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Original Research

Effect of Peri-Implant Disease on Adropin Levels: A Cross-Sectional Pilot Study

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ABSTRACT

Objective: Adropin is a peptide hormone related to the inflammatory process of several systemic diseases. The inflammatory characteristics of peri-implant diseases are known. This study aimed to measure and compare the level of adropin in peri-implant sulcus fluid (PISF) in patients with peri-implant disease.

Methods: Overall, 75 individuals were included in this cross-sectional study. Each of the three study groups [healthy (H), peri-implant mucositis (PM), and peri-implantitis (PI)] consisted of 25 patients. During the periodontal examination, periodontal pocket depth (PD), plaque index (PI), and gingival index (GI) scores were recorded, and marginal bone loss (MBL) was measured using ImageJ. PISF samples were collected from dental implants. Adropin level in PISF was analyzed using the enzyme-linked immunosorbent assay (ELISA) technique. All clinical and biochemical parameters were statistically analyzed using SPSS v22.

Results: PD, PI, and GI parameters were noted to be significantly higher in the PM and PI groups compared with the H group. PI group showed statistically significant differences related to MBL compared with the other groups ($p<0.05$).

Conclusion: Therefore, adropin may prove to be a useful diagnostic tool in the diagnosis of peri-implant disease. However, further studies are needed to explore the different biochemical parameters in PISF, thereby helping to understand the interaction of adropin with other mediators.

Keywords: Adropin, periodontal disease, peri-implant disease

INTRODUCTION

Dental implant treatment has become widespread and has garnered popularity because of various factors, such as prolonged life expectancy, aging, increased tooth loss, and discomfort from fixed dentures and removable prosthesis (1). Nevertheless, the widespread use of dental implants has led to an increase in biological complications. The most significant among these complications are peri-implant mucositis (PM) and peri-implantitis (PI) (2). PM is a reversible inflammation of the soft tissues around the implant without clinical and radiographical bone loss. On the other hand, PI is the decrease in alveolar bone associated with inflammation of the bone and soft supporting tissues of the dental implant. PM is considered an initial lesion and may return with patient self-care or periodontal therapy (3).

The development of infection and inflammation around the dental implants are closely related to the presence of microorganisms. The salivary glycoproteins may attach to the exposed inorganic surfaces shortly after implant placement. Subsequently, microorganisms colonize on this glycoprotein layer. Finally, in peri-implant diseases, a gram-negative anaerobic microflora, generally similar to periodontitis, becomes dominant (4). Although the primary etiological agent for the onset of periodontal and peri-implant diseases is dental plaque, the immune mechanisms triggered by host-bacterial interactions in the body also release a large number of inflammatory mediators, such as cytokines (by disrupting the balance between protective and destructive immune mechanisms), which are critical factors of destruction. Some biological mediators, such as cytokines, peptides, and hormones, were noted to be related to periodontal and peri-implant disease (5). Moreover, almost all mediators related to periodontal and peri-implant disease were noted to be present in the gingival crevicular fluid (GCF) and peri-implant sulcus fluid (PISF). Once the periodontal disease begins, the capillary vessels dilate, and serum proteins are released into the GCF and PISF, besides an increase in the fluid flow rate. Therefore, PISF has the potential to provide crucial information regarding the periodontal health and disease conditions owing to its unique structure (6).

