Romanian Journal of Oral Rehabilitation
Vol. 9, No. 3, July- Septembre 2017

RISK PREDICTORS IN PERIODONTAL DISEASE

Solomon Sorina Mihaela[1], Iovan Gianina[1*], Pãsãrin Liliana[2], Sufaru Irina Georgeta[3], Mârţu Ioana[3], Luchian Ionuţ[3], Mârţu Maria Alexandra[4], Mârţu Silvia[4].

[1]Assist. Professor, PhD, Periodontology Dept., Faculty of Dental Medicine "Grigore T. Popa" U.M.Ph., Iasi, Romania
[2]Lecturer, PhD, Odonto-Periodontology Dept., Faculty of Dental Medicine "Grigore T. Popa" U.M.Ph., Iasi, Romania
[3]Univ. Assist., PhD, Faculty of Dental Medicine "Grigore T. Popa" U.M.Ph., Iasi, Romania
[4]Univ. Professor, PhD, Odonto-Periodontology Dept., Faculty of Dental Medicine "Grigore T. Popa" U.M.Ph., Iasi, Romania

***Coressponden Author* :** *Iovan Gianina[1*], e-mail: gianinaiovan@yahoo.com*

Abstract. Progress in understanding the etiopathogenesis of periodontal disease has led to a reconsideration of the importance of the role of different risk factors in disease processes. Risk factors act in a very personal way. The same set of risk factors that cause increased susceptibility to periodontitis in a person may have no effect on another person. Changing or eliminating a risk factor (eg smoking cessation) can alter the risk of disease or increase treatment success, whether or not known pathogenic mechanism. Numerous consistent evidence suggests the possible contribution of diabetes, smoking, and stress to periodontal destruction. The exact assessment of the risk factors for any condition depends on the degree of scientific or technical reproducibility and the validity of the diagnostic test used. Recently, attention has been paid to the risk assessment of periodontitis, mainly because the earlier paradigm regarding the etiology and progression of the disease implies an ubiquitous condition - gingivitis, which would lead to periodontitis. **Conclusions**. The concept of risk is a complex notion in permanent dynamic (risk factors / risk predictors). Dentists should be encouraged to communicate with general practitioners about the health of their patients, and general practitioners should be alerted to the possible risks of severe / aggressive forms of periodontal disease.
Key words: *risk factors, periodontitis, risk factors assessment*

Introduction

Progress in understanding the etiopathogenesis of periodontal disease has led to a reconsideration of the importance of the role of different risk factors in disease processes.

The risk is represented by the likelihood that a person develops a disease within a certain amount of time. Risk factors sum up the characteristics of individuals who place them in the high risk category of developing a disease. The risk factor is defined as "any characteristic, behaviour or exposure associated with a certain disease." [1].

A risk factor is an aspect of personal behavior, lifestyle, exposure to environmental factors, or an innate or inherited feature that, based on epidemiological evidence, is associated with a condition that influences health. Risk factors act in a very personal way. The same set of risk factors that cause increased susceptibility (to periodontitis) to a person may have no effect on another person. Risk factors are not necessarily causative [2, 3].

Depending on the duration of action, we can meet acute risk factors such as atomic bomb radiation and chronic risk factors such as radiation (sun exposure) in melanoma, smoking in many chronic diseases, hypertension in heart disease, obesity [4-8]. Changing or eliminating a risk factor (eg cessation of smoking) can alter the risk of illness or increase the success of treatment, whether or not the pathogenic mechanism is known.

Contemporary periodontology focuses on factors associated with the host. This evolution is stimulated by new evidence suggesting a link between systemic factors and the severity of periodontal disease.

Periodontal pathogens are essential for the progression of periodontal disease but are not sufficient to explain

differences in the severity of periodontal disease. It is now accepted that bacterial infection by complex interrelations with the response of the influenced host, in turn, by behavioral factors leads to periodontitis. Mature dental biofilms can host a large variety of bacterial genera. Molecular detection of the microflora in the oral cavity has led to identification of approximately 700 bacterial species or phylotypes [9]. Species compositions of dental biofilms vary greatly from sample to sample and are site-specific. From initial colonization to formation of mature and potentially pathogenic supra- and subgingival communities, dental biofilms pass through several stages, including colonization, growth of commensal bacteria, and integration and invasion of pathogenic species [10, 11]. Such opportunistic pathogens co-exist with other biofilm residents until changed environmental conditions favor their expansion and expression of their pathogenic properties.

