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Araştırma/ Research Article

THE LEPTIN LEVELS OF OBESE AND NORMAL WEIGHT ADOLESCENTS WITH HEALTHY GINGIVA AND GINGIVITIS: EFFECTS OF PERIODONTAL THERAPY ON THE PARAMETERS

PERİODONTAL OLARAK SAĞLIKLI VE GİNGİVİTİSLİ OBEZ VE NORMAL KİLOLU ADOLESANLARDA LEPTİN SEVİYELERİ: PERİODONTAL TEDAVİNİN BU DEĞERLER ÜZERİNE ETKİLERİ

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ABSTRACT

Aim: The purpose of our study was to assess the role of leptin, a hormone secreted by adipose tissue, in the association of obesity and periodontal disease.

Material and Methods: Fifty-six adolescents volunteered to participate in this study. The participants were divided into two groups (obese / normal) and each group was then divided into two subgroups (gingivitis / healthy gingiva). All of the adolescents were measured for clinical indexes such as plaque index (PI) and gingival index (GI). Levels of leptin in the gingival crevicular fluid (GCF) samples and serum leptin levels were determined in blood samples by enzyme linked immune sorbent assay (ELISA).

Results: Blood leptin concentration (BLC) was higher in obese subjects than normal weight subjects (p<0.001). Although not statistically significant, BLC was higher in subjects with gingivitis (p=0.68) and decreased after periodontal therapy (p=0.90). GCF leptin concentration (GLC) levels were also higher in subjects with healthy gingiva (p=0.003) and the obese group (p=0.78), and it increased significantly after periodontal therapy (p<0.001). PI was positively correlated with BLC, PI and GI was negatively correlated with GLC, BLC and GLC were negatively correlated.

Conclusion: While the periodontal disease progressed, there was a decrease in GCF leptin concentration and an increase in blood leptin concentration. This observation suggests that leptin may be a protective agent for gingiva. Greater decrease of GCF leptin concentration in obese subjects with gingivitis than in normal weight subjects with gingivitis can be evidence that disease can be more severe in obese subjects.

Key words: Obesity, gingivitis, gingival crevicular fluid

ÖZ

Amaç: Çalışmamızın amacı yağ dokusu tarafından salgılanan bir hormon olan leptinin obezite ve periodontal hastalık ilişkisindeki rolününün değerlendirilmesidir.

Gereç ve Yöntem: Çalışmamıza gönüllü olarak 56 adolesan birey katıldı. Bireyler vücut kitle indeksine göre obez ve normal kilolu olarak iki gruba; her bir grup, kendi arasında gingivitisli ve periodontal sağlıklı dişetine sahip olanlar şeklinde iki alt gruba ayrıldı. Çalışmaya dahil edilen bütün bireylerin plak indeksi (PI) ve gingival indek (GI) gibi klinik indeksleri kaydedildi. Dişeti oluğu sıvısı (DOS) ve kan serumu leptin seviyeleri enzyme linked immune sorbent assay (ELISA) testi ile değerlendirildi.

Bulgular: Obez bireylerin kan leptin konsantrasyonunun (KLK) normal kilolu bireylerin KLK'sından daha yüksek olduğu tespit edildi (p<0.001). İstatistiksel olarak fark olmamasına rağmen gingivitisli bireylerin KLK'sı daha yüksekti (p=0.68) ve periodontal tedaviden sonra azaldı (p=0.90). Dişeti oluğu sıvısı leptin konsantrasyonu (DLK) periodontal sağlıklı dişetine sahip bireylerde (p=0.003) ve obez grupta (p=0.78) daha yüksekti ve periodontal tedavi sonrası istatistiksel anlamlı şekilde arttı (p<0.001). PI, KLK ile pozitif; PI ve GI, DKL ile negatif korelasyon gösterdi. KLK ve DLK arasında ise negatif korelasyon tespit edildi.

Sonuç: Dişetinde sağlıktan hastalığa doğru gidildikçe DLK düşerken, KLK yükselme eğilimi göstermektedir. Bu durum leptinin dişetinde koruyucu bir ajan olabileceğini düşündürmektedir. Obez gingivitisli bireylerde normal kilolu bireylere göre DLK'nun daha çok düşmesi, hastalığın daha ağır seyredebileceğine dair bir kanıt olabilir.

