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REVIEW ARTICLE

Relationship between periodontal and cardiovascular diseases

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Summary

Periodontal and cardiovascular diseases share many common risk factors like metabolic syndrome, diabetes, dyslipidemia and arterial hypertension. The review discusses multifaceted relationship between periodontal and cardiovascular diseases.

The data available today demonstrate close relationship between periodontal disease and cardiovascular disease, that makes it necessary to clarify possible dental complaints obtaining medical history and inspect his oral cavity during observation of patients with cardiovascular diseases, diabetes mellitus, metabolic syndrome, and if any of them are found it is necessary to refer person to dentist. On the other hand, to increase the effectiveness of periodontal diseases treatment, it is reasonable to refer dentist's patient to physician to clarify existing somatic pathology.

Keywords

Periodontal disease, cardiovascular disease, risk factors

Chronical inflammatory diseases of periodontium (gingivitis, periodontitis) take the second place of occurrence between dental pathologies after caries. According with the World Health Organization more than 60% of European population and around 50% of the USA population have signs of chronic gums inflammation [1].

Periodontitis is the disease of dentoalveolar system that is characterized with the development of acute or chronic inflammatory process, periodontall tissue destruction and alveolar bone tissue destruction [1]. American Academy of Periodontology considers periodontitis as an inflammatory disease of bacterial genesis [2].

The significance of this problem is determined by long chronic course of inflammatory process, negative influence on patient's organism and lowered life quality. Impaired microcirculation and the presence of periodontopathogenic organisms are the main factors leading to inflammation development in periodontal tissues.

Somatic disorders like cardiovascular diseases (CVD), diabetes mellitus (DM), gastrointestinal tract

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disorders, systemic osteoporosis, respiratory system diseases have significant impact on etiopathogenesis of periodontal diseases [3].

Cardiovascular system diseases are often accompanied with changes of oral cavity organs and tissues. Periodontal diseases and CVD have many common risk factors: metabolic syndrome (MS), DM, dyslipidemia, arterial hypertension (AH).

Close connection between DM and periodontal disease are well known and based on numerous studies that had been performed in the nineties and that allow to consider periodontitis as one of the main DM complications [4]. Big number of reviews and studies indicates the presence of the linkage between MS and periodontal diseases.

In this review we will discuss connection between periodontal diseases and CVD.

Periodontal pathology and AH

Epidemiological data indicate potential connection between periodontitis with elevated blood pressure (BP) and AH prevalence. Results of crossover studies allow to propose that presence of periodontitis in patients with AH can increase the risk and degree of target organs lesions [5, 6]. Elevated BP in patients with periodontal diseases is reported in several studies.

One study performed by Polish scientists (Franek T. et al. (2010)) demonstrated that in the presence of periodontal pathology (periodontitis and gingivitis) patients with DM 2 type had left ventricle hypertrophy (left ventricular myocardial mass index, LVMMI) together with elevated systolic and diastolic BP [7].

Pilot study that had been done in Brazil (Vieira C.L. et al. (2011)) involved 79 patients with heterozygous familial hypercholesterolemia and periodontitis. Patients who had severe periodontitis had elevated diastolic BP, higher cholesterol, triglycerides, glucose levels and values of pulse wave and carotid arteries' intima-media thickness comparing with patients who had moderate periodontitis [8]. Only the connection between severe periodontitis and diastolic BP levels has been proved (Odds ratio (OR)=3,1, confidence interval (CI): 1,1-8,5, P=0,03) after correction and exclusion of common atherosclerosis risk factors. Another Brazilian study (Vidal F. et al. (2011)) demonstrated significant association between AH and severe form of chronic periodontitis (OR=4,04, 95% CI: 1,92–8,49) and common form of chronic periodontitis (OR=2,18, CI:1,04–4,56) [9].

Independent association of periodontitis and AH has been detected in Chinese study (Zhang L. et al. (2011) in adult Uigurs (1415 Uigurs older than 18 years) living in the countryside [10]. Dispersed logistical regression analysis of the results after age, sex, body mass index (BMI) correction, waist circumference, impaired carbohydrate metabolism, dyslipidemia and chronic diseases correction demonstrated that periodontitis was evidently associated with AH (OR=1,75, CI: 1,3–2,36, P<0,01).