The bacterial composition of mature biofilms sampled in the gingival sulcus of periodontally healthy subjects over an extended time period shows a high level of temporal stability. In contrast, in subjects whose clinical status changes from health to disease or vice versa, many bacterial species disappear or emerge [12]. Likewise, periodontal diseases are considered to be opportunistic polymicrobial infections.

Considering biofilms a nuisance, without any benefit to the host, may be a big mistake. Not only do biofilms affect the host, there is mounting evidence that the host's responses similarly influence the metabolism and composition of biofilms. In a healthy person, host defense and biofilms co-exist in a mutually beneficial symbiotic state. Bacteria are released continuously from dental biofilms, and to a large extent are eliminated before they elicit any host response.

Significant bacterial invasion is not observed in subjects with clinically healthy periodontal tissues. Various physiological mechanisms are in place to maintain tissue integrity; bacterial products are rinsed off by the continuous saliva flow, crevicular fluid flushes the gingival sulcus, and the high turnover of the junctional and gingival epithelia eliminates bacteria-loaded superficial cells.

Some individuals are at greater risk of periodontitis. One of the best predictors of disease progression seems to be the history of periodontal disease.

Development and progression of periodontal disease in an individual are "personalized" by a number of endogenous and exogenous factors. Assessment, knowledge and proper management of these factors facilitate the prevention of disease or its containment in the case of an existing periodontal condition.

The risk factors for periodontal disease include local and systemic factors. Among the local ones we can count the poor oral hygiene, carious lesions, malocclusion, absent teeth which have not been replaced, parafunctions, oral breathing, smoking, iatrogenies etc.

The systemic factors can be divided in physiologic factors (like puberty, pregnancy, menopause) and pathologic general factors which include systemic diseases, such as diabetes, cardiovascular diseases, osteoporosis, kidney disease, atherosclerosis etc. [13-18].

Systemic Risk Factors of the Host

Age

As people age, their risk for developing periodontal disease increases. Over half of the adult population has gingivitis, a less severe form of periodontal disease surrounding three to four teeth, and nearly 30% have significant periodontal disease. In a study of people over 70 years old, 86% had at least moderate periodontitis or a severe form of periodontal disease, and over one-fourth of this 86% had lost their teeth. The study also showed that the disease accounted for a majority of tooth extractions in patients older than 35 years of age [19, 20].

Diabetes Mellitus.

The systemic condition has long been associated with an increase in the risk and severity of periodontal disease. There

are numerous arguments that refer to the pathogenesis and control of diabetes. The mechanism for increasing risk in diabetics is probably related to: increased susceptibility to infections, compromise immune response, altered healing mechanisms, combination of these factors, modified periodontal microflora (suggested as a possible reason for increased risk of periodontitis in diabetics) [21].

Diabetes participates in accelerating periodontal disease by: reducing the resistance of periodontal tissues; producing some tissue changes that increase the effects of local factors. Diabetes mellitus, when not controlled, is characterized by a decrease in resistance to infection so as to result in an increased susceptibility of the organism to infection, vascular deficiencies and an increase in the severity of the inflammatory response. As a result, oral tissues are more susceptible to irritants in the oral cavity [22].

Diabetes is therefore a risk factor for periodontal disease. Loss of periodontal attachment and bone tissue have a much higher prevalence and severity in poorly controlled diabetics, and the incidence increases after puberty and age.

Deficiency or lack of insulin production is due to the destruction of beta-secreting insulin cells in the pancreas. The trigger may be a virus that induces an autoimmune response.

The adverse effects of metabolic dysfunction could be mediated through several mechanisms including glucose intolerance, lipid profile disturbances and substance secretion in adipose tissue or by another mechanism. The possibility that these mechanisms could act at the same time is not excluded.

