

# PERIODONTAL DISEASE IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS: CARDIOVASCULAR RISK AND SIDE EFFECTS OF CORTICOTHERAPY INVOLVING ORAL HEALTH

Dan Piperea-Sianu<sup>1</sup>, Alexandru G. Croitoru<sup>1,2</sup>, Adela Maria Ceau<sup>1</sup>, Alice Piperea-Sianu<sup>3</sup>, Daniela Badita<sup>1,4</sup>, Stefan Cristea<sup>1,5</sup>, Sorin Stefan Arama<sup>1,2</sup>, Carina Mihai<sup>1,6</sup>

<sup>1</sup>Carol Davila University of Medicine and Pharmacy, Bucharest

<sup>2</sup>Faculty of Dental Medicine, Department of Physiopathology and Immunology

<sup>3</sup>Department of Analytical Chemistry, Titu Maiorescu University, Faculty of Pharmacy, Bucharest

<sup>4</sup>Department of Physiology, Faculty of Dental Medicine, Bucharest

<sup>5</sup>Department of Orthopaedics and Traumatology, Sf. Pantelimon Hospital, Faculty of Medicine, Bucharest

<sup>6</sup>Department of Internal Medicine and Rheumatology, Cantacuzino Hospital, Faculty of Medicine, Bucharest

## Abstract

Systemic lupus erythematosus (SLE) and periodontal disease (PD) are two chronic inflammatory diseases that share common pathogenetic mechanisms. Therefore, it is thought that a correlation between the two pathologies might exist. PD itself, when not associated with SLE, does not cause major cardiovascular events, but it contributes to the development of atherosclerosis, which is the major cause of death among patients with SLE. This article aims to summarize the available literature concerning the association between these two disorders (PD prevalence in patients with SLE, correlations between periodontal damage and SLEDAI activity score), to present the main mechanisms by which the two pathologies affect the cardiovascular system and to evaluate the impact of SLE corticosteroid therapy on periodontal tissue.

**Keywords:** systemic lupus erythematosus, periodontal disease, cardiovascular risk, corticotherapy

## INTRODUCTION

Systemic lupus erythematosus (SLE) is a multi-systemic autoimmune disease, characterized by a chronic inflammatory process. The impairment targets a range of tissues and organs, including the skin, joints, serous membranes and the nervous system. The etiology of the disease is complex and not completely understood, but it is admitted that genetic and environmental factors are involved. Disease prevalence varies between 15 and 50 cases in 100.000 inhabitants and it is more common in black people. Literature suggests a predilection for SLE in young women, the female:male ratio lying between 5:1 and 9:1. SLE is characterized by a B cell hyperactivity, resulting in the production of IgG and immune com-

plexes. Certain antibodies (auto-antibodies) cause cellular damage by a type II hypersensitivity reaction or by participating in the formation of immune complexes. These will develop deposits in tissues and organs, causing tissue damage. The evolution of the disease alternates periods of flares and remission.

(1)

Periodontal disease (PD) (Fig. 1, 2) is a chronic inflammatory oral disease that affects the support tissue around the teeth. PD's etiology is likely microbial, involving germs grouped in microbial complexes according to virulence. Contributing factors are tartar, morphological changes of teeth and dental arches, and systemic factors (systemic impairments, corticosteroid therapy, cytostatic medication, anti-epileptic drugs etc.). PD's onset is influenced by the

Correspondence address:

Dan Piperea-Sianu, MScD, Carol Davila University of Medicine and Pharmacy, 37 Dionisie Lupu St., Bucharest

E-mail: sianu.dan@gmail.com

presence and direct action of pathogenic agents, but the evolution of PD is strictly dependent on the host immune response. The disease progresses gradually from mild reversible gingivitis to the following: damage of the deep marginal periodontal tissue, destruction of the alveolar bone and loss of contact between the tooth and the support tissue. PD prevalence in the general population lies between 10-15% for medium and severe forms. (2-5)



**FIGURE 1.** Female patient with SLE, who presents inferior diastema and medium insertion of lower labial frenulum. Supragingival and subgingival tartar on lower central incisors, with gingival retraction and bleeding on probing (courtesy of Dan Piperea-Sianu and Carina Mihai)



