Recent decades have brought significant progress in understanding the role of cytokines in many aspects of the development of periodontal disease associated with systemic disorders and increased risk of oral cancer. A thorough search of articles was carried out on the databases PubMed on the association of periodontal disease and obstetric pathologies, systemic diseases and cancer. Refs cited are examples of support already common idea that periodontal disease may affect the initiation and/or development of serious pathological conditions. Drawn from the literature review findings confirm that chronic untreated periodontal inflammatory processes have their own important part in promoting systemic diseases and also are associated with an increased risk of developing cancer diseases.

Ostatnie dekady przyniosły istotny postęp w zrozumieniu roli cytokin w wielu aspektach rozwoju chorób przyzębia powiązanych z układowymi zaburzeniami ogólnoustrojowymi i ze zwiększonym ryzykiem raka jamy ustnej. W pracy dokonano przeglądu piśmiennictwa dostępnego w PubMed dotyczącego związku chorób przyzębia z patologiami położniczymi, schorzeniami układowymi oraz nowotworowymi. Cytowane pozycje piśmiennictwa stanowią przykłady wsparcia dla powszechnej już koncepcji, że choroby przyzębia mogą mieć wpływ na inicjację lub rozwój poważnych stanów patologicznych. Wysięnte na podstawie przeglądu piśmiennictwa wnioski potwierdzają, że przewlekłe nieleczone procesy zapalne przyzębia mają swój istotny udział w promowaniu chorób układowych, a także wiążą się ze wzmożonym ryzykiem rozwoju schorzeń nowotworowych.

Introduction

Cytokines are peptides or small proteins acting as intercellular messengers between tissues and the immune system. Virtually they are secreted by immune cells and act on other cells to exchange signals regulating appropriate immune responses. They are secreted by specific cells of immune system. Their general function as sensors and intercellular signaling peptides for transmission of “cell talk” (information) gives rise to particular biological activities. After binding with high affinity to specific receptors on target cells cytokines are capable of regulating pluripotent activities as: cellular growth, differentiation, proliferation, migration, angiogenesis and fibrosis as well as apoptosis of the multiple cell types. In addition they are able to regulate the specific immune responses. Thus net cytokine activity in any clinical or biological context is a complex issue because of the variety and multiple activities of cytokines. Released to blood they behave like hormones having influence on different tissues and organs frequently far away from source of production.

This review article discusses the host response in periodontal diseases (PD) with the emphasis of selected cytokines, produced under the pathological conditions. The pace of research in this field has greatly accelerated in the last decade. Here we provide an analysis of studies published in this area during this period. Literature was selected through a search of PubMed electronic database. One author (T.K.S.) carried out the search, and any disagreement regarding the selection of studies was resolved by consensus between two of the authors (T.K.S. and K.G.). The keywords used for search were immune innate response related to pathogenesis of periodontitis and possible associations with systemic diseases. The search was restricted to English-language articles, published from 1998 to April 2015. Additionally, a manual search in the cytokine production, cytokine functions and periodontal tissues destruction in the journals and appropriate articles was performed. Totally, over 50 selected literature sources were reviewed. The material contained in segments of our paper includes mechanisms of the formation of the innate immune reactions and some aspects of specific immune response. Of our particular interest are the so-called “inflammatory” cytokines, which involve both proinflammatory cytokine molecules IL-6, designated as an inflammatory cytokine, owing to its temporal association with the inflammatory processes has specifically turned our attention. In this context, macrophages and other cells near the interface with the external environment may serve as detection or “sentinel” cells...
that release inflammatory cytokines in response to various environmental stimuli and microbes are just one class. TNF-α is the first cytokine secreted by endotoxin-activated macrophages exerts cytotoxic effect as well as participates in differentiation and growth modulatory activities on many different target cells [2]. TNF-α is now known as a pleiotropic mediator and angiogenic cytokine that stimulate and enhances the production of other cytokines, activates inflammatory leukocytes, resulting in production of other proinflammatory cytokine such as IL-1, IL-6, and IL-8 and additional TNF-α. This factor may be viewed as a key cytokine that activates many other cytokines in the periodontal cavity of endodontosis patients [3].

Undoubtedly activated macrophages play a critical role in the pathogenesis of stomatological inflammatory conditions. The secreted TNF-α may play an important role in the local and the systemic manifestations of periodontal lesions. Variety of its effects, such as growth promotion, growth inhibition, angiogenesis, cytotoxicity, inflammation, and immunomodulation, has been implicated in several inflammatory conditions. Because of its importance in other inflammatory processes, it is likely that this cytokine plays a role in the pathogenesis of PD.

