+P+)] and 29 periodontally healthy subjects [15 (CAD-P-) and 14 patients with coronary artery disease (CAD+P-)]. GCF and serum samples were obtained and probing pocket depth (PPD), clinical attachment level (CAL), plaque index (PI) and gingival index (GI) were recorded at baseline and three months post-treatment. GCF and serum IL 17 levels were analyzed by enzyme-linked immunosorbent assay (ELISA).

Results: We observed significant improvements in the whole mouth and sample tooth periodontal parameters (both with $p < .001$) and as well as a reduction in GCF volume ($p < .05$) following periodontal treatment in periodontitis groups (CAD-P+ and CAD+P+). Serum IL 17 levels significantly decreased in CAD+P+ group following the periodontal therapy (baseline: 24.39 (13.04) pg/ml; 3rd month 19.16 (15.07) pg/ml, $p < .05$) while no significant alterations were observed in GCF samples.

Conclusion: IL 17 is linked to proinflammatory response in atherosclerosis. Its post-treatment decrease in CAD+P+ group suggests IL 17 might be a useful biomarker for CAD-periodontitis relationship.

Keywords: Interleukin 17, Periodontal disease, Coronary artery disease, Inflammation.

1. INTRODUCTION

Periodontitis and cardiovascular disease (CVD) are both highly prevalent worldwide, and an altered immune response plays a crucial role in the pathogenesis of both conditions (1, 2). A substantial amount of data, including meta-analyses, has demonstrated a relationship between CVD and periodontitis. According to these studies, periodontal disease severity is associated with CVD risk and periodontitis is recognized as a risk factor for future cardiovascular issues (3, 4, 5). These epidemiological findings support the biological plausibility of a connection between periodontal disease and CVD, yet a definitive mechanism linking the two diseases has not been fully elucidated. The widely accepted opinion is that bacteremia from the ulcerated gingiva induces endothelial injury and activates the host immune response. As a result of immune activation, inflammatory cytokines may induce adaptive immunity, thereby promoting atherothrombogenesis (6). Recently, Corredor et al. (7) reinforces this paradigm by demonstrating the presence of subgingival plaque bacterial complexes in the blood of patients with CAD.

The Th1/Th2 paradigm provided the foundation for understanding the pathogenesis of several inflammatory conditions, including periodontitis. However, the discovery of Th17 cells has greatly broaden the understanding of autoimmunity and inflammation, addressing gaps that the Th1/Th2 paradigm could not explain in host immunity (8, 9). This paradigm shift has directed focus toward the role of Th17 cells in the pathogenesis of periodontitis. Different research groups have reported elevated IL 17 in periodontally inflamed tissues (10) and in GCF samples (11, 12). Additionally, a study on gingival biopsies found a positive correlation between IL 17 expression and clinical attachment loss (13).

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The impact of IL 17 on distinct parts of the cardiovascular system has been extensively studied. In an in vitro study, IL 17 was found to induce the synthesis of IL 6 and IL 8 in endothelial cells (14). When combined with TNFα, IL 17 significantly increased the levels of adhesion molecules, leading to enhanced leukocyte aggregation and endothelial activation (15, 16). Additionally, under in vitro conditions, IL 17A alone or in combination with IFNɣ elevated IL 8 and IL 6 levels in vascular smooth muscle cells compared to unstimulated cells (17). Beyond these in vitro findings, a clinical study revealed that serum IL 17A levels are positively correlated with the formation of complex plaque structures in asymptomatic individuals with ischemic symptoms (18). These results suggest that IL 17 may be a critical factor in the pathogenesis of CAD.

A meta-analysis consists of six randomized clinical trial showed that non-surgical periodontal therapy caused significant reduction in C reactive protein (CRP) in CAD patients and concluded that periodontal treatment could be an important preventive strategy for major cardiovascular events (19).

Based on these information, we hypothesized that non-surgical periodontal therapy may play an important role in improving IL 17 levels which is believed to be playing a crucial role in the relationship between periodontitis and CAD. The aim of this study is to determine the effect of non-surgical periodontal therapy on GCF and serum levels of IL 17 in chronic periodontitis patients with and without CAD.