**FIGURE 2.** Female patient with SLE, with total maxillary edentulism and partial mandibular edentulism (Kennedy class I mod 2) restored with removable acrylic dentures: maxillary complete denture and mandibular partial denture, engaged with dental wire clasps. The patient presents plaque deposits and untreated complicated multiple dental caries. Supragingival and subgingival tartar, signs of gingival inflammation, gingival retraction, pathologic tooth migration and 3<sup>rd</sup> grade mobility in the remaining mandibular incisors. (courtesy of Dan Piperea-Sianu and Carina Mihai)

## LINKS BETWEEN PD AND SLE: PATHOGENIC HYPOTHESES AND EPIDEMIOLOGICAL DATA

PD and SLE are two disorders with multifactorial etiology, sharing pathogenic mechanisms such as high serum levels of proinflammatory cytokines and  $\beta$ 2-glycoprotein-I dependent anticardiolipin antibodies. Due to pathogenic similarities, there may be a relationship between the two disorders. It is also known that patients with SLE are highly susceptible to infections due to the following: (a) alteration of cellular immune response (T cell lymphopenia, impaired L<sub>Tc</sub> activity, reduced NK cells level and diminished NK cell function), (b) impairment of humoral immune response (anti-receptor Fc $\gamma$  antibodies, antibodies against cytoplasmic components of neutrophils, hypo- $\gamma$ -globulinemia), (c) deficiencies of phagocytosis (failure to generate super oxide radicals), (d) cytokine defects and other immune abnormalities, (e) certain elements specific for the disease (immunosuppressive medication, corticosteroid therapy, biological therapy, transient or permanent splenic dysfunction). Therefore, predisposition to infection of patients with SLE may influence the body's defense mechanisms against periodontal microbial flora. (6,7)

In a study on 15 patients with SLE, aged between 22 and 53 years, Ramos Sales *et al* attempted to verify the existence of correlations between the extent of periodontal damage and the SLE activity score (SLEDAI). Regarding PD prevalence in the study group, periodontal damage, measured by the depth of periodontal pockets (PPD)  $\geq$  3 mm, was found in 7 patients of 15, with a resulting prevalence of 46.7%. Small differences were identified between the average SLEDAI score in patients that suffer from both SLE and PD (3.42) and those with healthy periodontal tissue (3.5). When analyzing individual components of the SLEDAI score, only C3 serum levels indicates a statistically significant relationship with the frequency of visible plaque areas. Thus, the increase in the amount of plaque, is correlated with reduced C3 serum levels, which can be explained by the consumption of C3 in the course of the systemic inflammatory process. (8)

Ramos Sales *et al* state that their data regarding the prevalence of PD in patients with SLE are consistent with other studies. They found a prevalence of 46.7% in the study group (n = 15). Other studies also reported an increased prevalence of periodontal

damage in patients with lupus, compared to healthy population: Kobayashi et al 70% (compared with control, 50%), Novo et al 60% and Rhodus et al 93.8%. In the studies we analyzed, that are currently available in the literature, we observed a higher prevalence of PD in patients with SLE (between 46% and 94%) compared to the general population. PD is a pathological complex that brings together several types of changes in the marginal periodontal tissue. Due to the multitude of pathologic entities, there is still no consensus regarding the diagnostic criteria for PD, therefore its prevalence in the population varies widely, between 10-15% for medium and severe forms, while exceeding 50% for mild forms (5,8-11)

In a recent study, Al-Mutairi et al evaluates the periodontal status in a group of 25 female patients with SLE, in comparison to a control group comprising 50 women not suffering from SLE. Average percentage of PPD  $\geq$  5 mm was higher among patients with SLE compared to the control group (11.3% versus 5.6%). Clinical attachment loss (CAL) is also revealed as being modified with more than 2 mm in 75.8% of teeth evaluated in SLE patients and in 71.9% of the teeth in the control group. The results state that, even if the periodontal damage is more advanced in patients with SLE, the difference cannot be considered statistically significant. Results with statistical significance were reported in SLE patients with recent flares ( $<$  1 year), compared to the stable ones, and also in patients with active disease (arthritis) compared to those without flares. Patients with recent flares ( $<$  1 year) showed a smaller periodontal damage (measured by the percentage of periodontal pockets and lower CAL) compared to the stable group ( $>$  1 year). Patients with lupus arthritis (active disease) showed greater periodontal damage compared to those without flares, regarding the percentage of PPD  $\geq$  5 mm. (7)

