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ARTYKUŁ SPECJALNY / *STATE-OF-THE-ART REVIEW*

Oral cavity infections: why should cardiologists care about them?

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INTRODUCTION

Bacterial focal infection is an important and prevalent phenomenon, hampering precise and fast medical diagnosis, including cardiological diagnosis. This has been observed by many cardiologists taking care of patients with infective endocarditis, patients qualified for cardiosurgery, or patients with other cardiological afflictions. Leucocytosis as well as increased C-reactive protein (CRP), tumour necrosis factor alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6) plasma level confirm this phenomenon, although they do not localise it. That is when detailed, often in-depth diagnostic tests are performed in order to identify the source and characteristics of inflammatory process.

In recent years, especially in the last two decades, more attention has been paid to the coincidence of oral diseases, periodontitis in particular, and many cardiological, internal

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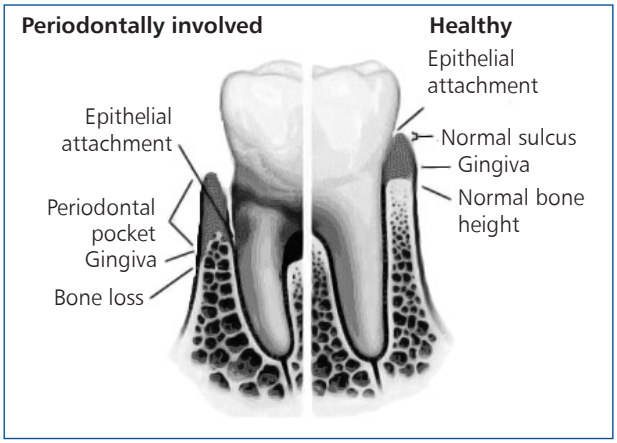

Figure 1. Healthy and diseased periodontal tissues (source: www.drfudge.com)

medicine, haematological, gynaecological, obstetric, paediatric, and oncological problems. In national and international medical literature many interesting reports have been published describing complex pathological mechanisms, as well as many case reports presenting therapeutic procedures applied and achieved treatment results.

Periodontology deals with pathologies of the periodontium — the tissues that surround and support the teeth. We would like to bring awareness to the core of infection foci within the oral cavity, with the source within periodontal tissues, in patients diagnosed and treated for cardiological problems, who are often also periodontal patients, subjected to integrated diagnostics and interdisciplinary therapy.

The term periodontium (*periodoncium*), as a complex of tissues directly surrounding a tooth, was introduced at the end of the 19th century. Nowadays it is classified as a morphological-functional entity (*periodontium*) comprising gingiva, periodontal ligament, root cementum, and alveolar bone (Fig. 1) [1–22].

AETIOLOGY AND EPIDEMIOLOGY OF PERIODONTAL PATHOLOGIES IN THE ORAL CAVITY

Epidemiological surveys of the World Health Organisation, carried out in 35 countries, have proven that in the adult population aged 35–44 years periodontal diseases (PD) afflict more than 75% (in seven countries), 40–75% (in 13 countries), and less than 40% of individuals (in 15 countries). Periodontal diseases are more prevalent among men, and their clinical intensity increases with age in all the studied populations, depending on the oral hygiene level, social-economic status, tobacco smoking, and systemic conditions.

Trials performed in recent years have proven the correlation between prevalence of PD and specific genotype. This particularly applies to the genes encoding pro-inflammatory cytokines: IL-1α and IL-1β.

As far as systemic conditions are concerned, the factors often indicated as coexisting with PD are diabetes and osteoporosis. Diabetes is a proper periodontitis risk factor. It is characterised among others by a drop in efficiency of immunological mechanisms, infections, and microangiopathies and increased collagenolytic activity and atherosclerosis progression pace. Osteoporosis affects most women of post-menopausal age and coincides with destruction of jaw bone structures, which is often additionally aggravated by tobacco smoking.