Despite the existence of possible mechanisms of mediation, up to the biological mechanisms, we have found and confirmed the connection of these metabolic dysfunctions with periodontal disease, so there is an alternative involving a biological explanation that must be taken into account when the dentist evaluates and treats patients with these types of pathology.

Therefore, diabetes is an important risk factor for parodontopathy. It is also known that patients with diabetes have compromised the ability to respond to bacterial infections, and this may increase their risk of parodontopathy. Now, however, the possibility if the periodontal damage does affect the systemic condition of the diabetic is being extensively studied.

The accumulation in diabetic tissues of advanced glycosylation end products alters the integrity and functions of affected tissues. This may be the mechanism responsible for some complications seen in diabetics. Well-controlled diabetics with good oral hygiene are not at high risk of developing periodontitis. In fact, well-controlled diabetics have fewer systemic complications compared to poorly controlled diabetics and have been shown to respond well to periodontal therapy.Also, control of periodontal disease may help patients improve metabolic control. Obesity, which is common in type 2 diabetes, may also predispose a person to periodontal diseases [23, 24].

Smoking and Tobacco

Smoking has long been associated with adverse effects on systemic health (respiratory diseases, cancer). There is a clear relationship between smoking and periodontal disease (statistical analysis of 1971-75 data from the National Health and Nutritional Examination Survey in the United States). Over time, numerous studies have provided robust evidence to support an increased risk relationship between smoking and the severity of periodontal disease.

Possible mechanisms include impaired immune response, reduced vasculature, low antibody synthesis, impaired phagocytosis and chemotactic functions of PMN. Smoking seems to diminish local oxygen levels. It has suggested that partial oxygen pressure may favor the growth of anaerobic pathogens.Smoking also inhibits immunological function and negatively affects immunoglobulin levels, which may increase susceptibility to typical and unusual microbial pathogens [25].

The gingival bleeding in smokers is “less severe” than in non-smokers, which could be related to the vasoconstrictive effect of the nicotine. The main vasoconstrictive property of nicotine exerts its effect at the end-arterial vasculature of the gingivae. And other tobacco components can also induce tissue necrosis and ulceration seen in the disease. Smokeless tobacco users have an incidence of gingivitis and gingival bleeding that is similar to the incidence among non-users. Nevertheless, use of this form of tobacco is known to produce a painless loss of gingival tissues and alveolar bone destruction in the area of chronic tobacco contact, as a result of collagen breakdown due to increased release of collagenase.

Animal studies have shown that local nicotine delivery negatively impacts bone healing, which may be related to inhibited expression of various growth factors and delayed revascularization [26]. These findings might help explain the diminished treatment response to surgical periodontal procedures, especially that involving tissue regeneration. This means that tobacco smoking may exert a masking effect on gingival symptoms of inflammation, which might give smoking patients a false sense of assurance of gingival health [27]. Smoking upregulates the expression of pro-inflammatory cytokines, such as interleukin-1, this contributes to increased tissue damage and alveolar bone resorption. Interleukin-1 genotype-positive smokers are more susceptible to severe adult periodontitis.

Atherosclerosis

Periodontal disease (PD) and cardiovascular disease (CVD) are highly prevalent in the modern community. Both pathologies are chronic inflammatory disorders, which are influenced by multiple risk factors. In part, these factors such as age, smoking, and diabetes overlap between PD and CVD. Epidemiological studies suggest that PD is strongly associated with increased CVD risk [28, 29]. Biochemical and physiological analyses involving in vitro experiments, animal models, and clinical studies provided evidence for the substantial impact of periodontal pathogens, their virulence factors, and bacterial endotoxins on all general pathogenic CVD mechanisms such as endothelial dysfunction, systemic inflammation, oxidative stress, foam cell formation, lipid accumulation, vascular remodeling, and atherothrombosis. Interventional studies showed moderate beneficial effects of PD treatment on reducing systemic inflammation and endothelial dysfunction [30].

