INTRODUCTION
More than a hundred years ago, the relationship between infections in the oral cavity, tooth extraction and cardiovascular diseases (infective endocarditis) [1] was established, which led in the middle of the twentieth century in the practice of medicine to the appointment of antibiotics for the prevention of endocarditis in invasive stomatological interventions [2]. After 1950, the theory of the development of infections associated with infections of the tooth-jaw system is expanding, and it is also given an etiological role in a number of other anatomical areas far removed from the oral cavity. In the last two decades, infections of the oral cavity as the cause of systemic disease, with a special emphasis on periodontal disease and their possible association with atherosclerotic vascular diseases, were again the focus of attention. [3, 4].

THE AIM
The aim of this review is to familiarize the broad sections of the medical community with the link between periodontal tissue diseases and atherosclerosis.

MATERIALS AND METHODS
A thorough comprehensive analysis and generalization of scientific research concerning the main and periodical publications related to periodontal tissue diseases in the context of atherosclerosis has been carried out.

REVIEW AND DISCUSSION
Periodontal disease is a serious problem of the present. [5]. They have a high prevalence, reduce the quality of life and chewing, have a negative effect on aesthetics, lead to disability and loss of teeth, are the cause of most cases of complete loss of teeth and are chronic diseases with potential negative consequences for health in general, promote the development of atherosclerotic vascular diseases [6]. Disease of periodontal tissues can be prevented by introducing preventive measures, for example, maintaining proper oral hygiene, brushing teeth, dental floss and regular professional hygiene of the oral cavity (by cleaning ultrasound of the roots of teeth and teeth with subsequent brushing polishing).

Periodontal disease is a group of diseases that arise from the accumulation of plaque, with or without the
development of the inflammatory process, the destruction of periodontium, including the gums itself, periodontal ligament and alveolar bone. Clinically, furrow of the gums deepens, forming a pocket, disrupting the attachment of gums to the root surface, while the biofilm on the surface of the teeth migrates apical, attaching connective tissue and appears alveolar bone loss, gingival recession [7].

Different microorganisms colonize the dental plaque above and below the edge of the gum, to form over and under gums layers of dental plaque. The over gums plaque is primarily populated Streptococcus Sanguis, Streptococcus oralis, Streptococcus mutans, Actinomyces naeslundii i Actinomyces odontolyticus. Next, the secondary colonizers, such as the Fusobacterium nucleatum, and soon form conglomeration, consisting of millions of gram-positive, gram-negative bacteria and cocci, which form a biofilm.

Over time, the microflora of the area of the attached gums goes from predominantly gram-positive to primary gram-negative, which includes a large number of obligate, anaerobic, gram-negative microbes, for example Porphyromonas gingivalis, Tannerella Forssythia, Treponema denticola, Selenomonas noxia, Campylobacter rectus, microarrophil Aggregatibacter (formerly Actinobacillus) Actinomycetemcomitans, Prevotella intermedia, and spirochetes [7]. In addition, Chlamyphila pneumoniae, Mycoplasma, Helicobacter pylori, Candida species, Epstein-Bar virus, cytomegalovirus, herpesviruses, amebi, methane-forming prokaryotic microbes (methanogens classified as arheium) are found in periodontal pockets.

Bacterial-endothelial cell interactions occur in periodontal pockets, creating and exchanging signals between microorganisms and adjacent cells of the immune system. Proinflammatory cytokines, as well as chemokines, are released, attracting dendritic cells, T-lymphocytes, B-lymphocytes, macrophages and neutrophils, which are involved in the innate and acquired immune responses and the inflammatory process [3]. Some microorganisms are likely to be involved in periodontal diseases, for example Porphyromonas ginvialis, Aggregatibacter (formerly Actinobacillus) actinomycetemcomitans and Prevotella intermedia, are attracted and assimilated by receptor-mediated endocytosis in the epithelium cells lining the ash fenurrow. Thus, endotoxin (e.g., lipopolysaccharide) produces microorganisms, for example, Porphyromonas ginvialis, protected from the immune system and can multiply within the cells, and maybe may circulate systemically through the bloodstream, causing a generalized immune response [2, 4].

Cardiovascular diseases, the basis of which is atherosclerosis, is the most common cause of morbidity and mortality of the adult population in the whole world [8]. Atherosclerotic vascular disease can lead to coronary heart disease (stable angina and acute coronary syndrome), coronary artery disease (impaired cerebrovascular flow, or stroke and transient ischemic attacks) and peripheral vascular disease.

