The effect of menopause on levels of cortisol, alpha-amylase, dopamine, and prolactin in women with periodontitis and healthy controls: a cross sectional study*

Menopozun sağlıklı ve periodontitisli kadınlarda kortizol, alfa-amilaz, dopamin ve prolaktin seviyeleri üzerine etkisi: kesitsel bir çalışma

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Abstract

Aim: In this study, we aimed to investigate the effects of menopause on serum levels of cortisol, alpha-amylase, dopamine, and prolactin in women with periodontitis and healthy controls.

Methods: The study included a total of 80 women. Patients were diagnosed according to the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions criteria. The clinical examination included plaque index (PI), gingival index (GI), probing depth (PD), and clinical attachment loss (AL) measurements. The systemic levels of cortisol, alpha-amylase, dopamine, and prolactin were measured biochemically. Data were analyzed statistically.

Results: The mean participant age was 44.32±3.23 (range: 33–55) years. The mean PI was 0.98±0.10, GI 0.94±0.31, PD 2.59±0.23 mm, and AL 2.65±0.16 mm. While prolactin levels were statistically significantly lower in menopausal women ($p<0.05$), the changes in cortisol, alpha-amylase, and dopamine levels were not significant ($p>0.05$). Levels of cortisol, dopamine and prolactin were found to be significantly high in women with periodontitis ($p<0.05$).

Conclusion: It was found that menopause had no effect on the clinical periodontal parameters and levels of cortisol, alpha-amylase, and dopamine in women with periodontitis and healthy controls. However, menopause was associated with decreased prolactin levels, independent of the presence of periodontal disease.

Keywords: menopause; periodontitis; stress hormones

Öz

Amaç: Bu çalışmada menopozun sağlıklı ve periodontitisli kadınlarda serum kortizol, alfa-amilaz, dopamin ve prolaktin seviyeleri üzerindeki etkisini araştırmak amaçlanmıştır.

Yöntem: Çalışmaya toplam 80 kadın dahil edildi. Hastalar, Periodontal ve Peri-İmplant Hastalık ve Durumların Sınıflandırılmasına Dair 2017 Dünya Çalıştayı kriterlerine göre teşhis edildi. Klinik muayenede plak indeksi (Pİ), gingival indeks (Gİ), sondalama cep derinliği (SCD) ve klinik ataşman kaybı (KAK) ölçümleri yapıldı. Sistemik kortizol, alfa-amilaz, dopamin ve prolaktin seviyeleri biyokimyasal olarak ölçüldü. Veriler istatistiksel olarak analiz edildi.

Bulgular: Ortalama katılımcı yaşı 44,32±3,23 (aralık: 33–55) yıl idi. Ortalama Pİ 0,98±0,10; Gİ 0,94±0,31; SCD 2,59±0,23 mm, KAK 2,65±0,16 mm idi. Menopozlu kadınlarda prolaktin seviyeleri istatistiksel olarak anlamlı biçimde daha düşükken ($p<0,05$), kortizol, alfa-amilaz ve dopamin seviyelerindeki değişimler anlamlı değildi ($p>0,05$). Periodontitisli kadınlarda kortizol, dopamin ve prolaktin seviyeleri anlamlı biçimde yüksekti ($p<0,05$).

Sonuç: Menopozun sağlıklı ve periodontitisli kadınlarda klinik periodontal parametreler ve kortizol, alfa-amilaz ve dopamin seviyeleri üzerinde etkisi olmadığı görüldü. Ancak menopoz periodontal hastalık varlığından bağımsız olarak azalmış prolaktin seviyeleri ile ilişkili idi.

Anahtar sözcükler: menopoz; periodontitis; psikolojik stres

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INTRODUCTION

Periodontitis is a common, multifactorial inflammatory disease that causes the destruction of soft and hard tissues supporting the teeth (1). It is the 6th complication of diabetes and is associated with low quality of life and social inequality (2). The risk factors include genetics, impaired host immune response, systemic diseases, smoking, and poor oral hygiene (3). Although microbial dental plaque plays a fundamental role in the pathogenesis, systemic and environmental risk factors are associated with the onset and progression of the disease (4, 5).

Stress, an environmental factor, plays an important role in the etiology and progression of periodontal diseases by stimulating the hypothalamic–pituitary–adrenocortical (HPA) and sympathetic adrenomedullary systems (6). As a result, corticotropin-releasing factor (CRF) is released by the hypothalamus, which stimulates the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary lobe. ACTH also causes cortisol release from the adrenal cortex. Thus, an alarm reaction is produced to cope with stress, with the secretion of a number of biochemical substances such as cortisol, alpha-amylase, dopamine, and prolactin (7).