The concept of a role of periodontal pathogens in exacerbating atherosclerosis progression is not new. The findings of a number of epidemiological studies have indicated an association between periodontal and cardiovascular diseases. Serological studies have shown a link between elevated periodontal bacterial antibody titres and atherosclerotic vascular disease [31]. The results of case–control studies have confirmed the correlation between periodontal and cardiovascular diseases after adjusting for confounding factors. Results from the Oral Infections and Vascular Disease Epidemiology Study revealed an association between periodontal pathogens and atherosclerosis [32]. Furthermore, the prevalence and incidence of coronary heart disease are significantly increased in patients with periodontal disease [33]; cardiovascular diseases in patients with periodontitis are 25–50% higher than in healthy individuals [34].

Specifically, severe periodontitis has been associated with increased intima–media thickening [33]. Furthermore, poor self-reported oral health and tooth loss are positively associated with coronary atherosclerotic burden. These reports indicate that periodontal disease can independently predict cardiovascular disease [35]. Numerous studies have evaluated the impact of periodontal treatment, with or without antimicrobial therapy, on systemic inflammation or endothelial dysfunction and have shown mixed results. Thus, although meta-analyses of clinical trials support an association between periodontal disease and cardiovascular disorders, including atherosclerosis, large longitudinal studies are

needed to strengthen the current evidence supporting periodontal disease as an independent risk factor for cardiovascular disease.

Osteoporosis

Several potential mechanisms by which osteoporosis and periodontal diseases may be associated have been proposed. First, osteoporosis results in loss of BMD throughout the body, including the maxilla and the mandible. The resulting low density in the jawbones leads to increased alveolar porosity, altered trabecular pattern and more rapid alveolar bone resorption following invasion by periodontal pathogens. Second, systemic factors affecting bone remodelling may also modify the local tissue response to periodontal infection, such as increased systemic release of IL-1 and IL-6 [36].

The association of osteoporosis in postmenopausal women with periodontitis, attachment loss and gingival recession has been reported. Reduced bone mineral density was associated with increased clinical attachment loss. Therefore, studies provide evidence of an association between osteoporosis and clinical attachment loss in humans.

The relationship between periodontal disease and plasma cytokines, vitamin D and bone mineral density in postmenopausal women, with and without osteoporosis, has been investigated, and it was found that periodontal disease was more common in women with osteoporosis and was associated with lower vitamin D and higher concentrations of RANKL and osteoprotegerin. Sub-antimicrobial doses of doxycycline in postmenopausal women have shown a possible benefit in reducing the progression of attachment loss with an effect on serum biomarkers of bone loss [37]. Most studies indicate improved periodontal status in women on hormone replacement therapy／estrogen replacement therapy, characterized by increased alveolar bone mass and improved alveolar crest height, reduced clinical attachment loss and reduced periodontal inflammation.

Psychosocial Stress

Psychosocial stress has been associated with periodontal disease. In the Second World War, the soldiers on the battlefield presented the so-called trench mouth, a condition known as acute necrotizing ulcerative gingivitis -ANUG. This form of periodontal disease is known to be stress-related. The stress-induced periodontal destruction mechanism is not yet well defined. It has been known for many years that increases in corticosteroids (exogenous or endogenous) diminish the immune response. Psychosocial stress can predispose a susceptible host by: diminishing the immune response to pathogenic bacteria and altering healing mechanisms.

The role of stress in aggravating systemic conditions (cardiovascular disease) is well documented. However, the evidence to support a relationship between psychosocial stress and periodontal disease is limited. In the case-control study on the relationship between psychosocial factors and adult periodontitis, antibody positive individuals for the B. forsythus periodontal pathogen and who had elevated values on the depression scale, had a 5.3 probability of having periodontitis compared with negative individuals for anti-B. fosythus antibodies and depression [38].

Although these data are suggestive, it is premature to make concluding statements about the relationship between stress and the destruction in periodontal disease.