Tobacco usage intensifies plaque and calculus deposition, escalates PD, and impairs their treatment. A correlation was proven between the number of cigarettes smoked and disease activity.

Socio-economic status also influences the potential of PD development. Patients with lower financial status were observed to be more prone to oral hygiene neglect, poor diet, and addictions.

Many researchers point to the common risk factors for ischaemic heart disease and PD (Fig. 2).

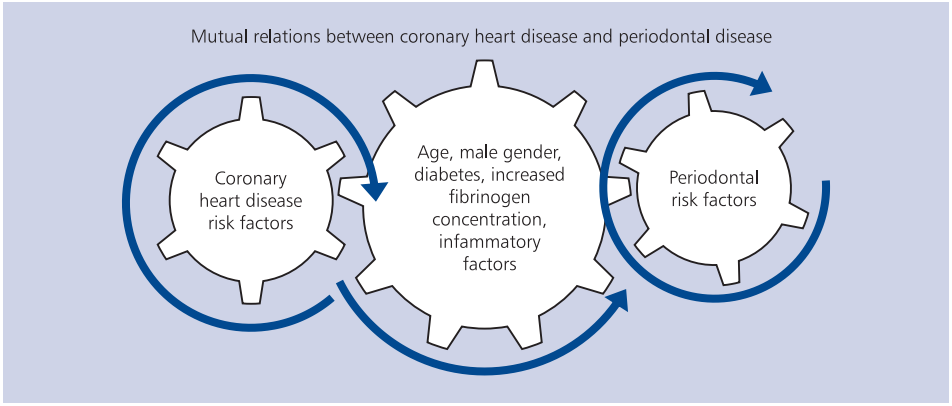

Figure 2. Common risk factors for coronary heart disease and periodontal diseases. Chart modified according to Czerniuk et al. (PAMW 1999, C1, 5: 433–436)

Periodontitis is an entity of complex aetiology, but about 90% of the adult population aged 35–44 years exhibit the presence of bacterial biofilm (bacterial plaque and calculus), localised in a pathognomonic way in the area of the gingival margin along tooth crowns. The area of most distinctive biofilm accumulation is the lingual aspect of the lower teeth, especially in the incisors region. This process relates very often to all the retained teeth as well as gangrenous tooth roots, presenting another source of potential focal infection. This has been reaffirmed in many studies in the last 25 years [22–28].

PATHOPHYSIOLOGY OF PATHOLOGICAL CHANGES WITHIN PERIODONTAL TISSUES

In healthy conditions the oral cavity is physiologically inhabited by Gram-positive bacteria, which are saprophytes. When periodontitis develops, they become a minority, overwhelmed by Gram-negative anaerobic bacteria such as *Prorphyromonas gingivalis*, *Prevotella intermedia*, *Aggregatibacter actinomycetemcomitans*, *Tannerella forsythensis*, and *Treponema denticola*. These species are a source of pathogenic bacterial factors: chemotaxins, enzymes, endotoxins, and specific antigens, activating anti-inflammatory defence as well as the immunological reaction of the host. All of the components mentioned above were identified in periodontal pockets — gaps between teeth and gingiva. Recent studies on 13,000 cases, carried out by Haffajee et al. [22] who analysed the bacterial composition of subgingival plaque by means of DNA hybridisation, have proven that in the areas of PD the most prevalent bacterial species were: *P. gingivalis*, *T. forsythensis*, and *T. denticola*, qualified together as a so-called "red complex", and which were mainly identified in points where bleeding on probing was also observed during periodontal examination. The question arises, whether the activity of inflammatory mediators, released due to the effect of activity of the pathogens mentioned above, is only confined to this space, or does it affect, in a direct (by means of blood vessels) or indirect way, by initiating a cytokine-inflammatory cascade, other, separated body structures, such as the endothelia. This may lead to distant consequences, e.g. acute coronary syndrome (ACS). There is strong evidence from cross-sectional studies that serum C-reactive protein (CRP) in periodontitis patients is elevated compared to healthy controls. Patients with cardiovascular disease (CVD) were found to exhibit more severe periodontitis than cardiovascularly healthy controls. Regarding serum CRP the American Heart Association distinguishes between three concentration intervals with increasing risk for coronary heart disease as follows: low: CRP < 0.1 mg/dL; moderate: CRP 0.1–0.3 mg/dL; and high: CRP > 0.3 mg/dL. The increase of serum CRP caused by periodontitis may be one link connecting or explaining the correlation between PD and CVD. However, there is no information whether different types of periodontitis (chronic [ChP] / aggressive [AgP]) cause different levels of systemic inflammation. Serum neutrophil elastase is another systemic inflammatory parameter. Serum elastase levels are increased in chronic infections such as chronic obstructive pulmonary disease. Serum neutrophil elastase is elevated in obese pre-hypertensive women and is associated with airflow dysfunction. Furthermore, serum neutrophil elastase activity is increased in isolated systolic hypertension and is associated with pulse wave velocity. Thus, increased serum neutrophil elastase is considered a risk factor for CVD and respiratory disease.