Correlation between different characteristics of periodontal condition and AH has been estimated by Iwashima Y. et.al (2014) in Japanese people living in urban zone. This study involved 1643 participants who did not have cardiovascular disease(CVD) (average age 66,6 years, 43,4% of females). Patients with more than three changed periodontal characteristics had AH risk = 1,82 (95% CI: 2,23-2,72; P=0,003) [11].

The presence of periodontal pathology is connected with higher risk of extragenital pathology and unfavorable outcomes of pregnancy, including AH in pregnant women. One Indian study (Pralhad S. et al (2013)) involved 200 pregnant women, 100 of them had AH during pregnancy, 100 women did not have AH during pregnancy [12]. The occurrence of periodontal diseases was 65,5% and it was significantly higher (p<0,0001) in women with AH (relative risk (RR)=1,5, 95% CI: 1,3–1,9).

Swedish study (Zeigler C.C. et al. (2015)) involved patients of 12-18 years with obesity revealed the connection between the presence of pathological periodontal pockets (pocked depth ⩾ 4mm) and diastolic BP (p=0,006). Detected association did not depend on cardiovascular events risk factors or periodontal diseases [13].

German study (Jockel-Schneider Y. et al. (2014)) detected significantly higher pulse wave velocity (p=0,00004), higher augmentation index (p=0,0049) and lowered pulse blood pressure (p=0,028) in patients with severe periodontitis comparing with people without periodontal pathology [14].

Prospective pilot interventional study that involved patients with refractory AH and chronic periodontitis [15] and estimated the influence of therapeutic periodontal treatment on AH, LVMMI and pulse wave velocity. Systolic and diastolic BP values reduced by 12,5 mm Hg. and 10,0 mm Hg., respectively, and LVMMI and pulse wave velocity decreased by 12,9 g and 0,9 m/s, respectively, after treatment of chronic periodontitis (p<0,01).

In order to estimate possible influence of oral cavity hygiene on BP levels, Korean scientists used the data of 19560 adult patients from national represen-

tative survey Korea National Health and Nutrition Examination Survey (KNHANES)in 2008-2010 [16]. Performed analysis demonstrated that people who don't pay enough attention to oral cavity hygiene have higher AH prevalence before periodontitis development. Authors proposed to consider the condition of oral health as an independent predictor of AH hygiene.

Periodontal pathology and stroke

Association between periodontitis and stroke has been investigated in several studies [17, 18].

The link between periodontitis and hemorrhagic stroke has been estimated using multivariate logistic regression analysis taking into account age, gender, income, education, AH, DM, BMI, CVD, family history, smoking and alcohol consumption [17]. The connection between stroke and hemorrhagic stroke has been identified (OR=2,5, 95% CI: 1,1–5,6), with the highest risk for male patients and patients with obesity.

Association between clinical and radiologic markers of periodontal diseases and ischemic stroke has been investigated in another prospective study [18]. Between all studied stomatological parameters the most significant connection has been established for Bleeding on Probing (BOP) index (OR = 1,049; 95% CI = 1,012-1,88, p= 0,009) and bone tissue loss >20% (OR = 1,053; 95% CI = 1,017-1,091, p = 0,004).

Connection between periodontal stomatological parameters and stroke (OR = 1,58; 95% CI 1,1–3,022) had been observed in Senegalese population by Diouf M. et al (2015) [19].

Periodontal pathology and dyslipidemia

Results of numerous studies indicate that dyslipidemia can be related to periodontal pathology in somatically healthy people. For example, in one Iranian study (Golpasand Hagh L. et al. (2014)) average values of total cholesterol (TC) and triglycerides (TG) have been significantly higher in patients with periodontitis (p<0,001), at the same time the frequency of TC and TG pathological levels has been evidently higher in periodontitis group, comparing with patients with healthy periodontium (p=0,002 and p=0,015, respectively) [20]. In Indian study (Sandi R.M. et al. (2014)) patients with chronic periodontits had significant elevation of TC and low density lipids (LDL) cholesterol levels (p<0,05) comparing with patients who had healthy periodontium [21]. Lipid profile characteristics improve after treatment of periodontal diseases in patients with periodontitis [22, 23].