**Etiology and pathogenesis of periodontal disease (PD)**

**Epidemiology of inflammatory diseases including periodontitis and periapical lesions** indicates that these maladies threaten frequently and profoundly modern societies. Although most of recent reports on deleterious effects on the body and specifically harmful to dentition it must be noted that without the inflammatory process, life as we know it could not survive. Inflammation involves the secretion, release and activities of biochemical agents from the cells located around vascularized tissues that defend the host organisms against infection, tissue healing and repair. Currently increased interest in vast spectrum of activities of cells and special molecules they are able to produce focused on cytokines. TNF-α derived from macrophages, PMNs, being pro-inflammatory cytokine activates lymphocytes (T and B cells) and macrophages as well as stimulates bone resorption and this point will be discussed in sequence [4].

**Periodontal infection in the mouth has systemic implications; individuals with periodontal infections have elevated concentrations of circulating inflammatory markers, strongly and directly correlates with serum concentrations of inflammatory markers [5].** Chronic, continuous or severe infections at levels beyond the capacity of innate immunity are mediated by adaptive immunity, which is much more specific toward exogenous antigens. Adaptive immunity is also called specific immunity, and antibodies to membranes respond more vigorously to repeated exposures to the same antigen. The major components of adaptive immunity are T and B lymphocytes. The TNF-α is produced both by macrophages and Th1 lymphocytes. The biological effects of TNF-α include activation of leukocytes such as lymphocytes (T and B cells), macrophages and natural killer cells; fever induction; acute-phase protein release; cytokine and chemokine gene expression and endothelial cell activation [4]. This cytokine is reported to stimulate bone resorption. However, IL-1 has been found to be 500-fold more potent than TNF-α in mediating bone resorption [6].

LPS, known as endotoxin released from the infected root canals, stimulates macrophages to secrete proinflammatory cytokines, such as IL-1 and TNF-α. When present at the site of inflammation, macrophages have pivotal roles in the regulation of connective tissue destruction and repair; innate, nonspecific immunity and the onset, regulation and outcome of antigen-specific, acquired, immunity [7]. In response to bacterial encounter or activation signal of another character they produce a variety of biologically active molecules which are cytokines IL-1, IL-8 [8], IL-6, GM-CSF [9], TNF-α IL-12 [10], IL-10 [11], growth factors, IFN-α, IFN-β [12], arachidonic acid metabolites, free radicals, metalloproteinase enzymes [8], β-endorphin influencing cells of the immune system and met-enkephalin (Met-enk) [10] with added to different and well established role as a neurotransmitter activities of cytokines. Macrophages may also serve as antigen-presenting cells (APCs) in the essential initial steps of the induction of acquired immunity. They process the antigen and present it to the antigen-specific clones of T helper lymphocytes by a mechanism involving the recognition by the lymphocytes of an major histocompatibility complex class II (MHC II) molecule on the macrophages [7].

IL-1 has been identified and established as a central mediator of periapical and pulpal inflammation. This molecule is produced by macrophages, PMNs, osteoclasts and epithelial cells, chemotactically attracts and activates PMNs, stimulates the production of prostaglandins, proteolytic enzymes and cytokines IL-6, IL-8. In addition stimulates bone resorption and inhibits bone formation. IL-1 together with IL-6 and TNF-α have been shown to induce an acute-phase response-fever, an elevation in the erythrocyte sedimentation rate and major shifts in the types of serum proteins synthesized by hepatocytes [13].

The IL-6 is an integral mediator of the acute phase response to injury and infection. The major sources of IL-6 production are monocytes and macrophages, type 2 helper T lymphocytes (Th2), activated B cells and PMNs. Epithelial cells, vascular endothelial cells and fibroblasts have also been shown to release IL-6. This cytokine induces bone resorption [10].

Interestingly, majority of reports on salivary TNF-α levels have failed to provide evidence of association with periodontitis often because the levels of TNF-α in saliva are very low [14,15]. Although, one study did report significantly elevated levels of TNF-α in periodontitis patients as compared to healthy controls [20]. In contrast this study demonstrated elevated salivary levels of TNF-α in patients who had clinical indicators of periodontitis, suggesting that this biomarker may serve in a panel of salivary biomarkers that could facilitate the screening, diagnosis, and management of PD. Higher TNF-α levels correlated well clinical criteria of periodontitis viz. more sites with bleeding on probing, probing depth and attachment loss [20,21].