Genetic Predisposition

The genetics or family heritage of periodontal disease has long been suspected. In their study on adult twins with periodontal disease, Michalowitcz et al. (1991) were the first to show that peridontitis is linked to genetics [39]. Subsequent studies have shown a similar link between juvenile periodontitis and genetic predisposition. The first evidence of a genetic marker specific for the susceptibility to adult chronic periodontitis was the discovery of a relationship between specific polymorphism of the IL-1 genotype

and expression of the phenotype of severe adult periodontitis. Subsequently, the first commercial genetic susceptibility test for periodontitis (PST, Medical Science Systems, Flagstaff Ariz) became available. The increased risk for patients with positive genotype in severe periodontitis is estimated at 6.8 times higher than in individuals with negative genotype. It is estimated that approximately 30% of the population may be positive for this genetic marker.Periodontitis is considered a complex disease where a particular gene is not associated with the disease. It links to various genes, each contributing a small portion of the risk [40].

Assessment of Risk Factors

The exact assessment of the risk factors for any condition depends on the degree of scientific or technical reproducibility and the validity of the diagnostic test used. Diagnostic tests have properties that can be quantitatively determinable (sensitivity, specificity and predictive value) and are regularly described in the literature. The value of the acquired diagnostic information makes "good" a test in order to make a clinical decision.

In assessing the risk of disease, periodontitis can be rather similar to common medical conditions. Recent attention has been paid to the risk assessment of periodontitis, mainly because the previous paradigm regarding the etiology and progression of the disease implies a ubiquitous condition - gingivitis, which inevitably led to periodontitis.

In an attempt to clarify the process of identifying high-risk individuals, the North Carolina Research Group has set up a 4-stage process:

Stage I	**Identifying** the risk factors associated with the disease
Stage II	**Developing** a risk assessment model Assume bringing together relevant risk factors into a multivariate model that identifies the combination of factors that will most effectively distinguish individuals at high risk from those at low risk of developing the disease
Stage III	***Evaluation.*** Screening of population groups for the detection of factors included in the risk assessment model. Using the model to predict the individual risk of developing the disease
Stage IV	***Targeting***. Applying sanogenic / disease prevention therapy to target high-risk individuals and assessing their effectiveness.

Conclusions

The concept of risk is a complex notion of permanently dynamic (risk factors / risk predictors).

Dentists should be encouraged to communicate with general practitioners about the health of their patients and general practitioners should be alerted to the possible risks of severe / aggressive forms of periodontal disease.

Risk models represent a major contribution in the diagnosis, evolution and treatment of periodontal disease but also in prognosis.