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Adropin is a peptide hormone first discovered in 2008 by Kumar et al. (7) It has an approximate molecular weight of 7.927 kDa, consists of 76 amino acids, and is encoded through the energy-related gene code (*ENHO*-energy homeostasis associated). A study conducted by Kumar et al. (7) observed that blood serum adropin levels increased in high-fat nutritional conditions, thereby suggesting that adropin hormone may play a role in the metabolism of lipogenesis in the liver. In another study, the lack of adropin hormone was observed to be associated with increased adipose tissue and insulin resistance. Therefore, it was concluded that the adropin molecule might be related to glucose metabolism, insulin resistance, dyslipidemia, and metabolic syndrome. Proving the association of adropin with insulin resistance and obesity opened the avenues for several clinical studies on this subject (8). In such a study conducted by Celik et al. (9), the serum adropin levels of patients with gestational diabetes mellitus (GDM) and healthy controls were compared, and the blood serum adropin levels were determined to be significantly lower in patients with GDM compared with the control group. Moreover, low adropin levels may be involved in the pathogenesis of diabetes. In another study by Wu et al. (10), the relationship between coronary atherosclerosis and serum adropin levels was investigated in patients with and without diabetes and revealed that serum adropin levels decreased with an increase in the coronary atherosclerosis score in all patients. After these milestone studies, low levels of adropin were proven to be associated with the progression of coronary atherosclerosis and increased risk of cardiovascular disease. Besides, further studies that explored adropin have revealed its protective and regulatory role in endothelial function (9).

In recent years, adropin has been considered an essential mediator in the pathogenesis of some systemic diseases, such as obesity, diabetes, cardiovascular diseases, and atherosclerosis. Furthermore, these systemic diseases have been noted to be related to the severity of the periodontal disease. Nonetheless, upon a literature review, we found no studies that evaluated adropin levels in PISF in patients with peri-implant diseases.

Hence, considering all this information, this study aimed to evaluate the PISF adropin levels in healthy and diseased dental implants to obtain meaningful information regarding the role of adropin in the etiopathogenesis of peri-implant diseases.

METHODS

Study population

Overall, 75 non-smoker individuals (36 females, 39 males) who were admitted to the Gaziantep University Faculty of Dentistry Periodontology for periodontal treatment were included in this cross-sectional study. This study was conducted per the Helsinki Declaration, and approval was obtained from the Gaziantep University Clinical Studies Ethics Committee on March 13, 2017, (No.: 2017/101). All participants were provided verbal or written information regarding the study, and their consent was obtained.

Main Points:

- Peri-implantitis and peri-implant mucositis are inflammatory diseases, because of that; sign of inflammatory process could be observed in peri-implanter sulcus fluid.
- Adropin can be a new biomarker in the peri-implanter sulcus fluid to identify these inflammatory conditions.
- Peri-implanter sulcus fluid can serve as a reservoir for inflammatory biomarkers.

Inclusion and Exclusion Criteria

The inclusion criteria were age over 18 years, no systemic diseases (such as diabetes, cardiovascular disease, atherosclerosis, and obesity), no antibiotics and anti-inflammatory drug use in the preceding 6 months, and no dental or periodontal treatment in the preceding 6 months. Besides, it was ensured that the dental implants were functional for at least 12 months after loading and were not supported by overdentures and bridges, and only dental implants with a single crown were included in the study. The 2017 EFP and AAP workshop criteria were considered when diagnosing healthy implants (H), peri-implant mucositis (PM), and peri-implantitis (PI) (11, 12). For standardization, tissue-level implants were not included in the study, and all study groups had Straumann (Basel, Switzerland) and MIS (C1, Savion, Israel) implants with conical connections.

Clinical Examination

Pocket depth (PD), plaque index (PI), and gingival index (GI) scores were recorded. Clinical periodontal and peri-implant examinations were performed by an initially calibrated periodontist (HG). Intraexaminer k values were 0.95 (PD) and 0.82 (CAL). Bleeding on probing was considered positive if bleeding occurred 15 seconds after probing. The clinical parameters were measured using a plastic periodontal probe (Hu-Friedy, USA). Furthermore, to determine the presence of bone loss around the dental implants, all patients underwent periapical or panoramic radiographs, and radiological bone loss (MBL) was measured using the ImageJ program (National Institutes of Health, Bethesda, MD, USA).

