GENERAL REVIEWS

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Cytokines in pathogenesis of peri-implantitis

Uloga citokina u patogenezi periimplantitisa

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Implants and their interaction with organism

General term of implantation implies insertion of biomaterials of different designs into the tissues. Oral implantation is a surgical insertion of aloplastic materials (metals, alloys**,** ceramics, polymers, carbons as well as their combinations) into the hard and soft tissues of the upper and lower jaws [1].

The essence of implantology lies in favorable reaction of the organism to the presence of foreign body or favorable response of the bone tissue to implant material. The organism reaction is the development of inflammation resulting in a complete recovery of tissues and acceptance of implants or its loss. Implantation is a traumatic damage of the soft and hard tissues. Regardless of how much the procedure has been carefully conducted, tissue response is controlled by mechanisms of bone healing metabolism, as well as by other biomechanisms. As with every other tissue damage, the organism reacts with inflammation with the aim to limit the damage or to replace the lost or damaged tissue with the processes of regeneration or reparation [2]. Metabolic activities of the bone marrow and the constant process for bone remodeling are important prerequisites of the long-term implant stability. Successuful outcome of implant placement depends on: implant material, design, adequate patient selection and proper indicators, careful surgical technique used and creation of functional and esthetic prosthetic restoration.

Each implant material should be: biocompatible, bioinert, biofunctional and bioadhesive [1].

Biocompatibility means that implant material is not toxic, cancerogenic, allergenic, *i.e.* induces no immune reaction. In other words, histocompatibility is a "harmony" of implant material and living tissues that do not harm each other. Bioinertia primarily refers to material insolubility and stability, and resistence to corrosion, in tissue fluids. Biofunctionality includes implant design, its strenght and ability to withstand loading conditions. Bioadhesion is characterized by close intimate contact of implant surface and the surrounding tissuess. Ideal implant material which meet all the four-mentioned criteria has not yet been produced, but the common opinion is that it is sufficient that the human organism tolerates inserted material.

The condition of peri-implant soft and hard tisuess is highly significant for implant longevity and function [3]. The main role of soft tissue surrounding implants is to provide the hermetic seal and protective barrier between oral cavity and the internal peri-implant bone, thus preventing invasion of various pathogens. Bone tissue, on the other hand is responsible for implant osseointegration, stability, overtime and distribution of masticatory forces. There are many contradictory facts concerning peri-implant tissue. It is believed that hemidesmosome and basal membrane, similar to natural tooth, are the mediators for epithelial cell adhesion to the implant surface [4].

Peri-implantitis

Peri-implantitis is defined as an inflammatory reaction with the loss of supporting bone in the tissues surrounding a functioning implant. Peri-implant diseases are classified according to the part of the oral tissue involved in the inflammatory process. If inflammation is located only the gingival

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tissue around the implant neck is defined as peri-implant mucositis. Progression of inflammation results in bone loss adjacent to the implant causing peri-implantitis. The onset of peri-implantitis is in the marginal bone adjacent to the coronary part of the implant while its apical part remains osseointegrated. The implant is clinically stable, while the last stadium where a complete loss of bone-to-implant contact occurs. If left untreated, it can result in implant loss. Numerous clinical studies have reported near 4% implant loss [4–6].

Risk factors that can lead to peri-implantitis are local (microbial plaque, parafunctions, smoking, poor oral hygiene) and general, *i.e.* susceptibility to peri-implantitis, is determined by genetic factors or the influence of some systemic diseases.

Two main etiological factors that significantly contribute to the onset of peri-implant mucositis and resorption of the marginal part of the bone tissue are bacterial infection and biomechanical factors resulting from the excessive loading the implants in function [7].

Excessive overload of implants can cause microfractures in marginal bone region and cause the loss of oseointegration around the neck of the implant.

Plaque accumulation and microbial contamination of peri-implant tissue cause inflammation of subepithelial connective tissue with massive inflammatory cell infiltrations. Epithelial seal is loosely fixed, suppuration can occur, clinical as well radiographical signs of tissue destruction can be observed.

A microbiological research has shown that subgingival bacterial flora, isolated in peri-implantitis, is completely different from the microbiological findings around implants with no signs of inflammation. Considering oral microflora as a possible risk factor for peri-implant tissue disease, the evidence suggest that no significant differences exist in the distribution of bacterial morphotypes around implants and teeth respectively.

Dominant microorganisms isolated from the subgingival plaque in the case of periimplantitis are Gram-negative bacilli and spirochetes. The number of spirochetes is in positive correlation with the quantity of plaque, pockets depth around the implants and bone resorption. Apart from spirochetes, other isolated bacilli are: *Prevotella intermedia, Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis, Fusobacterium nucleatum, Actinomyces i Haemophilus* [8].