Anahtar Kelimeler: Obezite, Gingivitis, Dişeti oluğu sıvısı

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INTRODUCTION

Gingivitis is a local infection, occurring when the balance between bacterial accumulation in the gingival sulcus and the defense response of the host are disturbed[1]. Although the most important etiological agent inducing inflammation is microorganisms, the role of chemical mediators is also great, such as leptin[2-4].

Leptin is a adipose tissue hormone that has functions in metabolic and vascular biology[5, 6]. It regulates food intake and energy metabolism with a negative feedback effect on the hypothalamus, and helps to prevent developing of obesity[6]. In fact, leptin plays an important role together with insulin in regulating energy balance and body weight; therefore, decreased leptin production in adipocytes or a marked resistance to leptin leads to the development of obesity[7]. Leptin also has functions in the immune system and protects the host against infection[3, 8].

Obesity is the accumulation of excess fat in the body that l disrupts health[9]. It is a complex multifactorial disease characterized by increased endocrine and metabolic changes, and occurs when the amount of energy taken by foods is greater than the amount of energy consumed by metabolism and physical activity[10]. Existing studies support the idea that adipose tissue stores inflammatory cytokines and increased body fat promotes an active host response in diseases (e.g., periodontal disease)[11-14]. The relationship between obesity and periodontal disease was first shown in 1977, and this relationship is supported by many subsequent studies[15, 16].

In the literature, there are different opinions explaining the relationship between obesity and periodontal disease. One of the opinions is that overweight adolescents have unhealthy and inadequate dietary habits, increasing the risk of periodontal disease[17, 18]. In another opinion, this association is explained by changes in host immunity and increased stress level due to excess fat gained in the early stages of life[17, 18].

In light of the available literature, it is also seen that adipose tissue-derived cytokines and hormones may play a pivotal role in the relationship between obesity and periodontal disease[12,19,20]. It may be because the fat tissue is not just a passive triglyceride reservoir; it also produces adipokines and adipocytokines which can affect periodontal tissues at high levels[21]. Various studies have demonstrated the close association between adipokines such as leptin, adiponectin and resistin, and the inflammatory process[22-25]. There are also studies evaluating healthy and diseased gingiva leptin concentration, and it has been reported that there may be a relationship between the progression of periodontal disease and leptin[2-4, 26, 27]. The aim of this study is to evaluate the effect of leptin, an adipose tissue-derived cytokine, in obesity and periodontal disease involvement.

MATERIALS AND METHODS

Subject selection

This study was approved by the ethics committee (Ataturk University Ethics committee of health sciences, No: 2007.2.1/8); and the Declaration of Helsinki protocols were followed. Fifty-six adolescents, 12 to 17 years of age, were included in this study. Informed consent forms prior to participation were signed by participants and their parents. The participants were divided into two groups with 28 each: obese and normal based on their body mass index (BMI) which was prepared for Turkish children by Bundak et al[28]. Each group was further divided into two subgroups: subjects with gingivitis (n=20) and subjects with healthy gingiva (n=8). Certain criteria were noted in the selection of the individuals included in the study: the participants had no history of systemic disease or periodontitis; they had not used any medicine that may affect their periodontal status; and they had not received periodontal treatment within six months. Also, smokers were excluded from the study.

According to present study protocol, periodontal parameters were assessed including gingival index (GI)[29] and plaque index (PI)[30] at six points around each tooth by Williams periodontal probe (Hu-Friedy, Chicago, IL, USA). Also, the measurements and the gingival crevicular fluid (GCF) samples were recorded by the same examiner (intra-exam calibration).

GCF and blood samples

The gingival crevicular fluid (GCF) samples were obtained from at least four sites for biochemical analyses (especially from the maxillary anterior area). Each tooth region was dried with air- spray and isolated carefully with cotton rolls without causing irritation. GCF samples were taken after PI recording, and before GI recording to prevent mechanical irritation and bleeding due to probing. Suction was used to prevent contamination with saliva and blood. GCF samples were collected by Periopaper paper strips (ProFlow Inc. , Amityville, NY, USA). They remained in sulcus for 30 seconds. Blood and saliva contaminated samples were not included. The quantity of GCF was

measured by the Periotron 8000 device (ProFlow Inc. , Amityville, NY, USA).

Four milliliters of peripheral venous blood samples were collected from participants. The samples were left for one hour at room temperature and then the serum was separated by centrifugation at 3000 rpm for 5 minutes.

Both serum and GCF samples were maintained in Eppendorf tubes under appropriate conditions (-80^{o}C).