2. METHODS

2.1. Subjects and Study Groups

This clinical trial was approved by Kırıkkale University Clinical Research Ethics Committee (project number: 2018/02/02) in accordance with the Declaration of Helsinki. Sixty-one individuals aged between 40-70 years were included and written informed consent was obtained. Patients were screened between February 2018 and March 2019. Baseline examinations of the participants who admitted to the Department of Periodontology were conducted and they were divided into 4 groups: Group 1 (CAD-P-): periodontally healthy individuals without stable coronary artery disease (n = 15); Group 2 (CAD-P+): chronic periodontitis patients without stable coronary artery disease (n = 16); Group 3 (CAD+P-): stable coronary artery disease patients with a healthy periodontium (n = 14); Group 4 (CAD+P+): stable coronary artery disease patients with chronic periodontitis (n = 16).

The exclusion criteria were determined as follows: individuals who smoke, who have had a myocardial infarction or bypass surgery within the last 6 months, who have unstable coronary artery disease symptoms, who have undergone periodontal therapy within the last 6 months, who have used antibiotics or anti-inflammatory drugs within the last 6 months, who have a systemic disorder other than coronary artery disease, who have fewer than 15 teeth, and pregnant or lactating women were all excluded.

Periodontal status was determined at the Kırıkkale University Department of Periodontology by assessing clinical and radiographic manifestations according to the criteria proposed by the Consensus Report of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions (20). Subjects with a PPD <3 mm, no attachment loss, no history of periodontal disease, and whole-mouth bleeding scores below 10% were classified as periodontally healthy individuals. Patients with a PPD ≥5 mm in at least two non-adjacent teeth per quadrant, bleeding on probing, other signs of inflammation, and periodontal bone loss affecting more than 30% of the root length were classified as having chronic periodontitis. Alveolar bone loss extending to the mid-third of the root and beyond was considered to be more than 30%. These criteria correspond to stage II/III periodontitis in the new classification system (20). To determine the coronary artery disease status of each participant, we evaluated cardiac reports approved by a cardiologist. Inclusion criteria for stable CAD patients were defined as having an obstruction in at least one major coronary artery, confirmed by angiography, and no current disease symptoms. Information about the medications used by patients during the study, including statins, was also collected. All periodontitis and CAD statuses were assessed by authors EO and SSS.

2.2. Clinical Parameters and Non-surgical Periodontal Therapy

Periodontal status was determined by measuring the whole mouth (WM), (PI) (21), (GI) (22), (PPD), and (CAL). Similarly, all clinical parameters were recorded for sampling teeth (ST). Panoramic radiographs were taken to assess the alveolar bone level. PPD and CAL were measured at six sites per tooth with a periodontal probe (Hu – Friedy, Chicago, IL, USA), while PI and GI were recorded at four sites.

All participants received oral hygiene instructions following diagnosis. In the periodontitis groups (CAD-P+ and CAD+P+), supragingival scaling and root debridement were performed using hand instruments (Hu-Friedy, Chicago, IL, USA). No antibiotics or anti-inflammatory drugs were prescribed. Patients in the CAD-P+ and CAD+P+ groups were recalled 12 weeks after non-surgical periodontal therapy.

Periodontal clinical measurements, along with GCF and serum sample collection, were recorded at two intervals (baseline and 3rd month following the periodontal treatment) in the periodontitis groups (CAD-P+ and CAD+P+). In the periodontally healthy groups (CAD-P- and CAD+P-), these measurements were taken only at baseline. All clinical measurements were conducted by a single investigator (SSS).