Data from the available literature, concerning the mechanisms by which PD influences SLE are few and inconclusive. Furthermore, there is a single study regarding the relationship between SLE serum markers and severity of PD. PD prevalence in patients with SLE is higher compared to the general population, but there is no consensus regarding a correlation between periodontal damage and the SLEDAI score. In most studies, however, the lack of a correlation between periodontal parameters and SLEDAI score is suggested. SLE pharmacological therapy reduces the biological inflammatory syndrome, a key element in periodontal destruction in PD. Also,

increasing the dose in rebound periods explains the diminished periodontal damage, compared to the stable patients ( $>$  1 year). (7)

## CARDIOVASCULAR RISK IN PD AND SLE

### C-reactive protein

C-Reactive protein (CRP) is a non-specific inflammatory marker, that is associated with increased risk for cardiovascular disease (CVD).

As a defense against the microbial attack towards the periodontal tissue, a non-specific systemic response appears. This is initially characterized by local cytokine production in the marginal periodontal tissue, and it later becomes systemic by stimulating hepatic synthesis of CRP and subsequently increasing its serum level. CRP works by forming deposits in the injured vessel, by binding to the affected cells and by binding the complement. Hence, it activates the phagocytes, that generate nitric oxide and contribute to the development of atheroma plaques. Also, the association between CRP and atherosclerotic plaques is explained by promoting the development of foam cells, by means of mediating the binding of LDL to macrophages. (12,13)

Current studies show a direct correlation between CRP serum levels and PD, in patients with PD that do not associate other systemic inflammatory diseases. CRP serum levels vary in direct proportion with the degree of periodontal damage and its levels are reduced 3 months after the correctly applied periodontal therapy. Studies focused on the PD-CRP-CVD correlation show an increased value of CRP in PD and CVD, when not associated in the same patient, and very high levels of CRP in patients associating these two pathologies (Genco et al reveals CRP levels of 8.7 mg/L in patients associating PD and CVD, in comparison to 1,14 mg/L in healthy individuals, and a decrease of 65% in its level 3 months after the beginning of treatment). (12-14)

Serum levels of CRP are generally correlated with inflammatory response during flares in illnesses, while literature indicates that SLE may be the exception. It was noted that most patients with SLE show only modestly increased levels of CRP, particularly in comparison to patients with rheumatoid arthritis (RA). (15)

The less important CRP elevation could be explained by increased clearance or decreased production of CRP. Bell et al, cited by Ferreira, shows that the presence of auto-antibodies anti-CRP in patients

with SLE stands for the increased clearance of this inflammatory marker, while Vugushin et al states that the rate of serum clearance of CRP in patients with SLE is similar to that of healthy individuals. (6,15)

Current studies use high-sensitivity CRP (HsCRP) to detect chronic micro-inflammation. Normal values of HsCRP lie between 0-3 mg/L, while high levels represent a risk factor for impaired cardiovascular function, being associated with the development and progression of atherosclerotic process, considered major cause of death in SLE. In a study conducted in 2012, Gheit et al compared a group of 45 women with SLE to 30 healthy women, none of the 75 patients having a history of cardiovascular events, clinical or electrocardiographic signs of cardiovascular impairment. The results indicated that HsCRP levels in SLE patients were significantly higher ( $4.84 \pm 3.91$  mg/L) compared to the ones of the healthy patients ( $1.74 \pm 0.61$  mg/L). (16)

In the aforementioned study conducted on 15 patients with SLE, Sales Ramos et al have identified a slightly increased average CRP serum level in patients associating SLE and PD, compared to those with no signs of PD (3.94 mg/L compared with 3.35 mg/L). Although not statistically significant, it is mentioned that there is a positive correlation between serum levels of CRP and the number of periodontal pockets with PPD  $\geq 4$  mm. This observation highlights that periodontal damage advances with the increase of CRP serum levels. (7)

Regarding the change in acute phase reactants during the independent evolution of PD and SLE, literature data provide various intervals for the CRP level. It is though unanimously accepted that its values are at least modestly higher than normal. There is only one study that assesses the relationship between the extent of periodontal damage and SLE markers (CRP). The authors of the study state that patients with both SLE and PD show higher levels of CRP compared with SLE patients without periodontal damage, but the results are not statistically significant. Thus, we believe that further studies are needed to analyze correlations between periodontal damage and serum markers of SLE. However, taking into consideration the separate evolution of the two diseases, the role of CRP as active atherosclerotic agent in these patients indicates the presence of an increased CV risk.