Periodontal treatment

All adolescents with gingivitis received periodontal treatment; phase-I periodontal therapy was performed and oral hygiene instructions were given. The treatment was not supported with any medication. These adolescents were followed up after mechanical periodontal treatment. After this treatment and follow-up, GCF and blood samples, measurements of clinical indexes were obtained again after a week.

Biochemical analysis

The strips were centrifuged at 3000 rpm, for 15 minutes two times, adding 100 ml of Hank's equilibration solution containing 0.5% bovine albumin in order to release the leptin contained in the strips. GCF and blood leptin levels were analyzed by standard enzyme-linked immunosorbent assay apparatus using Leptin ELISA plasma and serum kit (BioSource Int., Camarillo, CA, USA) according to the manufacturer's protocol[3].

To each reagent was placed 50 ml standard, control and samples, then 100 ml of anti-leptin conjugate was added to them. Then 50 ml of incubation buffer was added; horizontal shake was made at 700± 100 rpm and incubated for two hours and evacuated. The reagents were washed four times with 0.4 ml wash solution and then evacuated. Within 15 minutes, 100 ml of the chromogenic solution was added by pipette into the empty reagents. A horizontal shake was done at room temperature for 30 minutes at 700 ± 100 rpm, protected from sunlight. Then stop reagent was added to the 200 ml pipette. The leptin concentration values, blood leptin concentration (BLC) and GCF leptin concentration (GLC) were obtained by reading at 405 nm in spectrophotometer.

Data analysis

The statistical analysis was performed using a statistical software program (SPSS Inc., version 19.0, Chicago, IL, USA). In this study, the multivariate analysis of variance (MANOVA) test was used for differences in variables (BLC, GLC, GI and PI) because the number of dependent variables was more than two (p<0.05). The MANOVA test reduced the level of error that would result from an excessive number of tests.

Model=$Y_{1.2.3.4}$=Intercept+General health status+ gingival health status+gender+age

Normalities of distributions were tested using the Shapiro-Wilk test. ANOVA or Kruskal-Wallis test , Tukey or Mann-Whitney U test and Wilcoxon test were applied for statistical evaluation (p<0.05). In addition, Pearson's correlation test was used to determine the relationship between variables.

RESULTS

Demographic parameters

The distribution of adolescents according to general health status, gingival health status and gender are shown in Table 1.

Table 1. General health status, gingival health status and gender

General health status	Gingival health status	Gender
Healthy subjects (Normal weight) (n=28)	Healthy gingiva (n=8)	Female (n=5) Male (n=3)
	Gingivitis (n=20)	Bayan (n=13) Male (n=7)
Obese subjects (n=28)	Healthy gingiva (n=8)	Female (n=6) Male (n=2)
	Gingivitis (n=20)	Female (n=13) Male (n=7)
Total= 56	Total=56	Total=56

Clinical parameters

It was seen that general health status (p=0.35) and gingival health status (p<0.001) have a significant effect on GI. Also, gingival health status has a significant effect on PI (p<0.001). GI and PI were higher in the group with gingivitis (p<0.001) and decreased dramatically after the therapy (p<0.001) (Table 2).

MANOVA test values are summarized in Table 2. The general health status–gingival health status relation is summarized in Table 3. Also, Table 4 shows BLC, GLC, GI, PI levels before and after treatment.

Biochemical parameters

BLC: BLC levels of obese adolescents were higher than normal weight adolescents (p<0.001). When gingival health status was taken into account, the difference was not statistically significant, although the BLC was higher in gingivitis subjects (p=0.68). Also, BLC levels of females were found to be higher than men's (p=0.001) (Table 2).

Table 2. MANOVA test

Variable			N	$\overline{X}$	SS.	F	*p*
BLC	General health status	Normal weight	28	6.926	5.638	51.571	0.000
		Obese	28	20.051	8.023		
	Gingival health status	Healthy gingiva	16	12.350	9.965	0.170	0.682
		Gingivitis	40	13.944	9.459		
	Gender	Female	37	15.888	9.583	13.610	0.001
		Male	19	8.816	7.725		
GLC	General health status	Normal weight	28	1.750	0.724	0.076	0.784
		Obese	28	1.794	0.808		
	Gingival health status	Healthy gingiva	16	2.369	0.753	9.610	0.003
		Gingivitis	40	1.533	0.627		
	Gender	Female	37	1.798	0.720	0.373	0.545
		Male	19	1.722	0.853		
PI	General health status	Normal weight	28	1.506	0.829	0.267	0.608
		Obese	28	1.406	0.863		
	Gingival health status	Healthy gingiva	16	0.743	0.619	16.219	0.000
		Gingivitis	40	1.742	0.745		
	Gender	Female	37	1.398	0.887	0.471	0.496
		Male	19	1.568	0.750		
GI	General health status	Normal weight	28	0.933	0.621	4.722	0.035
		Obese	28	1.111	0.693		
	Gingival health status	Healthy gingiva	16	0.110	0.172	147.991	0.000
		Gingivitis	40	1.387	0.350		
	Gender	Female	37	1.030	0.711	0.010	0.919
		Male	19	1.006	0.558		