2.3. GCF and Serum Sampling

In the periodontitis groups (CAD-P+ and CAD+P+), GCF samples were collected from single-rooted teeth with a PPD of ≥5 mm and <7 mm, and ≥30% bone loss. For periodontally healthy individuals (CAD-P- and CAD+P-), maxillary anterior teeth were chosen for sampling. GCF samples were obtained by the method described by Rüdin et al. (23). Briefly, the crevicular site was isolated with cotton rolls and gently dried. Standardized strips were inserted into the gingival sulcus for 30 seconds to collect GCF from each tooth, and the GCF volume was determined by Periotron 800 (Oraflow Inc., Plainview, NY, USA). Two paper strips were collected from each participant and transferred into the Eppendorf tubes. Then, 250 µl of phosphate-buffered saline (PBS, pH 7.2) was added to the tubes, which were vortexed (Vortex, Velp Scientifica, Usmate Velate, Italy) for 1 minute, mixed on Orbital Shaker OS-10 (Biosan Inc., Riga, Latvia) for 20 minutes, and centrifuged in Hettich EBA 20 Centrifugal Machine (Hettich Inc., Tuttlingen, Germany) at 5800 rpm for 5 minutes.

Venous blood samples were obtained from the antecubital vein and collected in a BD Vacutainer ® SST™ II Advance Tube (Becton Dickinson Inc., NJ, USA). Each sample was centrifuged at 1500 rpm for 10 minutes and then isolated serum samples were transferred into the Eppendorf tubes. All samples were stored at – 80°C until analysis.

2.4. Biochemical Analysis

To prevent bias and ensure a blind lab analysis, each Eppendorf tube was assigned a number by author SSS during the collection of GCF and serum samples. The ELISA analysis was then carried out by author UK, who was unaware of the group assignments corresponding to each number.

GCF and serum IL 17 levels were measured by ELISA using a commercial kit (SEA063Hu, Cloud Clone Corp., Katy, TX, USA), following the manufacturer's instructions. Briefly, microplate wells were filled with 100 µl of the standard, serum, and GCF samples. Then, 100 µl of Detection Reagent A was added to each well. The plate was covered and incubated at 37°C for 60 minutes with gentle mixing. After incubation, the plate was washed with 350 µl of washing solution. Next, 100 µl of Detection Reagent B was added to each well, and the plate was incubated again at 37°C for 30 minutes. Following this, the wells were washed once more with the washing solution and 90 µl of substrate solution was added to each well. The plate was kept in the dark at 37°C for 20 minutes. The reaction was stopped by adding 50 µl of stop solution to each well. Optical densities were read at a wavelength of 450 nm. Standard concentrations and their corresponding optical density values, along with the optical density values of the samples, were recorded. A standard curve was plotted based on the optical densities and concentrations of the standards, and the concentrations of all samples were calculated using the linear regression equation derived from the standard curve. The sensitivity of the ELISA for IL 17 was less than 5.5 pg/ml, and the assay detection range for IL 17 was 15.6 pg/ml – 1000 pg/ml.

2.5. Statistical Analysis

The required sample size and power for the study were determined using the G Power Ver. 3.0.10 (Franz Faul, Universität Keil, Germany). To achieve 85% power with an effect size of f=0.25 and detect differences among groups, 14 participants were required in each group. Number and percentage (n, %) were used in the representation of demographic variables. Shapiro-Wilk test was conducted to detect the normal distribution of the data. Non-normally distributed data were presented as median (Interquartile Range – IQR). Kruskal-Wallis test was used to identify the differences among groups. In periodontitis groups (CAD-P+; CAD+P+), comparisons of variables at baseline and 3rd months post-treatment were evaluated using the Wilcoxon Signed Rank test. Mann-Whitney U test was applied to determine the groups leading to differences. SPSS for Windows Version 20.0 (SPSS Inc., Chicago, IL, USA) was used to conduct statistical analyses. Significance level set at p <.05.

3. RESULTS

3.1. Demographic Characteristics

A total of 61 individuals, aged between 40 and 70, 23 women (37.7%) and 38 men (62.2%), were included in this clinical study (Table 1). Regarding age comparison among groups, individuals in the CAD+P+ group were significantly older than the systemically healthy participants (p < .05). Similarly, gender distribution differed between groups (p < .05), with the CAD+P+ having significantly more males than the systemically healthy groups (CAD-P- and CAD-P+).