As in cases of other chronic infections or inflammatory processes, the host responds to bacteraemia and systemic spread of proinflammatory cytokines from periodontal pockets. The production of IL-6 is induced, which mediates the liver to produce CRP and other acute-phase proteins. This mechanism was the reason to follow serum IL-6 as a secondary outcome in this study. Bacteraemia after periodontal probing is observed more frequently in periodontitis than in gingivitis. The parakeratinised and ulcerated pocket epithelium of established gingivitis and periodontitis forms an easy port of entry for oral microorganisms. If the pocket walls of all periodontally compromised teeth in an untreated patient are combined, the wound surface due to periodontitis is estimated to be as large as 8 to 20 cm^2. The size of the wound surface depends primarily on periodontal pocket depths and not attachment loss. After periodontal treatment periodontal pockets may be resolved while clinical attachment loss (CAL) will persist. A correlation of serum elastase and CRP with mean periodontal pocket depth was found in individuals with a quite low mean attachment loss of 0.4 mm.

The present state of knowledge does not allow the exclusion of any of the hypotheses mentioned above, especially in view of the constantly increasing amount of case reports published in national and international periodicals in the last decade associating PD with cardiovascular incidents [22–28].

CLASSIFICATION OF PERIODONTAL DISEASES

It is worthwhile presenting an outline of characteristics of basic entities comprising the group of PD — gingivitis and periodontitis. The differences pertain to signs and symptoms, diagnosis, treatment course and prognosis. The aetiology of PD is complex, but in about 90% of the adult population the presence of bacterial biofilm, localised pathognomonically along the dento-gingival interface, has been observed. This process relates very often to all the retained teeth as well as gangrenous tooth roots, presenting another source of potential focal infection.

Gingivitis (gum disease) — most often results from the presence of bacterial plaque. It manifests itself with redness (colour change from pink, through vivid red, to grey-blue), spontaneous and tactile soreness, swelling, texture change and characteristic bleeding, that often occurs while eating or even while brushing teeth. Moreover, a purulent exudate (*supuratio*) can be also observed, especially after compressing marginal

gingiva in the area where it directly surrounds tooth/teeth. In the literature gingivitis is described as a reversible state that only affects gingiva. There is no loss of bone tissue — the structure in which teeth are embedded by periodontal fibres, connecting teeth surface and alveoli [1–6]. A few subgroups of this disease have been distinguished:

a) Gingivitis only due to dental plaque or additionally modified by local factors contributing to plaque accumulation, such as poor restorations (dental fillings, crowns), fixed dentures (bridges), but also naturally occurring, common malocclusions, such as teeth crowding or rotations along tooth axis.
b) Gingivitis modified by systemic factors: apart from dental plaque there are also some disturbances relating to the hormonal balance or haematopoietic system present. These patients often complain about spontaneous or provoked (by eating or tooth brushing) gingival bleeding. Pathological symptoms may be present in spite of relatively scarce amount of dental plaque, and biofilm removal diminishes clinical signs in most cases. Its presence significantly increases gingival bleeding. This subgroup includes distinct entities such as puberty-associated gingivitis, menstrual cycle-associated gingivitis, pregnancy-associated gingivitis, diabetes mellitus-associated gingivitis, and gingivitis associated with blood dyscrasias.
c) Gingival diseases modified by medications: drug-induced gingival overgrowth can often be observed about three months after introduction of pharmacological anti-convulsant therapy (phenytoin), immunosuppressive drugs (cyclosporine A), calcium channel antagonists, or — in the case of women — hormonal contraceptives. It manifests itself with gingival overgrowth in anterior maxillary and mandibular teeth, particularly in young people.
d) Gingival diseases modified by malnutrition. This entity pertains to vitamin deficiencies, mainly vitamins A, B, C, D, E, proteins, and unsaturated fatty acids (omega-3). The appropriate pharmacological supplementation, professional tooth cleaning by a dental hygienist, motivation, and improvement of daily oral hygiene are, in the majority of cases, an efficient way to control gingival inflammation.

The necrotising-ulcerative gingivitis (NUG) is a dental entity that needs special attention. NUG is painful and may destroy periodontal tissues in a short time. It is an acute, infectious, inflammatory gingival disease caused by specific bacterial flora (*Spirochaetes*, *Fusobacterii*). In a healthy oral cavity these species are saprophytes, which do not lead to pathological lesions. In the pathological situation, resulting from diminished immunity (malnutrition, vitamin deficiencies, negative protein balance, human immunodeficiency virus [HIV] infection), especially when it is additionally complicated with significant daily oral hygiene negligence, psychosocial stress, nicotine use, coexisting systemic diseases (acquired immunodeficiency syndrome — AIDS), or use of immunosuppressive drugs they lead to severe symptoms of acute gingival inflammatory disease. The signs of NUG include intense pain, spontaneous bleeding, unpleasant odour (fetor ex ore), necrosis of interdental papillae, especially on the labial side of mandibular teeth, pseudo-membranous gingival lesions, enlarged submandibular lymph nodes, anxiety, fever, and cachexia. In the past this entity was given different names: fusobacterial disease, Plaut Vincent's angina, ulceromembranose angina. As a result of gum structure destruction as well as rapid progression of inflammatory processes, NUG often continuously shades into necrotising ulcerative periodontitis (NUP). This disease also involves other periodontal tissue components: mandibular or maxillary alveolar bone and periodontal ligament. It is therefore an irreversible destruction of periodontal structures, manifesting itself after recovery in the form of linear gingival contour, resulting from permanent interdental papillae loss. Clinically the prevalence of NUG outweighs NUP. Still, both of the described entities are commonly recognised as potentially life-threatening and as such they should be diagnosed by physicians with different areas of expertise.

The above-mentioned conditions can, as a result of specific bacterial flora and inflammatory process activation that are often accompanied by cachexia, lead by means of blood and lymphatic vessels to sepsis including upper splanchnocranium areas, as well as infection foci in other organs, such as the heart. The authors wish to bring to cardiologists' attention the directly life-threatening character of this pathology, as often the pathologies originating from oral cavity, including the periodontium, are only associated with pain.

Periodontal disease — is a chronic infectious disease of tissues surrounding the teeth, leading to a progressive loss of mandibular or maxillary alveolar bone, formation of pathological periodontal pockets (spaces around teeth of more than 2 mm depth, enclosed by marginal gingiva, surrounding tooth neck and root surface), with or without gingival recessions (linear gingiva wastage) as well as characteristic decline of CAL. Clinical attachment is a band of connective tissue of about 2 mm height, located between the peak of maxillary and mandibular alveolar bone around individual teeth and gingival epithelium. It is assessed clinically by means of a periodontal probe and defined as the distance between the cemento-enamel junction (CEJ) and the most apical extension of the periodontal pocket. This value is considered an actual depth of the periodontal pocket and a proof of alveolar bone loss — increasing distance between periodontal pocket bottom and CEJ. In physiological state the periodontal pocket bottom is located at the CEJ — there is no bone loss [29, 30]. (Figs. 3, 4).