Periodontitis and atherosclerosis

The presence of distinct positive connection of clinical manifestations and inflammatory changes in atherosclerosis, CVD and periodontal diseases is indicated in several studies.

Consensus dedicated to periodontitis and atherosclerotic CVD that had been published in the American Journal of Cardiology and the Journal of Periodontology recommends to inform the patients with moderate and severe periodontitits about possible increased risk of cardiovascular diseases and the necessity to make cardiological examination [24].

Investigation of periodontal diseases occurrence in patients with acute myocardial infarction (AMI) and in patients with coronary heart disease (CHD) without AMI (Kodovazenitis G. et al. (2011)) revealed that periodontal diseases were more frequent in patients with AMI (38,3% and 17,5%, respectively, p=0,03) [25]. In another study Heaton B. et al. (2014) demonstrated the connection between increased marginal bone loss (MBLS) and increased risk of cardiovascular events in patients with CHD [26].

Crossover and analytical study of Marfil-Álvarez R. et al. (2014) investigated blood troponin I and myoglobin levels and estimated the association between severity of chronic periodontitis and occurrence of AMI. Indirect regression analysis demonstrated that the degree (Arbes index) and severity (Periodontal Inflammatory Severity Index) of chronic periodontitis correlated with troponin I levels after controlling influencing social, demographic and clinical factors (R change (2) == 0,041, p <0,02, and R (2) = 0,031, p = 0,04). The Arbes index value was connected with mioglobin levels (R change (2) =0,030, p< 0,01). The results of this study demonstrated that periodontitis degree and severity have positive correlation with acute myocardial infarction and its dimensions in troponin I and mioglobin blood levels.

Intima-media thickness (IMT) of carotid arteries was considered an objective indicator of connection between periodontal diseases and atherosclerosis in numerous studies.

Connection between carotid arteries IMT and flow-mediated dilatation (FMD) with periodontal pathology has been investigated in British meta-analysis (Orlandi M. et al. (2014)). Authors analyzed 2009 abstracts and 101 full-text articles. Meta-analysis demonstrated that periodontitis diagnosis was connected with IMT average growth by 0,08 mm (95% CI: 0,07-0,09) and FMD average difference of 5,1% comparing with the control group (95% CI: 2,08-8,11%). Meta-analysis of

periodontitis treatment influence on FMD has revealed average improvement by 6,64% (95% CI: 2,83-10,44%), that indicated improved endothelial function [28].

Patients with DM 2 type and periodontal diseases (gingivitis and periodontitis) had higher IMT values [29] comparing with the patients without periodontal pathology (0,804 ± 0,112 and 0,772 ± 0,127 versus 0,691 ± 0,151 mm, p <0,01 and p <0,05, respectively, OR = 5,25 for IMT⩾ 0,8 мм; 95% CI: 1,1-25).

In Chinese study (Yu H. et al. (2014)) that involved elderly patients (847 participants in the age of 70,64 ± 9.03 years with ⩾10 teeth remaining) the average dental plaque index reflecting oral cavity hygiene's condition correlated with maximal IMT and atherosclerotic plaque thickness in general (β = 0,068, p <0,001; OR = 2,051, p<0,001) and in patients without impaired carbohydrate metabolism (β = 0,066, p = 0,008; OR = 2.122, p = 0,009). In this study linear and dose-dependent correlation between average value of clinical attachment loss (CAL) index and maximal IMT has been found using multiple linear regression (p=0,006) and multivariate logistic regression analysis (p=0,025) after correction with common atherosclerosis risk factors in patients with impaired carbohydrate metabolism [30]. Each 1 mm CAL corresponded to 0,018 mm IMT increase. The risk of atherosclerotic plaque development increased by 18,3% with each CAL increase by 1 mm. Other parameters of periodontal condition also correlated with IMT and atherosclerotic plaque in patients with hyperglycemia.