Table1. *Demographic characteristics.*

Demographic Characteristics	CAD-P- (n=15)	CAD-P+ (n=16)	CAD+P- (n=14)	CAD+P+ (n=16)	p value
Age (mean±SD)	50.93±4.66*	53.59±7.97*	56.14±9.29	60.23±6.93	**.002**
Gender (n %)					
Female	7(46.6)*	10(62.5)*	4(28.5)	2(12.5)	**.02**
Male	8(53.3)	6(37.5)	10(71.4)	14(87.5)	

*CAD-P+, chronic periodontitis group; CAD+P-, coronary artery disease group without periodontitis; CAD+P+, coronary artery disease group with chronic periodontitis. SD, standard deviation. *Significant difference compared to CAD+P+.*

3.2. Clinical Parameters and GCF Volume at Baseline

Table 2 shows the WM and ST clinical parameters. At baseline, all recorded values, including WM and ST, in the periodontitis groups were significantly higher than those in periodontally healthy individuals (p < .001). Among periodontally healthy subjects, the CAD+P- group had significantly higher full-mouth CAL compared to the CAD-P- (p < .05). Additionally, within the periodontitis groups, the CAD+P+ group had

significantly higher full-mouth CAL compared to the CAD-P+ group (p < .001).

Table 2. *Comparison of initial clinical parameters of whole mouth (WM) and sampling teeth (ST) among groups.*

Clinical Parameters	CAD-P- Median (IQR)	CAD-P+ Median (IQR)	CAD+P- Median (IQR)	CAD+P+ Median (IQR)	p value
WMPI	0.00 (1.00)	**2.00 (0.00)***	0.12 (1.00)	**2.00 (0.00)***	**.001**
WMGI	0.00 (0.50)	**2.00 (0.013)***	0.00 (0.50)	**2.00 (0.50)***	**.001**
WMPPD (mm)	1.90 (0.53)	**2.57 (0.41)***	2.04 (0.40)	**3.10 (0.65)***	**.001**
WMCAL (mm)	1.90 (0.53)	**2.77 (0.70)*#**	**2.13 (0.60)†**	**3.69 (1.28)***	**.001**
STPI	0.00 (1.00)	**2.00 (0.00)***	0.00(1.00)	**2.00 (0.00)***	**.001**
STGI	0.00 (0.00)	**2.00 (0.00)***	0.00 (0.63)	**2.00 (0.50)***	**.001**
STPPD (mm)	2.00 (1.00)	**5.00 (0.63)***	2.00 (0.50)	**5.50 (1.00)***	**.001**
STCAL (mm)	2.00 (1.00)	**5.00 (1.13)***	2.00 (0.50)	**5.50 (1.00)***	**.001**

*CAD-P+, chronic periodontitis group; CAD+P-, coronary artery disease group without periodontitis; CAD+P+, coronary artery disease group with chronic periodontitis. WMPI, whole mouth plaque index; WMGI, whole mouth gingival index; WMPPD, whole mouth probing pocket depth; WMCAL, whole mouth clinical attachment level; STPI, sampling teeth plaque index; STGI, sampling teeth plaque index; STPPD, sampling teeth probing pocket depth; STCAL, sampling teeth clinical attachment level. *Significant difference compared with CAD+P- and CAD-P-, p < .001. #Significant difference compared with CAD+P+, p < .001. †Significant difference compared with CAD-P-, p < .05.*

At the initial measurements, we observed a significant difference in GCF volume between groups (p < .05, Table 3). GCF volume in the CAD-P+, CAD+P-, and CAD+P+ groups was significantly higher than the CAD-P- group (p < .05). Moreover, the CAD-P+ group had significantly higher GCF volume than the CAD+P- and CAD+P+ groups. Compared to the CAD+P+ group, the CAD+P- group exhibited a markedly lower GCF volume (p < .05).

