

AL Research Position in the Association of Periodontal Diseases with Acute Coronary Syndrome

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Abstract Due to their prevalence in the present, cardiovascular diseases, as well as inflammatory periodontal diseases, are considered social diseases. So, in Uzbekistan over the past 2 years, the number of patients with cardiovascular diseases aged 30 to 70 years is 53%. They are also one of the most common causes of death worldwide. Periodontal diseases, in turn, are among the most common diseases of the oral cavity and, along with caries, constitute the main cause of tooth loss. In this review, based on numerous randomized and single-blind studies, the association of inflammatory periodontal diseases of varying severity with coronary heart disease, in particular with the acute coronary syndrome (ACS), was revealed. In particular, the role of pro-inflammatory cytokines - C-reactive protein, IL-6, IL-8, TNF- α in maintaining the inflammatory process in periodontitis and progression of coronary artery disease is shown. The research is noteworthy and needs to be studied more closely.

Keywords Periodontitis, Cytokines, Interleukins, Ischemic heart disease, Acute coronary syndrome

Due to their prevalence in the present, cardiovascular diseases, as well as inflammatory periodontal diseases, are considered social diseases. So, in Uzbekistan over the past 2 years, the number of patients with cardiovascular diseases aged 30 to 70 years is 53%. They are also one of the most common causes of death worldwide [1]. Periodontal diseases, in turn, are among the most common diseases of the oral cavity and, along with caries, are the main cause of tooth loss [2,3]. Periodontal infections are also associated with the risk of some systemic diseases such as cardiovascular diseases, and autoimmune diseases such as rheumatoid arthritis [4]. In a study investigating the association between oral hygiene and cardiovascular disease, data from the National Health Insurance System - National Health Screening Cohort (NHISHEALS), including 247,696 people without a history of cardiovascular disease from 2002 to 2003, the presence of periodontal disease was associated with large tooth loss, which in turn has been associated with an increased risk of future serious cardiovascular events, including death, acute myocardial infarction, heart failure and stroke [40]. Common factors contributing to the incidence of both cardiovascular and chronic periodontal disease include aging, smoking, alcohol abuse, race and ethnicity, education and socioeconomic status, male gender, diabetes mellitus, and overweight or obesity [5,6]. Scientific evidence also points to the presence of genetic factors in periodontitis and cardiovascular disease [7].

Periodontitis is preceded by inflammation of the gums (gingivitis), which is reversible with "Proper treatment". As a result of periodontal inflammation, the tissues surrounding the tooth are infiltrated by neutrophils, macrophages and, subsequently, activated lymphocytes, releasing, for example, interleukin-1, prostaglandin E₂, and tumor necrosis factor- α (TNF- α) [8]. The significantly larger area of periodontal tissue, as well as its dense vascularization, allows bacteria, bacterial metabolic products, and inflammatory mediators to enter the bloodstream and thus contribute to endothelial dysfunction [9].

It has long been known that periodontitis itself is an independent risk factor contributing to the development of atherosclerotic vascular lesions, and the main mechanism is systemic inflammation [10]. Atherosclerosis is a chronic inflammatory process affecting the intima mainly of large and medium-sized arteries, leading to the formation of lipid deposits resulting from the accumulation of inflammatory cells and the formation of a fibro lipid structure called atherosclerotic plaque. Theories regarding the pathogenesis of atherosclerosis have changed over time [11]. Currently, the role of autoimmune and inflammatory conditions in the occurrence and progression of atherosclerosis and the development of its complications is emphasized by Bridge K.I., Philippou H., Ariens R. Endothelial dysfunction resulting from immune and inflammatory reactions in the vessel wall is the earliest and most important process in the development of atherosclerosis [11,12].