BLC levels of both obese–gingivitis are higher than BLC levels of normal weight–gingivitis (p<0.001), also those of obese–healthy gingiva were higher than those of normal weight–gingivitis (p=0.1) (Table 3). BLC was measured lower after treatment, but this difference was not statistically significant (p=0.09) (Table 4).

GLC: Although GLC levels were higher in obese adolescents compared to normal weight, this difference was not statistically significant (p=0.78). GLC levels were higher in adolescents with healthy gingiva than in gingivitis subjects (p=0.03) Also, there was no effect of gender on GLC levels was found (p=0.545) (Table 2).In obese adolescents, gingivitis was found to have a reducing effect on GLC levels (p=0.1)(Table 3).

Periodontal treatment has had a significant impact on GLC levels (p<0.001) (Table 4). After periodontal treatment, the GLC levels of the gingivitis group showed a significant increase, and it has been seen that it has reached a higher concentration than adolescents with healthy gingiva.

Correlation between dental health parameters

BLC showed a negative correlation with GLC (r=-0.16, p<0.10), but a positive correlation with PI (r=0.19, p<0.05). GLC was found to be inversely related to both GI and PI (r=-0.49, p<0.01; r=-0.54, p<0.01, respectively). There was a positive correlation between GI and PI as expected (r=0.73, p<0.01) (Table 5).

Table 3. BLC, GLC, PI and GI for general health status–gingival health status relation

BLC		MEAN ± SD	MEDIAN (MIN- MAX)
Normal weight	Gingivitis	7.6 ± 6.3	5.3 (0.8 – 18.2)[b]
	Healthy gingiva	5.3 ± 3.1	5.7 (0.8 – 9.9)[a]
Obese	Gingivitis	20.3 ± 7.6	19.8 (11.5 – 35.7)[b]
	Healthy gingiva	19.4 ± 9.4	18.6 (11.5 – 35.7)[a]
GLC			
Normal weight	Gingivitis	1.6 ± 0.6	1.4 (0.9 – 2.7)
	Healthy gingiva	2.2 ± 0.8	2.1 (1.3 – 3.5)
Obese	Gingivitis	1.5 ± 0.7	1.4 (0.7 – 2.9)[c]
	Healthy gingiva	2.5 ± 0.7	2.4 (1.8 – 3.8)[c]
PI			
Normal weight	Gingivitis	1.8 ± 0.6	1.6 (1 – 3)[d]
	Healthy gingiva	0.7 ± 0.6	0.5 (0 – 2)[d]
Obese	Gingivitis	1.6 ± 0.8	1.7 (0.1 – 3)
	Healthy gingiva	0.8 ± 0.7	0.6 (0.2 – 1.9)
GI			
Normal weight	Gingivitis	1.3 ± 0.3	1.3 (0.5 – 1.8)[e]
	Healthy gingiva	0.1 ± 0.2	0 (0 – 0.6)[e]
Obese	Gingivitis	1.5 ± 0.3	1.5 (0.7 – 2)[f]
	Healthy gingiva	0.1 ± 0.1	0.1 (0 – 0.3)[f]

There is statistically significant differences between the groups
[a]p=0.10, [b]p=0.00, [c]p=0.10, [d]p=0.008, [e]p=0.002 and [f]p=0.00

Table 4. BLC, GLC, PI and GI levels before and after treatment

Variable	Median (min-max) Before treatment	Median (min-max) After treatment	*p*
BLC	13.3 (0.8 – 35.7)	12.9 (0.8 – 28.5)	.090
GLC	1.4 (0.7 – 2.9)	2.7 (1.5 – 5.6)	.000
PI	1.6 (0.1 – 3)	0.3 (0 – 1.4)	.000
GI	1.4 (0.5 – 2)	0.1 (0 – 1)	.000

Table 5. The Pearson's correlation coefficients between variables

Variables	BLC	GLC	GI	PI
BLC	1	-0.16***	0.14	0.19**
GLC		1	-0.49*	-0.54*
GI			1	0.73*
PI				1

*p<0.01: highly meaningful relationship, **p<0.05: meaningful relationship and ***p<0.10: tendency in relationship

DISCUSSION

In the present study in obese and normal weight subjects, the effect of leptin was evaluated on periodontal disease in light of clinical and laboratory findings.