Table 3. *Comparison of initial GCF volume, IL 17 GCF and Serum levels among groups.*

	CAD-P- Median (IQR)	CAD-P+ Median (IQR)	CAD+P- Median (IQR)	CAD+P+ Median (IQR)	p value
GCF volume	32.00 (12.00)	**96.50 (53.00)*#**	**52.50 (41.63)***	**81.00 (30.00)*†**	**.001**
IL 17 /GCF (total amount) pg	**8.873 (8.2)#**	**5.508 (8.3)ɣ**	5.388 (2.5)	4.180 (3.3)	**.003**
IL 17/ GCF (concentration) pg/µl	**35.49 (32.30)#**	**22.03 (33.33)ɣ**	21.55 (9.84)	16.73 (13.34)	**.001**
IL 17/ Serum pg/ml	16.83 (8.96)	17.02 (9.42)	19.86 (8.86)	**24.39 (13.04)β**	**.044**

*CAD-P+, chronic periodontitis group; CAD+P-, coronary artery disease group without chronic periodontitis; CAD+P+, coronary artery disease group with chronic periodontitis. GCF, gingival crevicular fluid; IQR, interquartile range. *Significant difference compared with CAD-P-, p < .05. #Significant difference compared with CAD+P – and CAD+P+, p < .001. †Significant difference compared with CAD+P-, p < .05. ɣSignificant difference compared with CAD+P+, p < .05.βSignificant difference compared with CAD-P+, p < .05.*

3.3. IL 17 Levels in GCF and Serum at Baseline

At baseline, we observed a significant difference in IL 17 levels in GCF between the study groups (Table 3). The CAD-P – group had significantly higher levels of both the total amount (pg) and concentration (pg/ml) of IL 17 in GCF compared to the CAD+P- and CAD+P+ groups (p < .001). When evaluating the periodontitis groups, we found a significantly higher total amount and concentration of IL 17 in the CAD-P+ group compared to the CAD+P+ group (p < .05).

In addition to GCF, we measured serum IL 17 (pg/ml) levels at baseline. Levels in the CAD+P+ group were significantly higher compared to the CAD-P+ group (p < .05).

3.4. Clinical Parameters and GCF Volume in Chronic Periodontitis Patients after Initial Periodontal Therapy

In the chronic periodontitis groups (CAD-P+ and CAD+P+), a significant reduction was observed in all clinical parameters (including WM and ST) following non-surgical periodontal therapy compared to baseline (p < .001, Table 4). When comparing the two periodontitis groups, WMPPD and CAL in the CAD+P+ group were significantly higher than in the CAD-P+ group following treatment (p < .05, Table 4).

Table 4. *Comparison of clinical parameters of whole mouth (WM) and sampling teeth (ST) among groups at baseline and 3rd month in chronic periodontitis patients.*

Groups	Clinical Parameters	Baseline Median (IQR)	3rd month Median (IQR)	p value
CAD-P+	**WMPI**	2.00 (0.00)	**1.00 (0.75)***	**.001**
	WMGI	2.00 (0.013)	**1.00 (1.00)***	**.001**
	WMPPD (mm)	2.57 (0.41)	**2.26 (0.67)***	**.001**
	WMCAL (mm)	2.77 (0.70)	**2.33 (0.46)***	**.001**
	STPI	2.00 (0.00)	**1.00 (0.75)***	**.001**
	STGI	2.00 (0.00)	**1.00 (1.00)***	**.001**
	STPPD (mm)	5.00 (0.63)	**3.00 (1.50)***	**.001**
	STCAL (mm)	5.00 (1.13)	**3.00 (1.50)***	**.001**
CAD+P+	**WMPI**	2.00 (0.00)	**1.00 (0.94)***	**.001**
	WMGI	2.00 (0.50)	**1.00 (1.00)***	**.001**
	WMPPD (mm)	3.10 (0.65)	**2.50 (0.62)*#**	**.001**
	WMCAL (mm)	3.69 (1.28)	**3.03 (1.35)*†**	**.001**
	STPI	2.00 (0.00)	**1.00 (0.94)***	**.001**
	STGI	2.00 (0.50)	**1.00 (1.00)***	**.001**
	STPPD (mm)	5.50 (1.00)	**3.00 (1.50)***	**.001**
	STCAL (mm)	5.50 (1.00)	**3.25 (1.38)***	**.001**