References

1.Garcia RI, Nunn ME, Dietrich T. Risk calculation and periodontal outcomes. Periodontol 2000. 2009; 50:65-77
2.Luchian I, Mârţu I, Ioanid N, Goriuc A, Vâţă I, Hurjui L, Mârţu-Stefanache A, Tatarciuc M, Matei MN, Mârţu S. Salivary IL-1β: A Biochemical Marker that Predicts Periodontal Disease in Orthodontic Treatment. Rev. Chim. (Bucharest). 2016; 67(12): 2749-2483.
3.Mârțu S. Solomon S, Potârnichie O, Păsărin L, Mârţu A, Nicolaiciuc O, Ursărescu I. Evaluation of the prevalence of the periodontal disease versus systemic and local risk factors. Int. J. Med. Dent. 2013; 3(3): 212-218.
4.Solomon SM, Sincar C, Rudnic I, Păsărin L, Ursărescu IG, Mârţu MA, Ioanid N, Mârţu S. The assessment of renal biochemical markers and their role in periodontal disease. Rom. J. Oral Rehab. 2015; 7(3): 97-102.
5.Surdu A, Martu I, Ursarescu I, Rudnic I, Scutariu M, Mârțu S. The influence of dyslipidemia on the periodontal status in type 2 diabetes mellitus patients. Rom. J. Oral Rehab. 2014; 6(4): 38-44.
6.Păsărin L, Solomon S, Dănilă C, Teslaru S, Ursărescu I, Ioanid N, Mârțu S. Periodontal manifestations in the drug therapy of epileptic syndromes. Rom. J. Oral Rehab. 2014; 6(2): 58-63.
7.Sincar C, Solomon S, Rudnic I, Mârțu I, Mârțu S. The evaluation of the interrelation between chronic periodontitis and chronic renal disease by quantifying the glomerular filtration rate markers. Rom. J. Oral Rehab. 2013; 5(2): 62-68.
8.Macovei-Surdu A, Rudnic I, Mârțu I, Solomon S, Păsărin L, Mârțu S. Studies regarding the bidirectional relationship between the periodontal disease and hyperlipidaemia, Rom. J. Oral Rehab. 2013; 5(1):76-81.
9.Paster BJ, Boches SK, Galvin JL, Ericson RE, Lau CN, Levanos VA, Sahasrabudhe A, Dewhirst FE. Bacterial diversity in human subgingival plaque. J. Bacteriol. 2001; 183: 3770–3783.
10.Kolenbrander PE, Palmer RJ Jr, Rickard AH, Jakubovics NS, Chalmers NI, Diaz PI. Bacterial interactions and successions during plaque development. Periodontol 2000 2006; 42: 47–79.
11.Luchian I, Mârțu I, Goriuc A, Vâță I, Hurjui L, Matei MN, Mârțu S**.** Salivary PGE2 as a Potential Biochemical Marker during Orthodontic Treatment Associated with Periodontal Disease. *Rev. Chim. (Bucharest).* 2016; 67(10): 2119-212.
12.Socransky SS, Haffajee AD. Periodontal microbial ecology. Periodontol. 2000 2005; 38: 135–187.
13.Ursărescu IG, Mârțu–Ștefanache MA, Solomon SM, Păsărin L, Boatcă RM, Căruntu ID, Mârțu S. The assessment of Il-6 and RANKL in the association between chronic periodontitis and osteoporosis. Rev. Chim. (Bucharest). 2016; 67(2): 386-389.
14.Boatcă RM, Scutariu MM, Rudnic I, Mârțu–Ștefanache MA, Hurjui L, Ursărescu IG, Rezus E, Mârțu S. Evolution of inflammatory biochemical markers within periodontal therapy to patients with rheumatoid arthritis. Rev. Chim. (Bucharest). 2016; 67(4): 741-744.
15.Șufaru IG, Solomon SM, Păsărin L, Mârţu-Stefanache MA, Oanță AC, Ciocan-Pendefunda A, Mârțu S. Study regarding the quantification of RANKL levels in patients with chronic periodontitis and osteoporosis. Rom. J. Oral Rehab. 2016; 8(4): 47-51.
16.Boatcă M, Hurjui L, Rudnic I, Nicolaiciuc O, Mârţu S. Clinical and Biological Study of Rheumatoid Arthritis Influence on Salivary Biomarkers in Patients with Periodontal Disease. Balk J Dent Med. 2015; 19:150-152.
17.Solomon SM, Ursărescu IG, Păsărin L, Nistor I, Veisa G, Mârţu S. Assessment of Oral and Periodontal Parameters in Patients with End-Stage Chronic Kidney Disease. Balk J Dent Med. 2015; 19:153-157.
18.Veisa G, Donciu MD, Segal L, Hurjui L, Nistor I, Ursărescu IG, Mârțu S, Burlea L, Solomon S. Albumin as a prognostic factor for malnutrition and inflammation in chronic kidney disease *Rev. Chim. (Bucharest).* 2016; 67(1): 103-105.
19.Khalaf F, Al-Shammari , Areej K, Al-Khabbaz, Jassem M, Al-Ansari, et al. Risk indicators for tooth loss due to periodontal disease. J Periodontol. 2005; 76:1910–18.
20.Muzzi L, Nieri M, Cattabriga M, Rotundo R, Francescocairo, Prato GP. The potential prognostic value of some periodontal factors for tooth loss: A retrospective multilevel analysis on periodontal patients treated and maintained over 10 years. J Periodontol. 2006; 77:2084–9.
21.Mârţu MA, Stefanache T, Păsărin L, Foia L, Mârțu S. Evaluation of glycemia at the level of sulcular and capillary blood in diabetic patients with periodontal disease. Rom. J. Oral Rehab. 2013; 3(4): 286-290.
22.Potârnichie O, Arbune M, Ursărescu I, Mârțu S. Statistical study on diabetes mellitus incidence in periodontally affected patients. Rom. J. Oral Rehab. 2013; 5(1):10-14.
23.Mealey B. Diabetes and periodontal diseases. J Periodontol. 1999; 70:935–49.
24.Tervonen T, Oliver RC. Long term control of diabetes mellitus and periodontitis. J Clin Periodontol. 1993; 20:431–5.
25.Bergstrom J, Eliasson S. Jack Dock Exposure to tobacco smoking and periodontal health. J Clin Periodontol. 2000; 27:61–8.
26.Theiss, S.M., Boden, S.D., Hair, G., Titus, L., Morone, M.A. and Ugbo, J. The effect of nicotine on gene expression during spine fusion. Spine 2000; 25: 2588-2594.