Cortisol is a steroid glucocorticoid that protects the organism by being released from the adrenal cortex in response to changes in the body's physiological balance. As the cortisol level increases, the CRF and ACTH release is inhibited as negative feedback. In the presence of psychological stress, the HPA system is activated, resulting in significant increases in the salivary cortisol levels (8). Since these levels are closely related to serum cortisol levels, they reliably reflect the HPA system activity. Cortisol, one of the stress-related biomarkers of the HPA system, has been shown to be positively associated with the prevalence and severity of periodontitis (9).

Alpha-amylase is an enzyme found in the pancreas and saliva and is secreted from the salivary glands in response to sympathetic stimuli. Its measurement is considered a method to evaluate the sympathetic–adrenal medullary system (SAMS) activation. Chatterton et al. (10) reported a strong correlation between the serum levels of catecholamines and the salivary concentrations of alpha-amylase. Salivary amylase can be sampled noninvasively and is considered a stress biomarker (11).

Dopamine, epinephrine, and norepinephrine, synthesized from the amino acid tyrosine, are known as catecholamines. Epinephrine is synthesized and stored in the adrenal medulla, while norepinephrine is synthesized in the sympathetic nervous system. Catecholamines function in the body as hormones and neurotransmitters. They play an important role in the body's adaptation to acute and chronic stress (12).

Prolactin is secreted by the acidophilus cells of the anterior pituitary lobe and plays a role in the regulation of the immune system with regard to cellular and humoral immunity (13). Prolactin secretion exhibits a daily rhythm; it stays at a minimum in the afternoon and increases markedly soon after falling asleep. Prolactin levels are higher in young women with high estrogen concentrations, especially during pregnancy (14).

Stress is thought to play an important role in the etiology, progression, and treatment response in periodontal diseases. It has been shown that periodontal destruction is more common in people who have a heavy workload, troubled marriages, occupational problems, and psychological depression (15). It is stated that periodontitis is associated with a number of psychological disorders and factors. The relationship between stress and periodontal diseases is thought to result from the disruption of the balance between oral bacteria and the host's immune response, with an increase in the release of cytokines (such as interleukin-1 beta, interleukin-6, and interleukin-10) and decrease in the interferon-gamma production. Interestingly, stress and other risk factors for periodontal diseases have been reported to induce hypersensitivity of the HPA system (16).

Although the biological mechanisms that affect the progression of periodontitis have not been fully understood, stress has been reported to suppress the cellular immune response in three different ways (16): (i) HPA system activation, (ii) release of neuropeptides, and (iii) SAMS activation causing adrenaline and noradrenaline release. When stress is perceived by the brain, CRF is released from the hypothalamus. This hormone stimulates the anterior pituitary lobe and causes the release of ACTH. With ACTH's stressor effect, the CRF release increases by a factor of approximately 20. ACTH stimulates the cortex of the adrenal

Table 1. Patient clinical characteristics

Periodontitis classification		n	%	Mean age
Stage	I	18	45.00	44.52
	II	11	27.50	47.66
	III	7	17.50	48.27
	IV	4	10.00	52.35
Grade	A	27	33.75	46.26
	B	9	22.50	49.52
	C	4	10.00	53.36

gland and causes the release of cortisol. In addition, stress activates SAMS and causes adrenaline release from the medulla (17).

Menopause is one of the periods in life in which women experience physiological and psychological changes that can cause emotional stress (18). It is known that menopausal changes occur as a result of the decreased secretion of estrogen hormone (19). However, there is a lack of studies evaluating how menopause affects stress-related biochemical markers in periodontitis. Therefore, in this study we aimed to investigate the effect of menopause on levels of cortisol, alpha-amylase, dopamine, and prolactin in women with periodontitis and healthy controls. The null hypothesis was that there was a significant difference between the two groups in terms of stress hormones and periodontal parameters.

MATERIALS AND METHODS

The study included a total of 80 women aged between 32 and 57 years. The women with periodontitis presented to the periodontology department of the Atatürk University Faculty of Dentistry between May 2012 and July 2013. The postmenopausal women were referred to the periodontology department from the menopause clinic at the Atatürk University Faculty of Medicine.

Sample selection

The study included pre- and post-menopausal women who had no history of systemic disease, substance abuse, cigarette and/or alcohol consumption, antibiotic and/or antidepressant use, corticosteroid treatment (within the last three months), pregnancy and/or breastfeeding, hormone/estrogen replacement therapy, and periodontal treatment (within the last six months) and who had at least twenty teeth. Both medical and dental histories of the women included were taken.

The women included were divided into 4 groups: pre-menopausal (M-) healthy (P-) women (Group I, n=20), pre-menopausal (M-) women with periodontitis (P+) (Group II, n=20), post-menopausal (M+) healthy (P-) women (Group III, n=20), and post-menopausal (M+) women with periodontitis (P+) (Group IV, n=20).