PISF Sampling and Analysis

PISF samples were collected based on the radiographic data before performing the clinical measurements. Before sample collection, the implant was isolated with cotton pads, gently dried using air or water spray, and then the paper strips were placed into the pocket until slight pressure was felt. After waiting for 30 seconds, the paper strips (Periopaper®, OraFlow Inc., USA) were placed in a pre-calibrated Periotron 8000 instrument to measure PISF volume. The volume was then recorded after measurements. Samples were stored at –80°C until the analysis day. Adropin levels in PISF samples were measured per the manufacturer's instructions (Cloud-Clone Corp. Adropin kit) by using the enzyme-linked immunosorbent assay (ELISA) method (9).

Statistical Analysis

Statistical evaluation of the data was performed using IBM Statistical Package for the Social Sciences (IBM SPSS Corp.; Armonk, NY, USA) v22.0 for Mac. The Shapiro-Wilk test was used to assess whether the numerical data had a normal distribution. The Mann-Whitney U test was used to compare the non-normally distributed variables among groups. ANOVA and LSD multiple

Table 1. Differences, mean, and standard deviations of adropin levels in PISF

	PI (n=25) α	PM (n=25) β	H (n=25) γ	p
PI	2.42±0.55	2.39±0.38	0.23±0.29	*αγ, βγ
PD (mm)	6.56±2.25	5.45±2.31	1.32±1.63	*αγ, βγ
GI	2.73±0.06	2.36±0.35	0.16±0.21	*αγ, βγ
MBL (mm)	6.00±1.46	1.06±0.15	0.43±0.33	** αγ, αβ
PISF Volume (µL)	0.98±0.21	0.69±0.29	0.09±0.1	**αγ,*βγ
Adr (ng/30sn)	0.83±0.27	0.36±0.25	0.20±0.21	* αγ

PI(α): Peri–implantitis; PM(β): Peri–implant mucositis; H (γ): Peri–impalnter health; PI: Plaque index; PD: Probing depth; GI: Gingival index total; MBL: Marginal bone loss.
†mean±SD deviation.
*Statistically significant (p<0.05). **Statistically significant (p<0.001)

comparison tests were used for comparison of normally distributed numerical data, and Kruskal–Wallis and all pairwise tests were used for comparison of normally distributed data. Descriptive statistics were presented as mean±standard deviation. A value of p<0.05 was considered statistically significant.

RESULTS

The mean adropin levels in PISF and the standard deviations are listed in Table 1. Overall, 75 patients (H, n=25; PM, n=25; and PI, n=25) in the age range of 28–65 years completed the study. Although PD, PI, and GI parameters were observed to be significantly higher in the PM and PI groups compared with the H group, no statistically significant differences related to pocket depth (PD) and GI were noted between PM and PI groups. Regarding MBL, the PI group had significantly higher MBL than the other groups (p<0.05). A statistically significant difference was observed upon the comparison of H-PI and H-PM groups regarding the PISF volume parameter (p<0.05). Regarding the PISF adropin levels, a statistically significant difference was noted between PI and H groups (p>0.05), (p<0.05).

DISCUSSION

Currently, mediators like cytokines and hormones can be used to clinically diagnose periodontal diseases, as well as evaluate the treatment efficacy. Adropin is a peptide hormone involved in the endothelial function through activation of the vascular endothelial growth factor receptor-2 (VEGFR-2) and phosphatidyl inositol-3-phosphate kinase (PI3K) pathways in the vascular wall endothelium (13). Notably, endothelial wall dysfunction occurs in periodontal and peri-implant diseases (14). Therefore, we purposed to investigate the concentration of adropin in PISF samples in patients with the peri-implant disease, besides discerning differences, if any, between healthy and diseased implants. Furthermore, adropin levels in PISF has not been examined before, and this study is the first study on this subject. Based on this study findings, adropin levels in PISF were noted to be statistically significantly increased in patients of the PI group compared with the H group. Moreover, clinical data related to PI, GI, and PD values were concordant with other studies (15).