27.Bergstrom J, Bostrom L. Tobacco smoking and periodontal hemorrhagic responsiveness. J Clin Periodontol 2001; 28, 680-685.
28.Solomon S, Păsărin L, Mârţu A, Ursărescu I, Mârțu S. The periodontal management on T.I.A. or stroke patient: a case report. Rom. J. Oral Rehab. 2013; 5(1): 86-91.
29.Nicolaiciuc O, Ursărescu IG, Mârţu-Ştefanache A, Păsărin L, Tatarciuc D, Oanţă, C Mârţu S. Study on the risk markers for atherosclerosis in patients with severe periodontitis. Int. J. Med. Dent. 2015; 5(4): 301-306.
30.Nicolaiciuc O, Ursărescu-Şufaru IG, Mârţu I, Păsărin L, Zaharescu AM, Luchian I, Mârţu-Ştefanache MA, Mârţu S. Study on the effects of classical periodontal therapy on the lipid profile in hyperlipidemic and chronic periodontitis patients. Int. J. Med. Dent. 2016; 6(3): 194-199.
31.Hayashi C, Madrigal AG, Liu X et al. Pathogen-mediated inflammatory atherosclerosis is mediated in part via toll-like receptor 2-induced inflammatory responses. J Innate Immun 2010; 2: 334–43.
32.Desvarieux M, Demmer RT, Rundek T et al. Periodontal microbiota and carotid intima-media thickness: the Oral Infections and Vascular Disease Epidemiology Study (INVEST). Circulation 2005; 111: 576–82.
33.Kurita-Ochiai T, Yamamoto M. Periodontal pathogens and atherosclerosis: implications of inflammation and oxidative modification of LDL. Biomed Res Int 2014; 2014: 595981.
34.Bartova J, Sommerova P, Lyuya-Mi Y et al. Periodontitis as a risk factor of atherosclerosis. J Immunol Res 2014; 2014: 636893.
35.Rivera MF, Lee J-Y, Aneja M et al. Polymicrobial infection with major periodontal pathogens induced periodontal disease and aortic atherosclerosis in hyperlipidemic ApoE(null) mice. PLoS One 2013; 8: e57178.
36.Ursărescu IG, Pavăl D, Solomon SM, Păsărin L, Boatcă M, Nicolaiciuc O, Nițescu DC, Mârțu S. Study regarding the IL1-α and IL1-β levels in gingival crevicular fluid in patients with chronic periodontitis and osteoporosis. Rom. J. Oral Rehab. 2016; 8(1): 97-102.
37.Ursărescu IG, Păsărin L, Solomon S, Mârţu A, Mârțu S. Clinical Assessment of Drug Adjunctive Therapy Effects in Association with Chronic Generalized Periodontitis and Osteoporotic Disease. Balk J Dent Med. 2015; 19:158-162.
38.Moss ME, Beck JD, Kaplan BH, et al. Exploratory Case-Control Analysis of Psychosocial Factors and Adult Periodontitis. Journal of Periodontology 1996; 67(10):1060-1069
39.Michalowicz BS. Genetic and heritable risk factors in periodontal disease. J Periodontol. 1994;65(5 Suppl):479-88.
40.Tarannum F, Faizuddin M. Effect of gene polymorphisms on periodontal diseases. Indian J Human Gen. 2012, 18(1): 9–19.