The effects of leptin on immunological functions, bone development, energy homeostasis, nutrition, hematopoiesis and angiogenesis have been proven[21]. The immune system has various roles, such

as proliferation, apoptosis, chemotaxis, phagocytosis and differentiation of cells[2, 21]. It has been suggested that leptin, which is locally in high concentration, maintains the level of bone and that it protects the host from inflammation and infection[2]. Periodontal diseases are related to the immune system and inflammatory processes, also leptin has many interventions in the immunomechanism, suggesting that there may be a close relationship between periodontal disease and leptin. Therefore, there are many studies that address this issue[2-4, 26, 27].

Leptin is also known as an anti-obesity hormone; leptin is secreted by adipose tissue in the body and changes depending on body weight[6, 31]. In other studies, the relationship between leptin and periodontal diseases was also supported both in experimental studies[15] and clinical studies[19,32,33]; and it was reported that there is a positive association between body mass index and periodontal disease[17,34,35]. Researchers suggest that obesity is a risk factor for periodontal disease[32, 34, 36, 37].

Karthikeyan and Pradeep reported that leptin has protective effects against infection[2]. Another important finding of their study is that during the inflammation period, the local concentration of leptin decreases while the blood leptin concentration increases[3]. For this reason, our study was conducted on GCF and blood samples to investigate the importance of leptin in terms of gingiva health, to detect local and systemic levels during inflammation and to establish a correlation between the two values found. In addition, in order to obtain more comprehensive results, the relationship between these parameters and periodontal disease/periodontal treatment and treatment was evaluated in both obese and normal weight adolescents.

It is known that leptin concentrations are reduced in prolonged starvation and are increased in overfeeding[38]. In light of this information, our samples were taken on an empty stomach in the morning.

It has been reported that BLC is higher in obese people and decreased with weight loss[39-41]. Similarly, the BLC of obese adolescents was significantly higher in the present study. It has also been suggested in the literature that a positive correlation between leptin and body fat mass and BMI is more prominent in females, and that this is true for adolescents and adults[39, 40, 42]. As a matter of fact, when evaluated regardless of the group difference, it was seen in our study that BLC of females was significantly higher than the males'.

Many studies have shown that BLC increases in inflammatory stimuli[3, 43-45]. In one of these studies, Karthikeyan and Pradeep showed this increase in the presence of periodontal infection. Also, Purwar et al. reported that serum leptin levels were higher in periodontal disease[45] and Shi et al. have shown that plasma leptin concentration increased in periodontal disease[46]. Although it is not statistically significant, we found that the levels of BLC in the gingivitis group were higher in our study.

Our study evaluated not only BLC but also GLC. It has been reported that GLC is higher in healthy gingiva, falls with periodontal disease and when BMI is increased, GLC is increased[2-4, 26, 47, 48]. Although not statistically significant, GLC was higher in both female and obese subjects. Given the protective role of GLC on gingiva, a more significant reduction in leptin in diseased obesity, as in our study, may be interpreted as a greater susceptibility to obesity.

Similarly with literature, it was found that gender was not affect GLC level in our study[48]; also it was seen that the BLC decreased after the periodontal treatment[49, 50], whereas GLC increased[48, 51]. In addition, GI and PI decreased as expected. It was also found that PI and GI were negatively correlated with GLC[2, 3, 47] and positively correlated with BLC.

In conclusion: while the GLC decreases as the gingiva progresses from healthy to disease, leptin concentration of blood tends to increase, that is, BLC and GLC show negative correlation. This finding supports the idea that leptin may be a protective agent for gingivitis. For obese individuals, the more the GLC was reduced, compared to the normal weight gingivitis, the more likely it is that the disease will be more severe. In this regard, additional works done by evaluating the more biochemical markers and individual are needed.

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The authors report no conflicts of interest related to this study.

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