The process of atherosclerosis begins with lipid capture in the subendothelial layer of the arterial wall, followed by the production of biologically active substances: malonic dialdehyde (MDA) - modified low density lipoprotein (MDA-LDL), which stimulate vascular cells to form inflammatory molecules, thus involving monocytes and T-cells into the intima layer of the arterial wall [9]. Circulatory monocytes also join the vascular endothelium and are differentiated into macrophages which are absorbed by lipoproteins (xanthomas (foamy)) cells. They accumulate in the form of fatty streaks that develop into more complex fibro-fatty plaques. Monocytes and T cells are attached to the surface of the endothelial cells indirectly through chemical mediators, including ICAM-1 intercellular adhesion molecules (ICAM-1), endothelial-leukocyte adhesive molecules of the first type (ELAM-1), and vascular endothelium adhesion molecules (VCAM-1) [10]. Foam cells eventually die, leaving necrotic, rich in lipoproteins of the nucleus in the arterial wall, which can calcify. At the same time, smooth muscle cells in the arterial wall migrate to the intima layer (Tunica intima) and multiply. Atherosclerotic plaques are places of chronic inflammation.

Violations of cerebral circulation and acute coronary syndrome, which are the main adverse cardiovascular factors, arise in people who develop atherosclerotic plaques in the major and coronary arteries. These diseases occur when the fibrous membrane unstable ruptures the atherosclerotic plaque, causing tissue baring under the intima of vessels, as well as partial or complete blockage of the vessel due to aggregation of platelets and the formation of blood clots in situ.

Numerous epidemiological and invasive studies confirm the link between clinically diagnosed periodontal disease and coronary heart disease. A recent review (published in 2012) was performed by the American Heart Association (AHA) working group. They conducted an electronic search for literature on the relationship between periodontal disease and cardiovascular disease (with the exception of infectious endocarditis), Behcet's syndrome, Stevens-Johnson syndrome and Sjogren's syndrome. A total of 537 articles were analyzed in dental / periodontological (61%) and medical (39%) journals [11]. A survey on the prevalence of cardiovascular diseases and periodontal disease, anatomy, pathophysiology and microbiology of periodontal diseases, risk factors and pathogenetic mechanisms for cardiovascular diseases and periodontal disease, both indirect and direct development mechanism, and actual data on interactions are published. The relationship between cardiovascular disease and periodontal disease. It was concluded that «periodontal disease is associated with atherosclerosis, regardless of somatic pathology», but there was no evidence of causation and that for this reason, «statements that imply a causal relationship between periodontal diseases and specific cases of vascular atherosclerotic diseases are unfounded» [11].

A consensus statement from the European Federation of Periodontology and the American Academy of Periodontology (EFP / AAP) was published in 2013 [12]. The results of biological, epidemiological and first data obtained after invasive studies were published. Longitudinal studies have been conducted to evaluate the incidence of cardiovascular
disease, in which statistically significant risk factors for the development of atherosclerotic vascular disease, independent of the established cardiovascular risk factors, were in individuals with periodontal disease. Given the high prevalence of periodontal disease, this risk factor is considered important from the point of view of overall health.

Only moderate evidence was found that the treatment of periodontal diseases reduces CRP and improves the function of the endothelium. No data on the effect on the lipid profile were found, but biomarkers of coagulant activity and endothelial cellular activity, as well as arterial pressure and subclinical atherosclerosis, are improved from periodontal therapy. The working group came to the conclusion that:

1) there are significant epidemiological data that periodontitis is an increased risk for the development of cardiovascular disease;
2) while in vitro tests on animals and clinical studies confirm the interaction and biological mechanism, the presently available invasive tests are not reliable to draw further conclusions. Necessary well thought out invasive trials on the effects of treatment of periodontal tissue diseases on the prevention of atherosclerotic vascular diseases with clear clinical results «7».

Other authors also systematically reviewed epidemiological data on the relationship between periodontal disease and atherosclerotic vascular disease «13». All types of longitudinal tests were studied in the English and German-speaking countries. The researchers included only those studies that used as criteria for evaluating periodontal probing, clinical loss of connection and / or radiological evaluation of alveolar bone tissue loss. To compare the risk of developing atherosclerotic vascular disease in people with periodontal disease and those who do not suffer from periodontal disease, studies have been analyzed that evaluated patients who suffered the first signs of coronary heart disease (coronary heart disease, stable angina pectoris, acute coronary syndrome, death), who had cases of cerebrovascular diseases transient ischemic attacks, acute cerebrovascular disorders and peripheral vascular diseases. Only those studies that assessed the degree of relative risk and were monitored for the assessment of the mixed effects of age and sex were included in the evaluation of the relationship between periodontal disease and atherosclerotic vascular disease. A total of 12 studies (6 for coronary heart disease, 3 for cardiovascular exacerbations, 2 for coronary heart disease and cardiovascular exacerbations, 1 for peripheral vascular disease) were selected for this review.

It was concluded that there is evidence of an increased risk of atherosclerotic vascular disease in patients with periodontal tissue diseases compared to patients without periodontal disease, but these data can not be applied to all population groups.