Clinical measurements

According to the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions criteria (20), participants were defined as having periodontitis if interdental clinical attachment loss (AL) was detectable at ≥2 non-adjacent teeth, or a buccal or oral AL ≥3 mm with a probing depth (PD) ≥3 mm was detectable in ≥2 teeth. The degree of periodontitis was assessed based on a staging and grading system (20), where severity and complexity were classified into four stages (Stage I, II, III, IV) while the likelihood of disease progression was assessed with three grades (Grade A, B, C).

In the determination of periodontal health status, plaque index (PI) (21), gingival index (GI) (22), PD, and AL were assessed at six sites for each tooth by a single clinician (MT). For the PD measurement with the periodontal probe, the probe was placed parallel to the vertical axis of the tooth to reach the deepest point of the pocket, and the distance between the base of the pocket and the gingival border was manually recorded to the nearest millimeter mark. Similarly, AL was measured as the distance between the cemento-enamel junction (CEJ) and the bottom of the pocket.

Radiographic assessments

In all participants, orthopantomographs were taken with the use of a panoramic radiography device (60–80 kVp, 8–10 mA, 12.8 sec exposure time) (Planmeca Proline CC 2002, Helsinki, Finland) by an X-ray technician. In addition, periapical radiographs were taken of the areas where the sockets were deep, in order to confirm the periodontitis diagnosis.

Table 2. Measurements of periodontal clinical parameters (mean±standard deviation)

Groups		PI	GI	PD (mm)	AL (mm)
Healthy women	Pre-menopausal	0.52±0.14[a]	0.64±0.10[a]	1.85±0.12[a]	1.87±0.12[a]
	Post-menopausal	0.44±0.09[a]	0.52±0.12[a]	1.95±0.11[a]	1.69±0.24[a]
	p	0.864	0.653	0.598	0.653
Women with periodontitis	Pre-menopausal	1.42±0.12[a]	1.24±0.11[a]	3.53±0.11[a]	3.86±0.23[a]
	Post-menopausal	1.54±0.08[a]	1.36±0.92[a]	3.04±0.06[a]	3.18±0.05[a]
	p	0.643	0.542	0.765	0.567

Different superscripts show statistically significant differences between the groups in the same column.
AL: attachment loss; GI: gingival index; PD: probing depth; PI: plaque index

Table 3. Levels of cortisol, alpha-amylase, dopamine, and prolactin (mean±standard deviation)

Groups		Cortisol (µg/100ml)	Alpha-amylase (U/L)	Dopamin (µg/L)	Prolactin (ng/mL)
Healthy women	Pre-menopausal	7.24±2.35[a]	74.10±21.06[a]	232.19±27.8[a]	8.74±1.60[a]
	Post-menopausal	6.72±2.45[a]	69.84±11.13[a]	214.64±30.10[a]	4.20±1.40[b]
	p	0.733	0.598	0.943	*0.001*
Women with periodontitis	Pre-menopausal	13.26±0.89[a]	76.24±14.54[a]	276.71±34.81[a]	12.28±2.40[a]
	Post-menopausal	14.40±1.46[a]	72.25±12.09[a]	296.60±36.74[a]	6.84±1.16[b]
	p	0.753	0.564	0.673	*0.001*

Different superscripts show statistically significant differences between the groups in the same column.

Biochemical analysis

Ten ml venous blood was taken in the morning from patients whose clinical periodontal parameters had been recorded. It was centrifuged at 3000 rpm for 10 minutes at +4°C. The separated sera were put into sterile Eppendorf tubes and stored at -80 °C until the study was conducted. Before biochemical assessment, the serum samples were first kept at -20°C for one night. On the day of biochemical assessment, the serum samples were kept at room temperature for two hours and then placed in an autoanalyzer. Cortisol levels were analyzed by chemiluminescent immunometric assay using an autoanalyzer (Beckman Coulter DXI 800, USA) with a commercial kit (Beckman Coulter, USA). Alpha-amylase levels were analyzed photometrically by the International Federation of Clinical Chemistry and Laboratory Medicine EPS method using an autoanalyzer (Beckman Coulter AU 5800, Japan) with a commercial kit (Beckman Coulter, Japan). Dopamine levels were analyzed with the aid of high-performance liquid chromatography using an autoanalyzer (HP-Agilent 1100 Series, Germany) with a commercial kit (Chromsystems, Germany). Prolactin levels were analyzed by chemiluminescent immunometric assay using an autoanalyzer (Beckman Coulter DXI 800, USA) with a commercial kit (Beckman Coulter, USA).

Statistical analysis

Statistical analysis was performed using the SPSS (v. 20.0) software (SPSS Inc., Chicago, IL, USA). Normality of the data was checked by the Kolmogorov–Smirnov test. Data were also analyzed using the Mann–Whitney U test and Spearman correlation analysis. $p<0.05$ was considered statistically significant.