## Lipid profile

Current studies analyzing mortality in SLE show that it is 3-5 times higher than in the general population and has as major cause CV impairment. A bimodal pattern of causes of death in SLE has been described: (a) an early peak attributed to those cases where death occurs within one year of diagnosis, being caused by active lupus and its consequences and (b) a late peak, regarding those cases where death occurs more than 5 years after diagnosis, mainly due to atherosclerosis. (6)

Dyslipidemia is common in SLE and it may be a consequence of the disease itself or of the applied treatment. SLE directly affects the lipoprotein metabolism, resulting in elevated levels of triglycerides (TG) and VLDL and reduced levels of HDL and apolipoprotein A1 (apoA1). On the other hand, dyslipoproteinemia in patients with SLE undergoing treatment with glucocorticoids is characterized by elevated levels of VLDL, TG and total cholesterol. Calderon-Ticona et al show that a cause of dyslipidemia may be represented by the presence of auto-antibodies against proteins involved in lipoprotein metabolism. (6,17)

Patients with SLE may have altered HDL function. Normally, HDL plays an anti-inflammatory role by preventing the formation of oxidised LDL (ox-LDL) and foam cells that would otherwise lead to the development of atheroma plaques in the vasculature. Paraoxonase-1 (PON1) is an anti-oxidant component of the HDL that prevents lipoprotein oxidation and removes ox-LDL. PON activity is inversely proportional to the serum level of anti-apoA1 antibodies. Thus, Batuca et al, cited by Abdulaziz et al, show high levels of anti-HDL antibodies, anti-apoA1 antibodies in SLE patients compared to healthy individuals. Tripi et al also show that in SLE, PON1 activity is altered, hence its reduced level is correlated with CVD and cerebrovascular events. (6,18,19)

The atherogenic lipid panel consists of: (a) low HDL-cholesterol, (b) increased total cholesterol, (c) increased TG and LDL-cholesterol. Svenungsson et al determined the prevalence of CV risk factors in a study which compared three groups, each made up of 26 patients: with SLE and CVD, with SLE only and 26 healthy individuals. Therefore, it was shown that dyslipidemia, characterized by increased TG levels and low HDL levels, is common among SLE patients with CVD compared to the other two groups that both had similar lipid profiles, within normal li-

mits. On the other hand, LDL values did not differ significantly between the three groups. (20)

The changes in the lipid profile are not due to lifestyle. Biological inflammatory syndrome with a periodontal starting point appears due to episodes of bacteremia and dissemination of endotoxins. In the available literature, PD is associated with the presence of endotoxins. The studies conducted so far indicate that patients with PD have a higher CV risk compared to individuals with periodontal integrity, and also reveal the presence of pathogenic periodontal agents in the early atheroma plaques. (21)

Losche et al, cited by Thombre, demonstrates a relationship between periodontal changes and hyperlipidemia, by linking higher plasma TG levels and lower HDL-cholesterol in patients with periodontal damage, compared to healthy subjects. Thus, is it stood for the role of PD as a risk factor for hyperlipidemia. (21,22)

Analyzing serum parameters before and after periodontal treatment in a group of 50 patients with PD, Thombre et al showed a positive correlation between periodontal damage and levels of total cholesterol, LDL, VLDL, TG and HDL and a direct correlation between periodontal health and HDL. (21)

Cutler et al states that there is a tight correlation between the extent of periodontal damage, plasma lipid concentrations and the presence of anti-*Porphyromonas gingivalis* antibodies. This is explained by the fact that the high levels of TG may modulate the production of PMN IL-1b, as a consequence of the stimulation induced by *P.gingivalis*. Morrison et al noted that CRP, total cholesterol and fibrinogen are intermediary factors that correlate PD with a high CV risk. (23,24)

Atherosclerosis represents the major cause of death among patients with SLE and PD. Prospective studies are needed in order to clarify whether PD contributes to additional increase in the CV risk in patients with both SLE and PD.

## PHARMACOLOGIC TREATMENT OF SLE: SIDE EFFECTS INVOLVING ORAL HEALTH

Treatment of patients with SLE varies depending on disease severity and on the presence or absence of complications. Classes of drugs used in less severe cases include NSAIDs, glucocorticoids and antimalarials (hydroxychloroquine). Glucocorticoids are administered initially in high-dose, followed by a progressive decrease to the minimum effective dose.