Coronary artery disease associated with atherosclerotic inflammation and acute coronary syndrome is a condition leading to elevated levels of C-reactive protein (CRP) and

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leukocytosis [13]. Leukocytes take part in atherosclerosis through participation in the inflammatory process; they cause endothelial dysfunction, and microcirculation disorders, and have proteolytic, oxidative, and procoagulant effects [13].

Mechanisms of action of active inflammatory lesions of periodontal tissues on the wall of blood vessels remain the subject of numerous studies. The immune and inflammatory background of these dependencies is emphasized. Among several complementary hypotheses, two are the most important; the first involves the direct effect of bacteria and their toxins on the vessel wall during bacteremia; the second suggests that cytokines and inflammatory mediators released during chronic periodontal inflammation have the potential to affect the vessel wall [14,15]. Despite the abundance of data confirming the relationship between periodontitis and atherosclerosis, two common pathologies, so far too little attention has been paid to the search for their joint etiopathogenesis in order to limit their adverse social consequences [16,17].

The main point of the thesis that periodontitis affects the occurrence and progression of atherosclerosis is the fact that periodontitis causes subtle systemic inflammation [41].

A significant increase in the level of markers of the systemic inflammatory response, such as the number of leukocytes, the level of CRP, fibrinogen, is important in the pathogenesis of cardiovascular diseases. [20,21]. Determining the levels of these markers may be important in assessing the risk of developing the acute coronary syndrome. Experimental models show the effect of CRP on the occurrence of endothelial dysfunction, increased expression of adhesion molecules, and recruitment of monocytes to the vessel wall. In addition, CRP promotes the formation of reactive oxygen species, as well as the proliferation and migration of smooth muscle cells [22,23]. A systematic review and meta-analysis of a study of the correlation between periodontitis and CRP levels by Paraskevas et al. [35] demonstrated an increased level of CRP in the blood serum of patients with periodontitis compared to healthy people. It has also been shown that in patients with stable coronary artery disease, an increased level of CRP increases the risk of developing myocardial infarction, and in patients with myocardial infarction, it increases the risk of complications and worsens the prognosis [25–27]. A multicenter stability study has shown an association between inflammatory markers such as CRP and interleukin-6 and periodontitis. This study recruited a large number of patients but used the simplest indicator of periodontal disease, tooth loss [28]. In the present study, the level of highly sensitive CRP (hsCRP) correlated with parameters indicating the progression of the periodontitis, such as PD ($R=0.28$; $n=0.01$), without $PD \geq 4$ mm ($R=0.24$; $n=0.04$); in addition, there was a positive correlation with loss of clinical CAL attachment ($R=0.27$; $n=0.02$). Other results were obtained by Górski et al., who showed no correlation between CRP levels and periodontal markers [29] and demonstrated in their study statistically significantly higher levels of inflammatory

markers such as hsCRP and fibrinogen in people with chronic periodontitis than in people with healthy periodontium ($p < 0.001$); moreover, they proved a positive correlation between hsCRP and fibrinogen levels and measured periodontal parameters (PD, BoP, CAL).

Fibrinogen is a protein synthesized by hepatocytes and fibroblasts in response to inflammation. The level of blood fibrinogen correlates with the severity of atherosclerotic lesions, the risk of developing acute coronary syndrome, and mortality in patients with myocardial infarction. Fibrinogen is involved in the thrombotic process; it also has a pro-inflammatory effect, as it increases the expression of adhesion molecules and stimulates the production of inflammatory mediators by endothelial cells [31]. This is of additional importance in the study group of patients with acute myocardial infarction, where prothrombotic hyperactivity is a key pathogenetic factor. A study by Bohari et al. [9], who examined 317 patients with coronary artery disease and periodontitis, indicated a correlation between BoP and fibrinogen levels. Also, Gorski et al. [17] found a positive correlation between fibrinogen concentration and BoP values ($n=0.0587$), as well as between the number of lost teeth and fibrinogen level ($n=0.0003$). Serengek et al. [33], in turn, demonstrated significantly higher levels of hsCRP, fibrinogen, and globulins in patients with chronic periodontitis, as well as a higher tendency for erythrocyte aggregation than in individuals with healthy periodontium.