The INVEST (Oral Infections and Vascular Disease Epidemiology Study) study has added new results to already big number of epidemiological evidences of CVD and periodontal diseases connections [31]. 420 participants (average age in the beginning of study was 68 ± 8 years) have been observed during 3 years, and the results of this study revealed that average IMT has increased by 0,139 ± 0,008 mm during the observation period. Carotid artery IMT progression used to reduce after improvement of clinical or microbiological condition of periodontium.

Periodontal bacteria and atherosclerosis

Together with this possible mechanisms that determine the association of periodontal pathology and atherosclerosis remain unclear [32]. Periodontal bacteria and systemic inflammation markers are considered to be possible contributing factors. The results of INVEST [31] and several other studies [33, 34] indicate possible participation of periodontal bacteria and their connection with carotid arteries' IMT change. It has been detected that carotid arteries IMT elevates in parallel with the increase of periodontal bacteries number in dentoalveolar pockets [35], and using multiple logistic regression [36] it has been shown that IMT increases in periodontitis (OR=4,22, p<0,05) in case if two subgingival organisms *Prevotella nigrescens* (OR = 4.08; p < 0,05) and *Porphyromonas gingivalis* (OR =7,63; p < 0.01) are present.

The study of Tapashetti R.P. et al. (2014) considered C-reactive protein (CRP) as the main possible mediator for association of periodontal diseases and carotid artery IMT [37]. It has been noticed that average CRP levels were significantly higher in patients with chronic periodontitis (19,58 ± 17,03), comparing with the patients without periodontal pathology (5,54 ± 1,63, p<0,004). The average IMT value was significantly higher in patients with chronic periodontitis (1,09 ± 0,45) than in patients without periodontal pathology (0,57 ± 0,06, p <0,001). Significant correlation between CRP and IMT increase was identified in patients with chronic periodontitis (r = 0,863, p <0,001).

Inflammation is considered to be one of the factors destabilizing atherosclerotic plaque. It is supposed to think that infection with Chlamydia, Helicobacter and viruses can become the cause of inflammatory reaction [3]. Indeed, the relation between acute coronary syndrome and chronic infection with Gram-negative bacteria like *Chlamydia pneumoniae and Helicobacter pylori* has been described in literature.

Epidemiological parallels between oral cavity infections and CVD have been demonstrated in several studies in vitro and in vivo, that allows to propose possible connection between oral cavity bacteria and atherosclerosis. At the same time the interaction between oral cavity bacteria and CVD is very complicated and multifactorial.

Dysbiosis of subgingival biota is common for chronic periodontitis. Periodontitis starts to manifest with gingival inflammation and it is accompanied with periodontal pockets formation, which promotes growth and development of anaerobic Gram-negative bacteria like *Porphyromonas gingivalis, Prevotella intermedia, Aggregatibacter actinomycetemcomitans и Tannerella forsythia* [38].

The INVEST [31] study has revealed the prevalence of bacteria which are traditionally considered as periodontal diseases etiological agents and which are the most tightly connected with atherosclerosis progression. These bacteria have strong relation with periodontitis clinical manifestations and inflammatory markers. Periodontal bacteria, entering blood-

stream, can go inside endothelial cells, induce endothelial dysfunction and activate inflammatory and immune reactions. High titers of antibodies to periodontal bacteria have been detected in serological studies of atherosclerosis and other CVD.

Immune and infectious changes that occur in periodontium can influence the development and severity of CVD. One of these possibilities can be realized through oral cavity bacteria translocation into atherosclerotic plaque [39]. One Canadian-Brazilian joint study [39] estimated the spectrum of microorganisms living in dentogingival pockets and atherosclerotic plaques, and 17 equal plylotypes have been identified that can evidence possible bacterial translocation between periodontal pockets and coronary arteries. Similar possibility has been demonstrated by extraction of viable bacteria *Porphyromonas gingivalis* from atherosclerotic plaque [40]. DNA of periodontal bacteria was identified in 10 out of 17 coronary artery samples: *Porphyromonas gingivalis* was present in 52,9% of cases, *Aggregatibacter actinomycetemcomitans* - in 35,5% of cases, *Prevotella intermedia* – in 23,5%, and *Tannerella forsythia* – in 11,7% of cases [41, 42].