Some cytokines usually associated with chronic inflammation and tissue damage, such as IL-1, IL-6, TNF-α, are found in gingival crevicular fluid from clinically healthy sites, but in lower levels than in diseased sites [4]. In this context, the transition from a healthy-related to a disease-related inflammatory condition seems to be associated with quantitative and qualitative changes in the host inflammatory immune response. This research has contributed greatly to our understanding of the disease.

**The apical periodontitis is characterized by the presence of immunocompetent cells producing inflammatory mediators. Among them there are capable of long-range activities cytokines such as IL-6 and granulocyte-macrophage colony stimulating factors (GM-CSF).** The latter is a group of cytokines that regulate the proliferation and differentiation of hematopoietic cells. They functionally activate neutrophil leukocytes. GM-CSF is secreted by a large variety of cells, the possible principle sources being macrophages, endothelial cells, activated T cells and PMNs. There was a trend for higher levels of IL-6 and GM-CSF in symptomatic as compared to asymptomatic lesions. The authors suggested that furthermore releasing cytokines in active phase the apical periodontitis may induce changes in remote organs of the host [9].

**The MMPs are a family of zinc-dependent endopeptidases collectively capable of degrading all extracellular matrix components, including collagen and proteoglycans.** The MMPs have been suggested to play an important role in inflammatory conditions of periodontal, pulpal and periapical tissues, as well as dentin mineralization [22]. In addition, it was found to increase matrix metalloprotease (MMP)-9 activity in human osteoclasts, resulting in increased bone resorptive activity. These enzymes disintegrate native fibrillogenic interstitial collagens by cleaving the single peptide bond [23]. Several studies have shown that MMP-2 and -9 participate in the pathogenesis of pulp and periapical inflammation [22,24,25]. They detected those metalloproteinases in chronic periapical lesions. These results suggest that MMPs play an important role in the pulp tissue destruction of acute, inflamed pulp.

**Periodontal disease and cardiovascular disease (CVD)**

There has been a renewal of interest in recent years in the systemic effects of oral infections such as PD. As far back as 2001 Noack et al. [26] defined periodontitis as a local inflammatory process mediating destruction of periodontal tissues triggered by bacterial insult. However, this disease is also characterized by systemic inflammatory host responses that may contribute, in part, to reported higher risk for cardiovascular disease (CVD) among patients with periodontitis. Epidemiological studies show that individuals with periodontitis have a radically
amplified threat to develop CVD. Periodontal infections contribute to elevated systemic C-reactive protein (CRP) level. The positive correlation between CRP and PD might be a possible underlying pathway in the association between PD and the observed higher risk for CVD in these patients [27]. The results of Kopoppel et al. [28] support the observations of the earlier studies indicating that PD is associated with elevation in blood serum CRP and TNF-α level. Their study as well as others showed that CRP and TNF-α level decreased significantly in patients who underwent periodontal treatment.

Presently it is quite well established that CRP and TNF-α, are acute-phase proteins used for monitoring of inflammatory status; markers of inflammatory status, which have been identified as a major risk factor for atherosclerotic complications. CRP is one of the most sensitive acute-phase reactants. It increases rapidly in response to many disease conditions. Elevated CRP and TNF-α level in periodontitis patients have been reported by several groups. In studies of patients following an myocardial infarction (MI), those who have high TNF-α levels have the highest rate of recurrent cardiovascular events. Besides it may be concluded that clinically successful non-surgical periodontal therapy aimed to reduce circulating proinflammatory cytokines could be important additional preventive measure for CVD. Therefore there can be a possible causal relationship between pathogenesis of PD and CVD as inferred from the statistical significant outcome of above mentioned decreased inflammatory biomarkers after the periodontal treatment [28-30].

There is increasingly growing evidence that inflammatory mechanisms as well as unremitting infections play a foremost part in atherogenesis and CVD. Quite a few studies propose a relationship linking periodontal diseases and atherosclerosis [31]. Apparently such cytokine elevations as that seen in PD may supplement and enhance systemic vascular inflammation, atheroma formation and to the pre-existing risk for cardiovascular related conditions as for example atherosclerosis. Research suggested that PD, once established result in biological burden of endotoxin and inflammatory cytokines like TNF-α which makes easier launching and then building up the atherogenic and thromboembolic processes. PD with elevated bacterial exposure is associated with CVD events and early atherogenesis as measured by carotid intima-media thickening (CIMT), suggesting that the level of systemic bacterial exposure from periodontitis with CVD events and early atherogenesis as inferred from the statistical correlation between CRP and PD might be a major factor in the development of diabetic complications [39].