A study by Agnieszka Wojtkowska et al. demonstrated a correlation between WBC count and parameters indicative of periodontal disease severity such as PD ($R=0.27$; $n=0.02$), without $PD \geq 4$ mm ($R=0.28$; $n=0.02$), as well as % $PD \geq 4$ mm ($R=0.28$; $n=0.01$) [42].

Numerous epidemiological studies have shown a positive correlation between the number of leukocytes and the risk of developing coronary heart disease [12]. In the NHAHES I prospective epidemiological study, a group of people with a WBC count < 6600 cells/mm³ was compared with a group with a WBC count > 8100 cells/mm³. An increased white blood cell count was found to be associated with an increased risk of coronary heart disease in white men ($RR = 1.31$; 95% CI 1.07–1.61) and white women ($RR = 1.31$; 1.05–1.63) at the age of 45–74 years, of course, other cardiovascular risk factors must also be considered [34]. In a meta-analysis of the seven most important studies regarding the correlation between WBC count and coronary artery disease, which included 5337 participants with CAD, a difference between a WBC count less than or equal to 2800 cells/mm³ was associated with an overall RR of 1.4 [35].

An important observation in the studies was also the correlation between periodontal markers and measures of myocardial damage in heart failure. In a study by Agnieszka Wojtkowska et al., univariate analysis showed a significant association between BoP and BNP (natriuretic peptide) levels in the main group ($R=0.29$; $n=0.02$) [42]. Linear regression analysis using reverse exclusion showed that only CAL was a significant predictor of BNP. With an increase in CAL by one unit, the value of BNP increases by 31.33 units.

For left ventricular ejection fraction prediction, none of the analyzed models was statistically significant ($F < 1.62$; $n > 0.210$), and none of the analyzed variables was a significant predictor of left ventricular ejection fraction ($n > 0.05$). BNP is recognized as a prognostic marker in patients with the acute coronary syndrome. It is believed that BNP inhibits the growth of cardiomyocytes and fibroblasts, and disrupts the synthesis of collagen in relation not only to the myocardium but also to periodontal tissues [36]. These facts seem to confirm the thesis that periodontitis is associated with the biochemical characteristics of heart failure during myocardial infarction. This probably depends on the size of the damage to the heart, as Marfil-Alvarez *et al.* At the same time, the author pointed to a correlation between periodontitis and the size of myocardial infarction. This observation reflects higher levels of troponin and myoglobin depending on the degree of myocardial damage. This observation in patients with myocardial infarction is extremely important from a prognostic point of view. Perhaps an unfavorable prognostic factor in patients with myocardial infarction is not only the classical and reliably established level of BNP but also periodontitis. However, this requires further research on this issue.

An interesting observation is a relationship between the severity of periodontitis and the level of troponin (TnI). In a study by Agnieszka Wojtkowska *et al.*, the results of linear regression analysis showed that API and BoP are significant predictors of TnI level. For a 1% increase in API, TnI levels decrease by 0.3 units, and for a 1% increase in BoP, TnI levels increase by 0.26 units. This study is consistent with the results reported by Marfil-Alvarez *et al.*, who found a significant correlation between BoP and TnI level ($R = 0.21$, $n < 0.025$) [26].

Interestingly, the relationship between chronic periodontitis severity and TnI was mediated by total leukocyte count. On the contrary, the results obtained by Agnieszka Wojtkowska *et al.* for patients with acute myocardial infarction are very different from the data presented by Vedin *et al.* [41]. That's right, they found no association between periodontal disease, a simple indicator of which was tooth loss, and troponin levels. It should be noted, however, that this study focused on patients with stable coronary artery disease. In earlier studies, these authors did not show an association between tooth loss and myocardial infarction in this population [38].