The sample size was estimated to be 60 using the G*Power 3.1 software with an effect size of 0.50, power of 80%, and significance level of 5%. However, adjusting for a dropout rate of 33%, the required sample size was 80 individuals (23).

Study ethics

The study protocol was approved by the Ethics Committee of the Atatürk University Faculty of Dentistry (004/2012). Signed informed consent was obtained from all participants.

RESULTS

The mean participant age for Group I, II, III, and IV was 35.50±2.06, 38.25±4.52, 51.45±3.25, and 52.10±3.11 years, respectively (Table 1). The mean PI, GI, PD, and AL values for each group are shown in Table 2. In both healthy women and those with periodontitis, there was no statistically significant difference between pre-menopausal and post-menopausal participants in terms of mean PI, GI, PD and AL values ($p>0.05$).

The mean cortisol, alpha-amylase, dopamine, and prolactin levels for each group are shown in Table 3. In both healthy women and those with periodontitis, there was no significant difference between pre-menopausal and post-menopausal participants in terms of serum levels of cortisol, alpha-amylase, and dopamine ($p>0.05$). In both healthy women and those with periodontitis, the serum level of prolactin was significantly lower in post-menopausal participants than in pre-menopausal participants ($p<0.05$).

In women with periodontitis, a positive correlation was found between the pre- and post-menopausal values of periodontal parameters (PI, GI, PD, and AL) and stress-related biochemical markers (cortisol, alpha-amylase, dopamine, and prolactin).

DISCUSSION AND CONCLUSION

Cortisol, alpha-amylase, dopamine, and prolactin are biochemical substances released as a result of stress (19). Stress is one of the most important factors in the etiology and progression of periodontal diseases (24). Moreover, menopause is one of the main causes of emotional stress in women (21). Therefore, in the present study we aimed to investigate the effect of menopause on levels of cortisol, alpha-amylase, dopamine, and prolactin in pre- and post-menopausal women with and without periodontitis.

According to our findings, the serum level of prolactin was significantly lower in post-menopausal women than in pre-menopausal women, independent of the presence of periodontal disease. However, there was no significant difference between the groups in terms of the other parameters. Therefore, the null hypothesis was partially rejected.

Although it has been reported that menopause-related oral changes, such as burning mouth syndrome and xerostomia, are caused by hormonal changes and physiological aging, the present study found no significant difference between the groups in terms of periodontal clinical parameters. This is consistent with the results of previous studies (25,26) and can be explained by similar oral health behaviors before and after menopause (26).

Although the relationship between cortisol and periodontal diseases has been shown in many studies, there are a limited number of studies investigating the serum levels of cortisol in pre- and post-menopausal women (27–29). We found no significant difference between the groups of pre- and post-menopausal women with and without periodontitis, again in agreement with previous studies (30,31). However, there are also several contradictory studies reporting that the serum cortisol level increased with menopause and age (32,33). This can be explained by the small age difference between the pre- and post-menopausal groups included.

The present study found no significant difference between pre- and post-menopausal women in terms of mean serum levels of alpha-amylase, which is consistent with previous studies reporting no relationship between serum alpha-amylase and periodontal disease (34,35), indicating that menopause does not affect the relationship between periodontal disease and serum alpha-amylase and the pathogenesis of periodontal disease.

Similarly, no significant difference was found between the pre- and post-menopausal women in terms of mean serum levels of dopamine. To our knowledge, the literature contains no studies examining the relationship of serum dopamine to periodontal health or menopausal status. Thus, the association of serum dopamine release with menopause and periodontal health is yet to be elucidated.

We found that the serum level of prolactin was significantly lower in post-menopausal women than in pre-menopausal women, independent of the presence of periodontal disease. This finding is consistent with previous reports (36,37). However, the effect of menopause on serum prolactin levels is not fully understood, as a result of various age-related mechanisms (38). As in the study of el-Wakeel et al. (39), a positive correlation between serum prolactin levels and clinical periodontal parameters (PI, GI, PD, and AL) was

found in the present study, indicating the effect of inflammatory diseases and, thus, clinical utility as a biomarker for disease activity and prognosis (39).

In conclusion, we observed that menopause had no effect on the periodontal clinical parameters and serum levels of cortisol, alpha-amylase, and dopamine in healthy women and women with periodontitis. However, further studies with larger samples and longer periods of pre- and post-menopausal follow-up are needed, together with analyses of cortisol, alpha-amylase, dopamine, and prolactin in gingival crevicular fluid and saliva.

Conflict-of-interest and financial disclosure

The authors declare that they have no conflict of interest to disclose. The authors also declare that they did not receive any financial support for the study.

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