Chronic periodontitis represents about 80% of all PD cases and most often affects adults. The main reason is chronic bacterial infection, while the degree of periodontal tissue destruction refers to the number of local and systemic aetiological factors. Clinically the depostis of supra- and subgingival calculus can be observed, along with bacterial plaque

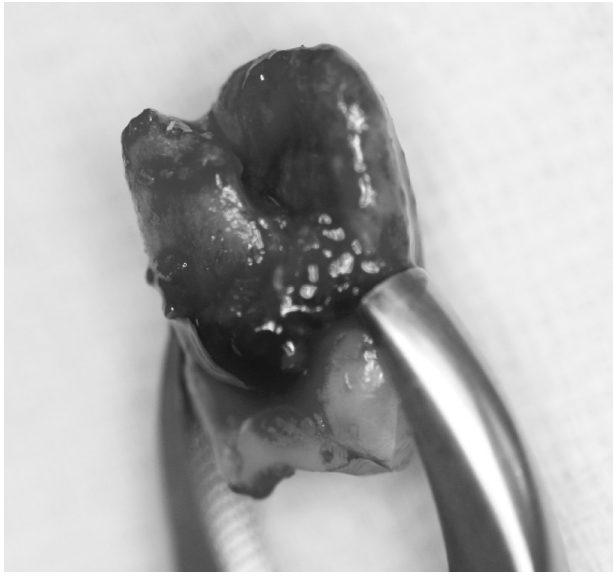

Figure 3. Extracted tooth 36 with inflammatory granulation tissue

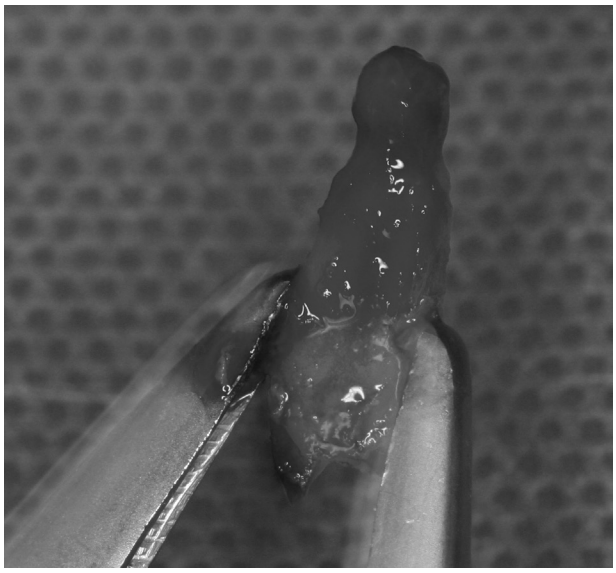

Figure 4. Tooth root with a radicular cyst and granulation tissue

on tooth surfaces. The probing depth exceeds 4 mm. In the periodontal pockets a non-specific bacterial flora can be found (*Eikenella corrodens*, *Fusobacterium nucleatum*, *Campylobacter rectus*, *Porphyromonas gingivalis*, *Prevotella intermedia*, *Aggregatibacter actinomycetemcomitans*, *Tanerella forsythia*, *Treponema denticola*). As well as local factors predisposing to the development of PD, it is also clinically associated with diabetes, HIV, cardiological diseases, and host immunological defence disorders.

Although this form of PD comprises most of the cases and affects adults, like most cardiological diseases, the authors would like also to point out some other kinds of PD.