An equally important and original result of the study by Agnieszka Wojtkowska *et al.* is a significant association of periodontitis with the risk of myocardial infarction. Logistic regression analysis showed that API and BoP are significant predictors of myocardial infarction. With an increase in API by 1%, the probability of myocardial infarction increases by 8% ($OR = 1.08$), and with an increase in PD by 1%, the probability of myocardial infarction decreases by 7% ($OR = 0.93$). These results are consistent with those of the PAROKRANK study of 805 people [39]. The relationship between moderate and severe periodontitis, objectively confirmed by radiographic bone loss, and the first

myocardial infarction has been demonstrated. A stability study is a study devoted to similar topics [28]. In contrast to the previous study, the PAROKRANK study showed no association of periodontal disease with the occurrence of a first myocardial infarction. However, while this study assessed various aspects of cardiovascular risk, including myocardial infarction, all analyses were based on one but a very simple indicator of periodontitis, the number of retained teeth. Since this was a multicentre observational study, the use of a general parameter of periodontal disease is warranted. Remaining in this aspect in sharp contrast to the present study, it also emphasizes its originality and methodological validity. First, the completeness and diversity of the periodontal data collected in this study are emphasized. Secondly, it concerns the acute phase of myocardial infarction that the nature of the disease justifies the difficulty in obtaining so much periodontal data. The fact that a 1% increase in the BoP ratio is accompanied by a 7% decrease in the risk of heart attack also requires comment. Of course, a higher BoP indicates greater severity of periodontitis. However, it should be remembered that during a dental examination, patients, by the standards for the treatment of acute coronary syndromes, were already on dual antiplatelet therapy, which undoubtedly increases the risk of bleeding [18]. Moreover, the severity of bleeding may be a clear indication of the effectiveness of antiplatelet therapy and may be a problem in dental treatment in the period after acute coronary syndrome [31]. The explanation for this unexpected relationship, therefore, can be seen in that it is a net effect of the severity of periodontitis and the increased tendency to bleed associated with dual antiplatelet therapy.

Metabolic syndrome is another important aspect to consider. It is well known that the syndrome is a risk factor for heart attack and is closely associated with high mortality [32]. The latter may be additionally associated with the frequent occurrence of coronary atherosclerosis in patients with a proinflammatory and prothrombotic state characteristic of the metabolic syndrome [33]. On the other hand, metabolic syndrome is also associated with periodontitis and tooth loss [14]. Key indicators of metabolic syndrome include visceral obesity, triglycerides, HDL cholesterol, blood pressure, and fasting blood glucose [35]. All markers associated with the metabolic syndrome showed increased values in this study group. Based on markers associated with the metabolic syndrome, an adjusted analysis was performed. This analysis confirmed that API and BoP are still important indicators of myocardial infarction, albeit with slightly less statistical significance compared to the analysis without metabolic syndrome markers (for API, respectively: $n=0.001$ and $n>0.001$; for PB, respectively: $n=0.006$ and $n=0.001$). With an increase in PI by 1%, the probability of a heart attack increases by 7% ($OR=1.07$), and with an increase in PB by 1%, the probability of a heart attack decreases by 5% ($OR=0.95$).

In summary, although disorders associated with metabolic syndrome undoubtedly influence the relationship between periodontitis and the risk of myocardial infarction,

periodontitis still has an independent effect on the occurrence of myocardial infarction.