In patients with vital organ damage, in those who do not respond to glucocorticoids or in those cases where glucocorticoids can not be reduced below the maximum acceptable dose for chronic treatment, immunosuppressants such as methotrexate, azathioprine cyclophosphamide, or mycophenolate mofetil will be associated. (7)

## Impact of corticotherapy on the periodontal tissue

Besides the already known general effects, systemic glucocorticoid therapy causes oral manifestations such as as oropharyngeal candidosis, changes in trabecular system of the upper and lower jaw and damage in the marginal periodontal tissue.

Beeraka et al have investigated the effects of long-term glucocorticoid therapy on oral health, assessing clinical and radiological changes. The evaluated periodontal parameters were plaque index (PI), gingival index (GI), CAL and PPD. The only statistically significant differences were recorded for PPD and CAL, showing unfavorable effect of glucocorticoids, represented by apical migration of CAL and increased PPD. (25)

Prolonged glucocorticoid therapy has plain consequences, such as an obvious decrease in calcium absorption, increased bone loss and high incidence of fractures. Bone loss is carried out in two phases: (a) the initial fast stage, during the first months, representing 10-15% of the loss, (b) slow phase, representing 2-5%, annually. These losses are dependent on dose and duration of therapy, and occur faster in the trabecular bone, compared to the cortical bone. Doses of Prednisone  $\geq 7.5$  mg/day cause important bone loss and double the risk of fracture in treatments lasting longer than 6 months. (25)

Loss of dental elements is dependent on many factors. Regarding corticotherapy, the major cause of tooth loss is the low bone mineral density (BMD), which, in association with occlusal masticatory forces, determines mobilization and avulsion. Klemetti et al states that individuals with increased BMD keep a larger number of teeth, with greater number of periodontal pockets, compared to the ones with low BMD, that is associated with horizontal bone atrophy, gingival retraction and tooth loss. Komerik et al have revealed that under corticotherapy, patients present a smaller number of teeth and decreased mandibular BMD compared to those not

submitted to corticotherapy, but without statistical significance. (25-27)

## CONCLUSIONS

SLE and PD are two conditions that share pathogenetic similarities and that are characterized by altered inflammatory response. Therefore, it is possible for these two diseases to influence each other regarding the clinical outcome. The susceptibility to infections, specific for SLE, may impair the antimicrobial oral defense against periodontal pathogenic agents and may therefore, determine the development of PD. This hypothesis explains the higher prevalence of PD among patients with SLE, compared to the general population. Regarding the relationship between SLEDAI activity score and the extent of periodontal damage, studies show an inverse correlation between the two, possibly due to the consumption of C3 component, as a result of the biological inflammatory syndrome determined by PD. Patients who associate SLE and PD seem to have a more severe periodontal damage (higher percentage of tooth surfaces with periodontal pockets and loss

of CAL) in comparison to those with PD, but without SLE.

Cardiovascular risk in patients with SLE is explained by the atherosclerotic process, developed due to chronic inflammation. The dyslipidemia found in patients with SLE, characterized by low HDL levels, increased TG and LDL levels, is involved in the process of atherogenesis. The association of PD in patients with SLE may increase the CV risk, but further studies are needed in order to conclude this premise.

Glucocorticoids in high doses for short periods of time improve periodontal symptoms by means of diminishing the inflammation. On the other hand, long-term glucocorticoids cause extended periodontal damage (by decreasing bone density and by determining the avulsion of teeth).

Regarding the management of SLE, rheumatologists should take into account the patients' high risk of developing PD, the potential effect of PD on the course of SLE and also the oral side effects of glucocorticoids.