Aggressive periodontitis exhibits a specific course of disease, affects young people, is characterised by specific bacterial flora, immune deficits, and familial prevalence. Except for the presence of periodontitis, AgP patients are otherwise clinically healthy. They exhibit rapid attachment loss and bone destruction and familial aggregation of the disease. Secondary features that are generally, but not universally, present are the following:

— amounts of microbial deposits are inconsistent with the severity of periodontal tissue destruction;
— elevated proportions of *A. actinomycetemcomitans* and, in some populations, *P. gingivalis* may be elevated;
— phagocyte abnormalities;
— hyper-responsive macrophage phenotype, including elevated levels of PGE_2 and IL-1β;
— progression of CAL and bone loss may be self-arresting.

Inflammatory serum markers such as CRP are elevated in AgP compared to ChP [31–36].

PERIODONTAL ABSCESSES

In clinical practice we most often encounter: gingival abscess, periodontal abscess, pericoronal abscess, and periapical abscess.

The pus within the abscess contains decomposed tissues. An abscess can be a manifestation of untreated aggressive or chronic periodontitis. The gingival abscess has a firmly taut, smooth, vividly red, painful, raised surface. No other periodontal tissues are affected. The periodontal abscess is located within periodontal structures, it penetrates them, and leads to their destruction. The pericoronal abscess is a suppurative infection around an erupting tooth. It often forms in adults around "wisdom teeth" (third molars) and is complicated by trismus, pain, increased body temperature, enlarged, and sore lymph nodes of the parapharyngeal and tongue area. Periapical abscess (periodontic-endodontic lesion) relates to the inflammation of the tooth root apex — apical periodontium. It can involve teeth with a necrotised pulp with ongoing inflammatory process and acute pain or endodontically treated teeth (referred to as non-vital teeth, after endodontic treatment). In both cases it can lead to the formation of suppurative fistulas located in the area of tooth root tip/tips (Fig. 5) [37].

PROPOSED COMMON FIELDS OF INTEREST FOR CARDIOLOGISTS AND PERIODONTISTS: PD IN PATIENTS WITH ACS

The inflammatory process taking place within atherosclerotic plaque can often lead to the destabilisation of this plaque, potentially leading to its rupture, which leads to a secondary thrombosis on the plaque surface and the development of ACS. The inflammatory factor, leading to this process, can be a bacterial pathogen, originating from periodontal tissues. Gram-negative, anaerobic bacterial flora is — above and beyond age, gender, tobacco smoking, diabetes, increased

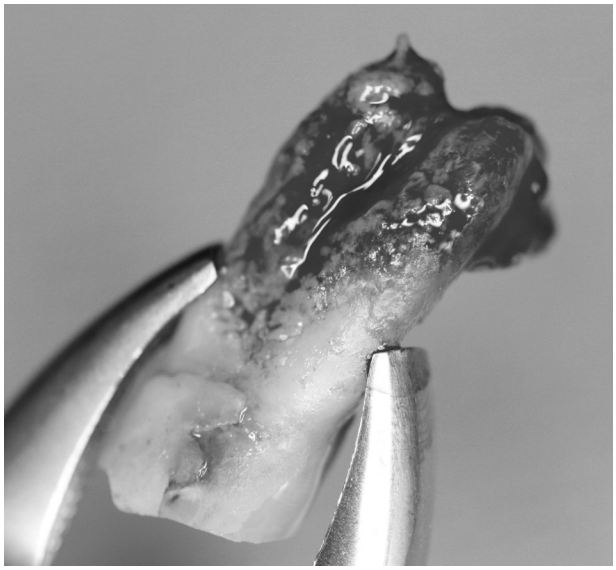

Figure 5. Premolar tooth with periapical abscess — post extraction

plasma fibrinogen and CRP concentration — a common factor linking PD and CVD. The chronic inflammatory reaction, often a derivative of local reaction, including periodontal inflammation, can lead to the destabilisation of atherosclerotic plaque and ACS. Prospective studies, also led by the authors on a group of patients with ACSs, have confirmed systemic activation of inflammatory reaction in patients with poor oral hygiene and/or PD, as expressed by increased concentration of selected inflammatory mediators: fibrinogen, CRP, IL-1, IL-6, and TNF-α.