Leptin and adiponectin, which are peptide hormones like adropin, are involved in similar functions in the body. It has been recently discovered that leptin and adiponectin, known for their effects on body weight regulation, body metabolism, and proliferation, have a direct effect on the immune responses and may be part of some inflammatory diseases. Leptin is thought to be a pro-inflammatory cytokine in the inflammatory response, whereas adiponectin mediates anti-inflammatory effects and functions in cell proliferation, differentiation, and regeneration (16, 17). When the literature was examined, different results were obtained regarding the relationship between periodontitis and leptin and adiponectin (16, 18-20). The reason for this difference is that most studies on leptin and adiponectin were cross-sectional, and the number of comparative studies was limited. Therefore, the cause-effect relationship between periodontitis and leptin and adiponectin levels has rarely been explored. Hence, because of the variation in the sample sizes and the differences between the qualifications and methods of these studies, no definite result could be achieved. In addition, a study investigating the level of VEGF in patients with periodontitis determined that the total amount of VEGF in GCF collected from the diseased regions was higher than that collected from clinically healthy regions (21). Johnson et al. (22) investigated the VEGF and IL-6 levels in patients who were healthy or had gingivitis, 4–6 mm periodontal pockets, and periodontitis, and observed that VEGF and IL-6 levels were lower in healthy individuals compared with patients with periodontitis. Although IL-6 concentration increases with increasing PD, VEGF concentration in 4–6 mm periodontal pockets was greater than that in >6 mm pockets. This finding is probably because of the increased VEGF owing to the increased vascular network in the initial and progressive phases during the transition from gingivitis to periodontitis. Another study compared the VEGF levels in patients who were healthy or had gingivitis, chronic periodontitis, and periodontal treatment. In chronic periodontitis, the VEGF level was noted to be significantly higher than the other groups, and the VEGF level decreased after the periodontal treatment (21). Notably, there is a relationship between adropin and VEGF levels. Therefore, considering this fact, it is appropriate to compare the present study data with VEGF. According to all these studies, the increase in adropin levels in patients with PI is thought to be due to the increase in VEGF, which is a pro-inflammatory factor in inflammatory diseases. Because adropin is a new mediator, more comprehensive and multicenter studies are needed to

fully understand the relationship between adropin, a peptide hormone, and several systemic diseases, in relation to the periodontal tissues. Considering all the past studies that discussed the role of adropin levels in the field of medicine, adropin levels in PISF may be increased because of the inflammatory character of peri-implant diseases (especially, peri-implantitis). Consequently, it can be stated that these inflammatory processes and responses are not only destructive but also protective in peri-implant disease. In addition, in recent years, adropin has been considered a crucial mediator in the pathogenesis of some systemic diseases, such as obesity, diabetes, cardiovascular diseases, and atherosclerosis.

In the present study, PI (23), PD, GI (24), and MBL values were recorded for the assessment of oral care and periodontal status of patients. These indexes were preferred because they were widely used and could be compared with other studies (25). PISF is affected by several factors, such as tooth brushing, mechanical irritation, probing, circadian rhythm, saliva-blood contamination, ambient temperature, individual body temperature, medications, smoking, and diabetes. In our study, to minimize the change in the PISF flow because of mechanical irritation from clinical measurements, PISF was collected before clinical measurements, based on the radiographs. PISF measurements of all individuals within the scope of the study were performed in the morning (09.00 am to 12.00 pm) to prevent PISF amounts from being affected by the circadian rhythm.

CONCLUSION

Within the limitations of the present study, it can be concluded that PI is an inflammatory condition that can result in resorption of alveolar bone. Adropin may be a future diagnostic tool for the peri-implant disease, especially in PI; however, to prove this, multicenter studies are needed that can evaluate the various biochemical parameters of peri-implant diseases.

Ethics Committee Approval: Ethics committee approval was received for this study from the Gaziantep University Clinical Studies Ethics Committee on 13/03/2017 (no: 2017/101).

Informed Consent: Written/Verbal informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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