## REFERENCES

1. Popescu E.D., Ionescu R. Compendiu de reumatologie. Bucuresti: Editura Tehnică; 2002.
2. Croitoru G.A.I., Mihai C., Piperea-Şianu D. et al. Implicațiile infecției parodontale la pacienții cu poliartrită reumatoidă. *Ro J Rheumatol.* 2013; 22:69-73.
3. Dumitriu H.T., Dumitriu S., Dumitriu A.S. Parodontologie, Bucuresti: Editura Viața Medicală Românească, 2009.
4. Papapanou P.N. Periodontal diseases: epidemiology, *Ann Periodontol.* 1996; 1:1-36.
5. Dumitriu S., Dumitriu H. Etiologia microbiana in parodontite marginale cronice Profilaxie si tratament antimicrobian. Bucuresti: Editura Cermaprint; 1996.
6. Almoallim H. Systemic Lupus Erythematosus (pdf). InTech; martie 2012.
7. Al-Mutairi K.D., Al-Zahrani M.S., Bahlas S.M. et al. Periodontal findings in systemic lupus erythematosus patients and healthy controls. *Saudi Med J.* 2015; 36:463-468
8. Ramos Sales LdA, Vassalo S., Chaves MdGAM et al. Periodontal disease and systemic lupus erythematosus activity. *Revista Interdisciplinar de Estudos Experimentais.* 2009; 1:14-20.
9. Rhodus N.L., Johnson D.K. The prevalence of oral manifestations of systemic lupus erythematosus. *Quintessence Int.* 1990; 21:461-465
10. Kobayashi T., Ito S., Yamamoto K., et al. Risk of periodontitis in systemic lupus erythematosus is associated with Fcγ receptor polymorphisms. *J Periodontol.* 2003; 74:378-384.
11. Novo E., Garcia-MacGregor E., Viera N. et al. Periodontitis and anti-neutrophil cytoplasmic antibodies in systemic lupus erythematosus and rheumatoid arthritis: a comparative study. *J Periodontol.* 1999; 70:185-188.
12. Manakil J. Periodontal disease – A clinician's guide (pdf). InTech; february 2012.
13. Croitoru G.A.I., Mihai C., Piperea-Şianu D. et al. Riscul cardiovascular la bolnavii cu poliartrită reumatoidă și boală parodontală. *Ro J Rheumatol.* 2013; 22:129-136.
14. Genco R.J., Glurich I., Haraszthy V. et al. Overview of risk factors for periodontal disease and implications for diabetes and cardiovascular disease. *Compend Contin Educ Dent.* 2001; 22:21-23.
15. Gaitonde S., Samols D., Kushner I. C-reactive protein and systemic lupus erythematosus. *Arthritis Rheum.* 2008; 59:1814-1820
16. Gheita T., El-Gazzar I. et al. High-sensitivity C-reactive protein (hs-CRP) in systemic lupus erythematosus patients without cardiac involvement; relation to disease activity, damage and intima-media thickness. *The Egyptian Rheumatologist.* 2012; 34:147–152.
17. Calderón-Ticona J., Garro B., García J. et al. Frecuencia de dislipidemia en pacientes con lupus eritematoso sistémico. *Rev Soc Peru Med Interna;* 2002; 15(1):16-20.
18. Tripi L.M., Manzi S., Chen Q. et al. Relationship of serum paraoxonase 1 activity and paraoxonase 1 genotype to risk of systemic lupus erythematosus. *Arthritis Rheum.* 2006; 54:1928-1939.
19. Batuca J.R., Ames P.R., Isenberg D.A. et al. Antibodies toward high-density lipoprotein components inhibit paraoxonase activity in patients with systemic lupus erythematosus. *Ann N Y Acad Sci.* 2007; 1108:137-146.
20. Svenungsson E., Jensen-Urstad K., Heimbürger M. Risk factors for cardiovascular disease in systemic lupus erythematosus. *Circulation.* 2001; 104:1887-1893.
21. Thombre V., Thombre A., Bhongade M. et al. Evaluation of Alteration in Serum Lipid Levels in Patients with Chronic Periodontitis Postperiodontal Therapy. *J Indian Acad Oral Med Radiol.* 2011; 23:312-315.

22. **Lösche W., Karapetow F., Pohl A. et al.** Plasma lipid and blood glucose levels in patients with destructive periodontal disease. *J Clin Periodontol.* 2000; 27:537-541.
23. **Cutler C.W., Shinedling E.A., Nunn M. et al.** Association between periodontitis and hiperlipidemia: Cause or effect?. *J Periodontol.* 1999; 70:1429-1434.
24. **Morrison H.J., Ellison L.F., Taylor G.W.** Periodontal disease and risk of fatal coronary heart and cerebrovascular diseases. *J Cardiovasc Risk.* 1999;6:7-11.
25. **Beeraka S.S., Natarajan K., Patil R. et al.** Clinical and radiological assessment of effects of long-term corticosteroid therapy on oral health. *Dent Res J.* 2013; 10:666-673.
26. **Klemetti E., Collin H.L., Forss H. et al.** Mineral status of skeleton and advanced periodontal disease. *J Clin Periodontol.* 1994; 21:184–188.
27. **Komerik N., Akkaya A., Yildiz M. et al.** Oral health in patients on inhaled corticosteroid treatment. *Oral Dis.* 2005; 11:303–8.