*CAD-P+, chronic periodontitis group; CAD+P+, coronary artery disease with chronic periodontitis group. WMPI, whole mouth plaque index; WMGI, whole mouth gingival index; WMPPD, whole mouth probing pocket depth; WMCAL, whole mouth clinical attachment level; STPI, sampling teeth plaque index; STGI, sampling teeth gingival index; STPPD, sampling teeth probing pocket depth; STCAL, sampling teeth clinical attachment level. IQR, interquartile range. *Significant difference compared to Baseline, p < .001. #Significant difference compared to WMPD in CAD-P+ group at 3rd month, p < .05. †Significant difference compared to WMCAL in CAD-P+ group at 3rd month, p < .05.*

Consistent with the clinical parameters, we observed a significant reduction in GCF volume in both periodontitis groups compared to baseline after periodontal therapy ($p < .05$, Table 5). At the 3rd month, the GCF volume in the CAD-P+ group was significantly higher than in the CAD+P+ group ($p < .05$, Table 5).

3.5. GCF and Serum IL 17 Data in Chronic Periodontitis Patients after Initial Periodontal Therapy

Following periodontal therapy, we evaluated IL 17 levels in GCF compared to baseline. There was no significant change in either group for the total amount and concentration after treatment ($p > .05$, Table 5).

Regarding serum IL 17 levels, we observed a significant reduction in the CAD+P+ group compared to baseline following therapy ($p < .05$, Table 5).

Table 5. *Comparison of GCF volume, GCF and Serum IL 17 levels at baseline and 3rd month in chronic periodontitis groups.*

Groups		Baseline Median (IQR)	3rd month Median (IQR)	p value
CAD-P+	GCF volume	96.50 (53.00)	**80.00 (35.00)*#**	**.002**
	IL 17 /GCF (total amount) (pg)	5.508 (8.3)	3.19 (9.9)	.617
	IL 17/ GCF (concentration) (pg/µl)	22.03 (33.33)	12.77 (39.9)	.617
	IL 17/ SERUM (pg/ml)	17.02 (9.42)	11.16 (14.77)	.197
CAD+P+	GCF volume	81.00 (30.00)	**67.50 (45.00)***	**.020**
	IL 17 /GCF (total amount) (pg)	4.180 (3.3)	3.59 (3.71)	.317
	IL 17/ GCF (concentration) (pg/µl)	16.73 (13.34)	14.37 (14.84)	.617
	IL 17/ Serum (pg/ml)	24.39 (13.04)	**19.16 (15.07)***	**.046**

*CAD-P+, chronic periodontitis group; CAD+P+, coronary artery disease with chronic periodontitis group. GCF, gingival crevicular fluid; IQR, interquartile range. *Significant difference compared to Baseline, p = .002; p = .02, p = .046. #Significant difference in GCF volume in compared to CAD+P+ at 3rd month, p = .04.*

4. DISCUSSION

Immune system plays a crucial role in maintaining periodontal health; however, an excessive immune response can lead to periodontal tissue damage through the release of inflammatory mediators and destructive enzymes (24). Atherosclerosis develops as a result of an immune-inflammatory response, which is the underlying cause of the majority of cardiovascular events (25). Periodontitis can contribute to the body's overall inflammatory load and exacerbate pre-existing conditions such as diabetes and atherosclerosis (26). Therefore, reducing the inflammatory burden in the body can also decrease the risk of atherosclerosis and subsequent cardiovascular events. Current findings suggest that periodontal therapy may lower CVD risk by controlling biomarkers associated with it. For example, Vidal et al. (27) reported a significant decrease in IL-6, CRP, and fibrinogen plasma levels three months after treatment. IL 17, which plays a key role in the pathogenesis of both periodontal disease and CVD, was found significantly higher in the serum of individuals with chronic periodontitis and CAD compared to healthy individuals (28). In this clinical trial, we demonstrated that non-surgical periodontal therapy significantly reduced serum IL 17 levels in stable CAD patients with chronic periodontitis, in line with a marked improvement in periodontal health.