Thus, the presence of periodontal bacteria in coronary and internal thoracic arteries can be connected with development and progression of atherosclerosis and also with valvular lesions, that has been proved by several experimental studies. The results of some of them indicate the role of Porhyromonas gingivalis in CVD pathogenesis in mice: the presence of periodontitis significantly increased the severity of atherosclerotic lesions, and it was possible to extract periodontal bacteria from vascular wall [2].

Periodontitis and systemic inflammation

Response to infection is often accompanied with secretion of proinflammatory cytokines like interleukin (IL) 1 beta (IL-1b), IL6, tumor necrosis factor alpha (TNF-α), that change lipid metabolism and promote hyper- and dyslipidemia. Proinflammatory cytokines like IL-1b, TNF-α , interferone γ induce prostaglandin E2 (PGE2) and matrix metalloproteinases (MMP) – molecules that contribute to the destruction of intercellular matrix of gingival and periodontal ligament and alveolar bone resorption [2].

Apart of this, proinflammatory cytokines cause systemic responses like elevation of CRP and fibrinogen levels. Systemic inflammatory response developing in case of periodontitis can be significant for vascular lesions, but at the same time direct action of periodontal bacteria on vascular wall remains unclear [43].

Periodontitis is considered as a risk factor for systemic inflammation because bacteria and inflammatory/proinflammatory cytokines can enter systemic circulation that can accordingly influence other organs and systems of organs [43, 44].

Numerous studies demonstrate elevated CRP levels in periodontal diseases. In Columbian study Ramirez J.H et al. (2014) revealed higher E-selectin (64,5 ± 30,9 versus 43,8 ± 22,2; p = 0,026) and myeloperoxidase (103 ± 114,5 versus 49,1 ± 35,6; p = 0,032) plasma levels, that also proved systemic character of inflammation [45].

Inflammation and endothelial dysfunction are linked with the development of atherosclerotic diseases. Periodontal infecting and subsequent increase of inflammatory markers' levels can be related to myocardial infarction, diseases of peripheral vessels and cerebrovascular disorders.

Treatment of periodontal diseases and CVD

Bad hygiene of oral cavity, irregular toothbrushing can be linked to endothelial dysfunction [46]. The use of dental floss and interdental toothbrush can reduce the risk of new cardiovascular events in patients with CHD and periodontitis (OR = 0,2, CI 0,06-0,6, p = 0,01), as it was demonstrated in the study of Reichert S. et al. (2015) [47].

In somatically healthy people with periodontitis the treatment of periodontium in the study of Leite A.C. et al. (2014) has been connected with the reduction of C-reactive protein (CRP) levels and high density lipids (HDL) cholesterol serum levels elevation [48]. In the study of Caúla A.L. et al. (2014) CRP, erythrocyte sedimentation rate (ESR), TC and triglycerids levels median has been reduced after 6 months of periodontal treatment (p <0,001, p <0,001, p <0,001, and p= 0,015, respectively) comparing with the patients treatment of whom had been delayed or who did not undergo treatment [49]. CRP levels reduction during periodontitis treatment has been also detected in other studies [7, 50].

In Australian study Cullinan M.P. et al. (2015) estimated TC, HDL cholesterol, LDL cholesterol, triglycerides, CRP, ESR, hemoglobin, white blood cells number, glomerulal filtration rate (GFR) and functional liver tests every year during 5 years [51]. This study involved 283 patients with CVD who had been subdivided into 2 groups: the 1st group (193 patients) used toothpaste with triclosan and the 2nd group (190 patients) used placebo-toothpaste. The use of toothpaste that contained triclosan was accompanied with

TC (p=0,03) and LDL cholesterol (p=0,04) levels reduction comparing with the placebo-toothpaste.

Inflammation markers and clinical parameters of patient's condition have been estimated in Chilean patients with periodontitis initially and then each 3 months up to 12 months after treatment in double blind randomized clinical trial that lasted 1 year. In the main group systemic antibiotics (amoxicillin and metronidazole) had been used for periodontitis treatment together with topical treatment. In the control group only topical treatment and placebo had been used.