Inflammation can be as a component of pathobiology of atherogenesis, and a trigger for rupture of the plaque. In addition, inflammation is inherent in the pathogenesis of periodontal diseases. Inflammation can rarely be considered as a localized process, as the occurrence of inflammation mediators in the system environment occurs when the inflammatory process occurs somewhere in the body. Therefore, it is possible that the inflammatory processes affect each other when present at the same time.

Several markers can be used to evaluate systemic inflammation. The inflammatory response is characteristic of the acute phase, as evidenced by an increase in the level of C-reactive protein (CRP) or highly susceptible CRP (hs CRP) associated with many chronic diseases and is part of the Framingham risk scale used to predict mortality from cardiovascular diseases or myocardial infarction «14». However, it is unknown whether this acute phase protein will be only a marker of the inflammatory process, because it participates in the pathophysiology of atherogenesis «13». It is present in newly formed atheromatous plaques and it is localized in conjunction with the activated complement. The US Preventive Measures Team concluded from a systematic review that there is strong evidence that CRP is associated with coronary heart disease but there is not enough evidence to support the idea that CRP should be targeted for therapy «15». A number of studies have shown that in individuals without atherosclerotic vascular disease in the history of a single, planned determination of CRP can predict future vascular problems, including acute coronary syndromes, cardiovascular attacks, peripheral vascular disease, and sudden cardiac death. Thus, CRP is an independent marker for future cardiovascular disease and adds information for prediction.

Another inflammatory biomarker that is consistently linked to cardiovascular risk is myeloperoxidase (MPO), an enzyme that is expressed in leukocytes and is associated with both inflammation and oxidative stress. Both processes play an important role in the pathobiology of coronary heart disease.

The metalloproteinases are involved in the dissolution of the fibrous membrane of the atheromatous plaque, which leads to the development of the most frequent cardiovascular diseases, and indicators of many other markers are elevated in cardiovascular diseases, but not to the same extent as in CRP, for example, lipoprotein-associated phospholipase A2, tissue inhibitors of matrix metalloproteinase, fibrinogen, interleukin 6 [IL-6], soluble molecules of intercellular adhesion type 1, macrophageal cytokine-1 inhibitors and soluble form of CD40 molecule ligand «15». In diseases of the periodontal, the systemic markers of inflammation, including CRP, tumor necrosis factor (TNF-a), IL-1, IL-6 and IL-8, are elevated. Consequently, periodontal disease, as well as chronic infections, contribute to an increase in chronic inflammatory agents due to the systemic spread of inflammatory mediators released by local tissue destruction, the immune-inflammatory response to parodonotopathogens, as well as the systematic proliferation of these pathogenic microorganisms and their products. This may contribute to both the development of atherosclerosis and the discontinuity of plaques in patients with periodontal disease. Epidemiological studies of the role of periodontal disease as an independent risk factor for atherosclerotic vascular disease were reviewed by authoritative organizations such as the American Heart...
Association (AHA) and the European Federation of Periodontology (EFP) / American Academy of Periodontology (AAP), as well as by other authors [11, 12, 16]. The authors who conducted the study came to the conclusion that there is evident evidence of the relationship between these two diseases, but this statement is not valid for all groups of the population. Although the available research findings show the tendency of periodontal interventions for systemic inflammation and some markers of atherosclerotic vascular disease and endothelial function, this is not consistent with all of our studies. In addition, transient inflammation and endothelial abnormalities were seen after the exacerbation of periodontal disease. Because in our knowledge of the relationship between diseases of periodontal tissues and atherosclerotic vascular diseases there are significant problems, more fundamental, epidemiological, invasive studies are needed.

Due to concern about this health problem, all health care professionals need to know that periodontal disease is a risk factor for the development of atherosclerotic vascular diseases, and prophylaxis, diagnosis, and treatment of periodontal diseases are of paramount importance. In addition, patients with periodontal disease who have other risk factors for development of atherosclerotic vascular disease, such as hypertension, obesity, smoking, dyslipidemia, diabetes mellitus or burdened family diagnosis that have not been visited by their doctor for the past 12 months should be recommended do it. Patients prone to periodontal disease with atherosclerotic vascular diseases associated with lifestyle features, should be advised in dental clinics on these issues within the framework of a comprehensive, periodontal treatment plan. They should be given recommendations, preferably together with doctors of other specialties, for example, programs to combat smoking and obesity. The treatment of patients with periodontal diseases that are prone to the risk of developing infectious endocarditis before dental procedures should be considered in accordance with existing recommendations [2]. The above measures and approaches, which are carried out in cooperation with representatives of all medical specialties, help to support the maximum dental and general health of the patient.

CONCLUSIONS

Consequently, recent studies have shown a clear, directly proportional association between periodontal tissue diseases and atherosclerosis, but the mechanisms for their development and interaction are not fully disclosed.

REFERENCES


Authors’ contributions:
According to the order of the Authorship.

Conflict of interest:
The Authors declare no conflict of interest.