Increased plaque accumulation and age-related degenerative changes contribute to severe gingival inflammation in the elderly population (29). In addition to traditional risk factors such as gender, smoking, total cholesterol levels, and systolic blood pressure, age is also recognized as a risk factor for CVD (30). The prevalence of CAD increases significantly with age in both men and women (31). These findings highlight the impact of aging on both periodontal disease and CAD. In our study, we observed a significantly higher mean age in the CAD+P+ group, consistent with the literature, indicating the cumulative effect of both diseases. Periodontal disease is more common and severe in men compared to women of similar age (32). Similarly, the prevalence of CAD is higher in men across different age groups (33). In this study, significantly more males were enrolled in the CAD+P+ group compared to the CAD-P- and CAD-P+ groups, which aligns with previous findings.

To assess the periodontal status of each individual, we recorded PI, GI, PPD, and CAL across all groups. At baseline, the WM and ST periodontal parameters were significantly lower in the CAD-P- and CAD+P- groups compared to the periodontitis groups, which is consistent with the clinical manifestations of periodontitis. Within the periodontitis groups, PPD and CAL were significantly higher in the CAD+P+ group. Similarly, previous studies have reported a significant increase in periodontal parameters in individuals with coronary heart disease compared to healthy individuals (34). Systemic conditions can alter the immune response of the periodontium to dental plaque, leading to an enhanced acquired immune response that results in deeper periodontal pockets and greater attachment loss compared to healthy individuals. In this study, the improvement in WMPPD and WMCAL in the CAD+P+ group was markedly greater than in the CAD-P+ group at the third month following periodontal therapy. The further improvement in WMPPD and WMCAL in the CAD+P+ group, compared to the CAD-P+ group, may be associated with the use of statins in individuals with CAD.

Statins are inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA) in cholesterol synthesis. They are widely used to lower blood cholesterol levels and treat atherosclerosis (35). Additionally, statins possess antioxidant, anti-inflammatory, and angiogenetic properties (36). Several studies have explored the effects of statins on the periodontium. For instance, a retrospective study reported a lesser extent of deep periodontal pockets in individuals taking statins compared to a control group, attributing this difference to the anti-inflammatory effects of statins (37). Moreover, a meta-analysis examining the effects of local statin administration alongside mechanical

periodontal therapy found reduced probing pocket depths in the statin groups compared to the control (38). Similarly, a study evaluating systemic statin use among hyperlipidemic individuals following non-surgical periodontal therapy observed significant clinical improvements in subjects on statins (39). In our study, following periodontal therapy, we observed a greater decrease in WMPPD and WMCAL in the CAD+P+ group compared to the CAD-P+ group. This difference may be attributed to the anti-inflammatory activity of statins in addition to the mechanical treatment.

GCF is used for biomarker analysis in periodontitis (40). The volume of GCF increases in the presence of inflammation (41), and medications can influence both its volume and content (42, 43). At baseline, we observed significant differences in GCF volume between the groups. The higher GCF volume in the periodontitis groups corroborates the association between increased GCF volume and inflammation. The lower GCF volume at baseline and following periodontal therapy in the CAD+P+ group, compared to the CAD-P+ group, aligns with the understanding that anti-inflammatory drugs can affect both the amount and content of GCF (42, 43). Additionally, we found a significant negative correlation between baseline GCF volume and statin use ($p < .05$), supporting the observation of lower GCF volumes in the CAD+P – and CAD+P+ groups. The inflammatory burden in the body can impact an individual's immune response; therefore, the elevated GCF volume in the CAD+P- group compared to the control group may be due to altered immunity.