Based on the analyzes performed, it can be concluded that periodontitis is a condition that can affect the risk of developing coronary heart disease, as well as its complications in the form of myocardial infarction, as it causes a mild systemic inflammatory response. Undoubtedly, public awareness of the possible clinical manifestations of periodontitis is insufficient. Given the prevalence of coronary heart disease, high mortality from cardiovascular diseases, and the widespread prevalence of periodontitis in Polish society, it is necessary to consider the periodontal health of patients with coronary heart disease and take appropriate preventative and therapeutic measures. presented. In addition, cardiovascular risk should be assessed in patients with periodontitis. Focusing on any possible correlation between periodontal inflammation and the occurrence of coronary heart disease is of paramount importance because this may be a modifiable risk factor. The importance of chronic periodontitis should be considered in both primary and secondary prevention of cardiovascular disease [26,27]. Moreover, even one extra brushing per day in healthy adult patients can reduce the incidence of atherosclerotic cardiovascular disease [5]. However, the available literature does not provide sufficient evidence to support or refute the potential benefit of periodontitis treatment in the secondary prevention of cardiovascular disease [37,38]. Undoubtedly, further trials are needed to conclude whether treatment of periodontal disease can help prevent the onset or recurrence of cardiovascular disease. According to a recently published consensus report in 2020, patients with periodontitis should be informed of a higher risk of cardiovascular diseases such as myocardial infarction or stroke, and therefore they should actively manage all cardiovascular risk factors (smoking, exercise, excessive physical exercise). weight, blood pressure, lipid and glucose control, and adequate periodontal therapy and periodontal care [27].

An obvious limitation in studies with extensive methodology is the relatively small number of patients. For two reasons, the drugs used in patients with coronary artery disease are also an undoubted limitation. First, the use of statins, known anti-inflammatory drugs, can change the severity of systemic inflammation. However, patients with acute myocardial infarction in most cases have not yet used statins, and blood samples were taken before starting the drug. In turn, antiplatelet agents, by their nature, may increase bleeding, including those associated with dental evaluation. Moreover, the periodontal examination was carried out 24 hours after the onset of myocardial infarction and, thus, the antiplatelet activity was fully activated. However, for ethical reasons, this restriction cannot be extended since it is impossible to delay the treatment of myocardial infarction to assess the condition of the periodontium. It should be emphasized, however, that both in the case of statins and antiplatelet drugs, the limitation arising from their use is somewhat weakened because almost

all patients received the same treatment. This proves the pharmacological homogeneity of the study group, which increases the reliability of the results. Another limitation is also the possible coexistence of other inflammatory processes in patients of the main group. For this purpose, special attention was paid to the exclusion from the study of patients in whom, at the time of inclusion in the physical examination or additional examinations, additional, in addition to periodontal, detectable foci of inflammation were detected.

One of the most important factors in obtaining accurate results is the evaluation of the results. Factors influencing the doubtfulness of the assessment may be the following: dentists themselves, varying pressure during the examination, and the use of various types of periodontal probes. A study examined data evaluation between investigators and investigators for a threshold probing depth greater than 1 mm and found an accuracy rate of 91.3% [1,29]. Probing depth may depend on whether a conical or parallel-sided probe was used, with a parallel probe generally resulting in greater probing depth [39]. However, when comparing both types, 89% of the results showed no difference [15]. In the present study, all dental evaluations were performed by one person using one type of probe. This can be seen as a limitation of the study, as the same subjective aspects of the assessment were repeated, and as a strength of the study, as it determines the uniformity of the assessment across the entire study group. Any dental assessment, in addition to measurable numerical values, has a certain amount of subjectivity, which cannot be avoided.

The cardiovascular risk factors examined in the study were generally accepted risk factors for periodontal disease. Common risk factors for both diseases include smoking, diabetes, male gender, age, obesity, dyslipidemia, and elevated levels of CRP and fibrinogen. Many common risk factors make it difficult to adapt to multivariate analysis, which should be considered a limitation of the study.

Thus, based on numerous studies cited above, we can conclude that in patients with acute myocardial infarction, the condition of the periodontium is worse than in persons without coronary heart disease. More severe periodontitis, plaque accumulation, and bleeding on probing are associated with acute myocardial infarction. Periodontitis is a risk factor for myocardial infarction and also affects the degree of post-infarction damage to the left ventricle, that is, remodeling, which means there is an inflammatory relationship between these two diseases.

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