Periodontitis may also contribute to the elevation of serum inflammation mediators through enhanced in vitro production of TNF-α, IL-1 and IL-6 by monocytes, as has been shown in patients with both diabetes and periodontitis. This may indicate an innate hyperresponsiveness of these monocytes to periodontal bacterial challenge [5]. Periodontitis may also play a role through the translocation of gram-negative species and their products from the periodontal biofilm into the circulation and through direct cytokinemia from the gingival crevicular fluid (i.e., translocation of cytokines from the periodontal space into the circulation) [37]. Periodontal treatment has been shown to reduce serum levels of inflammatory mediators, including IL-1, IL-6, TNF-α and CRP, in patients with and without diabetes [38]. Pro-inflammatory factors are reportedly increased in diabetes mellitus and contribute to insulin resistance by both stress activated JNK and the IkB/NF-κB pathway. Enhanced production of inflammatory cytokines is thought to contribute to insulin resistance and the destruction of beta cells in the pancreas and is thought to be a major factor in the development of diabetic complications [39].

Periodontal disease and adverse pregnancy outcomes

The association between periodontitis and some of the problems with pregnancy such as premature and/or low birth weight (PLBW) and diabetes (Gestational diabetes (GDM) or type 2 diabetes (T2D)) has been suggested [40-41]. Periodontitis are associated with induction of premature births and other gestational complications, which may compromise the subject throughout life. Periodontal pathogens maybe involved in this process, directly inducing fetal abnormalities, or inducing the inflammatory response and the contraction of myocytes, increasing the severity of PD. Maternal microscopic changes that occur in the oral cavity over the course of a normal pregnancy favor the prevalence of putative periodontal bacteria in women during all trimesters of pregnancy. The potential risk factors regarding PLBW have been the centre of many studies for several years. Recently, researchers suggest PD as an important risk factor in determining poor pregnancy outcomes, including PLBW due to translocation of bacterial products (specially LPS) or inflammatory mediators (specially IL-1, IL-6,TNF-α and PGE2) [45,46].

Periodontal disease and cancer

No doubt there is a link between PD and cancer. Evidently that people with PD may have a higher risk for cancer [47-52]. Studies have shown that appropriately treated PD is associated with a significantly lower overall risk of cancer, and reduced risks for malignancies of the digestive system, the oral cavity, the lungs, the female reproductive organs and the brain. The inflammatory cells and mediators produced in response to PD may account for these relationships [47]. In addition, the inflammation caused by PD may enhance cellular proliferation and mutagenesis, reduce adaptability to oxidative stress, promote angiogenesis and inhibit apoptosis [53-56]. The relationship between inflammation and cancer has been well documented in the recent literature, although the original hypotheses linking the two appeared more than a century ago. Periodontitis is a chronic inflammatory disease attacking the supporting tissues around the teeth, resulting in constant low-grade systemic inflammation with elevated levels of circulating inflammatory markers. It has been suggested that inflammatory markers produced in the immune response to periodontal disease include pro-inflammatory plasma cytokines, peripheral white blood cells, prostanoids, proteases including matrix metalloproteinases, and acute-phase proteins. It is also possible that the chronic inflammation induced by periodontal pathogens stimulate the immune system to initiate, leading to the breakdown of normal cell growth control, and potential carcinogenesis. Periodontal bacteria may also play a more direct role through local inflammatory responses and carcinogenic transformations [57].

Quantification of an association between PD and cancer is very difficult, since periodontal disease would have substantial implications for public health in terms of prevention and early diagnosis. Therefore, application of specific case-deifnitions of PD for use in population-based surveillance is crucial [51]. Cytokines appear to interact functionally in networks in the periodontium and integrate aspects of
innate and adaptive immunity. However, our understanding is far from complete, particularly how molecular and cellular pathways relate to disease pathogenesis. We should adopt consistent experimental approaches to gain better insight into the totality of cytokine interactions and their role in driving immune responses impacted our understanding of periodontitis? J Clin Periodontol. 2011; 38 (Suppl. 11): 60-64.