Sadeghi et al. (44) detected markedly higher IL 17 levels in the GCF of healthy individuals compared to those with chronic and aggressive periodontitis. The authors attributed this difference to the consumption of IL 17, which plays a prominent role in bone resorption in periodontitis. Similar studies have reported higher amounts of IL 17 in control groups compared to those with chronic periodontitis (45). For instance, Yetkin Ay et al. (46) observed lower IL 17 concentrations in the GCF of patients with aggressive periodontitis. Additionally, they did not find any significant difference in the total amount of IL 17 between groups, attributing this to the degradation of IL 17 in GCF and potential racial variations. Another study reported decreased IL 17 concentrations in regions adjacent to deep periodontal pockets (47), which they attributed to changes in the microenvironment during the early stages of periodontitis. Contrary to these findings, Majeed et al. (12) found higher total IL 17 levels in GCF samples from patients with chronic periodontitis compared to healthy controls. In line with the aforementioned studies, we detected low levels of IL 17 in the GCF samples of periodontitis groups. This finding may reflect either the degradation of IL 17 in GCF or alterations in the periodontal pocket environment. Additionally, we observed the lowest IL 17 levels in the CAD+P- group, which may be associated with the anti-inflammatory effects of statins.

According to Bartold et al. (26), the effect of periodontal treatment on a systemic condition needs to be evaluated to establish a plausible relationship. In this context, we assessed IL 17 levels following periodontal therapy in both GCF and serum samples. At baseline, serum samples showed significantly higher IL 17 levels in the CAD+P+ group compared to the CAD-P+ group, which may be attributed to the cumulative effect of coronary artery disease and periodontitis. Similarly, Qi et al. (28) reported elevated IL 23/IL 17 serum levels in individuals with both coronary heart disease and periodontitis. Following periodontal therapy, serum IL 17 levels were significantly reduced only in the CAD+P+ group, aligning with the notion that periodontal therapy decreases systemic biomarkers (48). Although a similar trend was observed in the CAD-P+ group, it was not statistically significant. Conversely, when comparing baseline and post-treatment samples, no significant changes in IL 17 levels were observed in the GCF samples of the CAD-P+ and CAD+P+ groups.

As previously mentioned, statins possess strong anti-inflammatory properties. To address why a significant change was observed only in serum samples, but not in GCF samples, following periodontal therapy in the CAD+P+ group, we examined the effect of statins. We divided the CAD+P+ group into statin (+) and statin (-) subgroups. When comparing IL 17 levels in GCF samples between statin (+) and statin (-) participants, no significant difference was observed ($p > .01$). Similarly, in serum samples, there was no marked difference between statin (+) and statin (-) individuals ($p > .01$). As noted earlier, statins have notable effects on both local and systemic cytokine levels in addition to clinical parameters. To fully elucidate the impact of statins on IL 17 expression levels, larger study groups are needed. Another potential factor contributing to the higher IL 17 levels in GCF following therapy could be the presence of dental plaque. The presence of dental plaque may have induced low-level inflammation, thereby masking the effect of therapy on IL 17 levels in GCF samples after periodontal treatment in the periodontitis groups.

Hashmi and Zeng (49) reported lower plasma IL 17 levels in stable angina patients compared to the unstable angina patients. We observed similar serum IL 17 levels both in CAD+P- and CAD-P- groups. This might be the reflection of a stable period in the CAD group.

In this study, some limitations should be acknowledged. In the study design, an additional time point before the third month of post treatment, such as the fourth week after periodontal therapy, could have been included to improve the oral hygiene habits of the study population, which would have ultimately improved the results. Additionally, implementing antimicrobial plaque control in the first week following periodontal treatment would have increased each patient's awareness of oral hygiene. Future studies with a better dental plaque control would yield significant findings in particular on GCF samples.

5. CONCLUSION

The increased expression of pro-inflammatory cytokine IL 17 in serum found in the present study suggests a possible association between chronic periodontitis and CAD. It can be thought that IL 17 plays a key role in connecting both

conditions. However, the current evidence is not strong enough to draw definitive conclusions. Future longitudinal studies with larger patient populations and controlling for confounding factors and comorbidities are needed to expand our knowledge and elucidate the role of periodontal inflammation in the pathogenesis of atherosclerotic disease.

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Research idea: SSS, EO, EB
Design of the study: SSS, EO
Acquisition of data for the study: SSS
Analysis of data for the study: UK, SSS
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