In the conducted study the authors have correlated the PD advancement with intensity and dynamics of inflammatory reaction in patients with ACS. The obtained results enabled the following conclusion to be drawn: in patients with ACS and more advanced PD higher mean plasma concentrations of IL-1, CRP, fibrinogen, and leukocyte levels were found in short-term (10–12 days after admission to the Intensive Cardiological Care Ward) and long-term (3–6 months after ACS incident) observation. In the long-term observation, also TNF-α and IL-6 levels were increased in this group.

CARDIOLOGISTS AND PERIODONTISTS — IS IT ALSO HEART FAILURE?

Congestive heart failure (CHF) is a clinical syndrome of different aetiological background, burdened with high morbidity and mortality. The amount of people suffering from CHF in Poland is estimated at one million. This disease costs about 2.2 billion PLN from the national health budget each year [38].

An important element in CHF pathophysiology is neurohormonal activation. One manifestation of this is an increase in plasma concentration of natriuretic peptides, which have a significant diagnostic and prognostic meaning in CHF. The basic natriuretic peptide with a recognised role in diagnostics as well as in monitoring the treatment of CHF patients is plasma concentration of N-terminal pro-B-type natriuretic peptide (NT-proBNP) [37, 39–46].

In the advanced stage of CHF the frequency of exacerbations and hospitalisations increases due to the haemodynamic dysregulation and natural course of the disease. The basis of this kind of disturbance can be in some cases related to the local or systemic inflammatory process. There is an association between decreased intensity of inflammatory processes, measured by serum inflammatory parameters concentration, and improvement of CHF patients' status and even prognosis. Many authors, including Japanese, have proven that the elimination of inflammatory state in the course of PD leads to a significant decrease of CRP and TNF-α concentration.

In a pilot study led by the authors of the present report, on a group of 11 patients, this conclusion has also been broadened by a mean decrease of NT-proBNP in a six-month observation after blood collection preceding periodontal treatment onset. The initial PD therapy included: dental deposits removal (scaling), root surface planing, lateral tooth surface polishing, extraction of gangrenous tooth roots as a potential source of bacterial infection, and elimination of deep periodontal pockets (over 3 mm). Once the PD treatment was finished, blood samples were collected again. The results of NT-proBNP levels were lower, indicating a significant decrease in the inflammatory component. Potential elimination of a chronic inflammatory state, due to the active inflammation of periodontal tissues, can provide additional profits, such as an improvement of endothelial function in this group of patients [Czerniuk M.R. 2015 unpublished, 41–46].

SUMMARY

Periodontal examination should be included in a routine medical proceeding in the case of patients admitted to cardiological wards and clinics. In case of any doubts concerning oral health or suspicion of any of the diseases described above, the cardiologist should always remember about the necessity of periodontal consultation. Our own observations point to the specific importance of such a consultation in patients with ACS, and maybe also in patients with CHF. Infection within the oral cavity can be a source of a chronic systemic inflammatory burden as well as infective endocarditis. Both the factors limiting the patient's contact with the periodontologist (fear of pain on the dental chair, poor previous dental experience, lack of awareness of potential risks, treatment restricted to pain relief) and those related to medical professionals of other specialties (lack of knowledge related to oral pathologies and diagnostics, considering other organs more relevant than the oral cavity, lack of dental consultants in the hospitals) should be eliminated.

It seems appropriate to postulate the initiation of interdisciplinary, cardiological-periodontal treatment. Patients presenting to cardiologists very often require periodontal con-

sultation, but also the periodontal patients should frequently be subjected to thorough internal medical diagnostics.

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Conflict of interest: *none declared*

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