Periodontal condition improved significantly 3 months after treatment (p=0,0001) in both groups and remained lower than basal level for 12 months. The main group of patients who received systemic antibacterial therapy demonstrated more significant improvement of periodontal condition (p=0,0001). CRP levels decreased with time, and this reduction was significant 9 and 12 months after therapy (p=0,024 and p=0,001, respectively) in both groups without significant differences between them. Fibrinogen levels reduced significantly only in the main group, 6 and 12 months after the treatment.

Experimental studies evidence that inhibition of vascular inflammation caused by endogenous mediators specifies a new approach for atherogenic events and periodontitis prevention.

Thus, periodontal diseases therapy is important not only for maintaining good health condition, but, possibly, as it is pointed out in several reviews [52. 53], to moderate pathological changes like atherosclerosis and CHD and subsequently AMI and stroke.

Drugs that are used for CVD treatment can influence periodontal condition. The most significant adverse effects negative for periodontium of selective calcium channel blockers (nifedipine, amlodipine, felodipine, lercanidipine, verapamil, diltiazem) are gingival hyperplasia (hemorrhage, painfulness, edema) and hypertrophic gingivitis [3].

Increased gingival hemorrhage can be observed during treatment with acetylsalicylic acid, clopidogrel, ticlopidine, warfarin, unfractionated heparin, low-molecular weight heparin (nadroparin, dalteparin, enoxaparin, bemiparin, repivarin), fondaparinux sodium, rivaroxaban, dabigatran etexilate, abciximab, eptifibatide,. Thrombolytic therapy (streptokinase, alteplase, tenecteplase, prourokinase) can also cause gingival hemorrhage [3].

Positive effects of CVD pharmacological therapy on periodontal condition are connected with the drugs of statins' group. Statins cause the following systemic (pleiotropic) effects: improvement of endothelial functional condition (restoration or improvement of endothelium-dependent dilatation), normalization (improvement) of rheological and reduction of thrombogenic properties of blood.

It is considered to be promising to reduce the activity of all inflammatory markers during therapy with statins, and the intensity of this effect does not depend on statins' action on lipids. It is supposed that anti-inflammatory action of these drugs precedes in time their hypolipodemic effect.

Antiinflammatory effect of lipid-lowering therapy is provided by such mechanisms like improved endothelial function due to increased NO synthase levels, atherosclerotic plaque stabilization, impaired thrombogenesis (due to decreased platelet aggregation and reduced fibrinogen and tissue plasminogen activator 1 type levels). Several studies demonstrated that statins reduce CRP concentration and can decrease secretion of several cytokines: IL-6, TNF-α.

Statins reduce bone resorption by inhibiting osteoclast formation and can lead to increased apoptosis of these cells, according with the results of systematic review that used PUBMED and BIREME [54] databases . Statins' effect on bone formation is related to increased expression of bone morphogenetic protein in osteoblasts. Decreased loss of alveolar bone osteal mass goes along with the reduction of periodontal inflammation clinical manifestations.

High doses of statins (80 mg of atorvastatin) comparing with low ones (10 mg) in the study of Subramanian S. et al. (2013) have led to the reduction of periodontal inflammation according with the results of positron-emission tomography and computer tomography in the beginning of treatment, and after 4 and 12 weeks [55]. There was also significant correlation between the reduction of periodontal inflammatory activity and the changes of carotid arteries (OR = 0,61, p< 0,001).

Conclusion

Discussed relation between CVD and periodontal diseases do not allow to estimate definitely their character. Together with this, all known data indicate the presence of tight connection between periodontal pathology and CVD, that makes it necessary for internal medicine specialists to pay attention to possible stomatological complaints acquiring patient's anamnesis and to perform oral cavity examination, and if any of them are found patient should be referred to stomatologist for consultation and treatment. At the

same time it is reasonable to send stomatological patient to internal medicine specialist in order to obtain more precise information about existing somatic pathology.

Conflict of interest: None declared

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