Mombeli and Lang [9] in 1994 were the first to report on the interaction of microbiological flora and implant failure. In cases of successful implants, *i.e.* osseointegrated cocci predominated, whereas in the cases of peri-implantitis a significant increase of spirochetes was observed. Progression to peri-implantitis from perimucositis does not always occur, just as every case if gingivitis does not progress to periodontitis. Microbial differences between partially and completely edentulous patients were explored [10].

Increase susceptibility to peri-implantitis was described in partially edentulous jaws [10].

The assessment of the degree of inflammation is based on clinical and radiographic findings. Clinical signs include the status of peri-implant soft tissue, implant stability and general signs of inflammation which are evident in the advanced stages of peri-implantitis: peri-implant soft tissue oedema, redness, bleeding on probing, increased probing depth, suppuration, pain.

Radiographic findings reveal increased bone resorption which is presented on the mesial and distal aspects of the implant neck as a V – shaped radiolucency. Although standard radiographic examination is the most common method used, it is not completely precise, because the buccal and oral aspects of the peri-implant bone tissue cannot be evaluated.

Cytokines in inflammation

Cytokines comprise a group of soluble, low molecular proteins, unspecific mediators of an inflammatory reaction that transfer various intercell signals necessary for the integrated cell response to different exogenous stimuli both in physiological and pathological conditions. Cytokines are secreted by lymfocytes**,** by the cells of the monocyte macrophage systems, by thrombocytes and many other non-circulating cells. They modulate inflammation and immune reactions by regulating the growth, mobility and differentiation of leukocytes and other cells, and all together are important in pathophysiology of numerous diseases [11].

Cytokines can be classified according to their similarity in dominant biological activities related to the target cells, similarities in their origin, structural similarity and similitary of the receptors through which they act.

Most of cytokines show biological effects through specific receptors on the membranes of target cells. Linking of cytokines to receptors triggers the intercell signals that result in specific changes in genetic expression of the target cells.

Some of cytokines express chemotactic effect, whereas the other express direct cytotoxic or antiviral effect.

Cytokines play an important role in pathogenesis of almost all of systemic and local diseases. They represent important mediators of physiological and pathological activities in the tissues of orofacial region [12]. One of the most spread out diseases of orofacial region is periodontal disease which when left untreated results in the loss of teeth, when dental implants can be used as a one of treatment modalities. Detection of cytokines in clinical laboratories is important because it can provide following of progression and activity of numerous disesase. In research laboratories, evaluation of cytokine gene expression has been investigeted expecting that this kind of research would provide better explanation of mechanisms of cytokine effect in the process of periodontal diseases.

The role of cytokines in peri-implantitis

Local response to peri-implant bacterial infection is in immunological and biochemical aspect very similar to the response in periodontal disease, which has been reported in many studies [13, 14].

Page et al. [15] set a hypothesis in 1997 that the progression of periodontal disease depends on: the presence and ac-

tivity of pathogenic bacteria; high local production of proinflammatory mediators (cytokines), extracellular matrix metalloproteinasis (MMP) and prostaglandin (PGE); low local production of inihibitors of inflammatory processes, particularly cytokines with immunosuppressive action, such as interleukin (IL) 10 (IL-10), factor of growth transformation beta 1 (TGF-β1) and MMP inhibitors.

Local balance of these mediators that reflects local activity of cells that produce them, determines the level of tissues destruction. Pathohistological substrate of disease consists of mononuclear cell infiltrate, the composition of which significantly transforms depending on the advancement of the process. Namely, predomination of T lympocytes in early lesions, is slowly replaced by B lymphocytes infiltrate in late, chronic or acute lesions.

Based on the determination of the produced cytokines profiles and types of cell infiltrates, there are at least three well – argumented and oppose theories of pathogenesis of the onset of periodontitis from the initial gingivitis.

Seymour et al. [16] in 1993 claim that the change of predominant T lymphocyte infiltrates in gingivitis into the dominant B lymphocyte infiltrate in periodontitis is mediated by the excessive local production of Th2 type cytokines. Th2 cytokines (IL-4, IL-5, IL-10, IL-13) cause local proliferation and differentation of B lymphocytes, local secretion of nonprotective antibodies specific for antigene bacteria determinants and hyperproduction of IL-1, which leads to the lesion progression.

This is not in agreement with Ebersole and Taubman [17] who claim that the local production of Th2 type cytokines is important for local immune response, because it stimulates the production of specific antibodies, as well as the production of anti-inflammatory cytokines: IL-4, IL-10, IL1 receptor antagonist (IL1-RA), which can stop the onset or delay the progression of periodontal lesion. According to the same authors, the onset, longevity and progression of the lesion is the consequence of specific $CD8^+$ T lymphocytes activities. Tissue damage caused by cytotoxic $CD8^+$ T lymphocytes, can be direct or is the result of production of proinflammatory cytokines (IFN-γ, IL-1) that stimulate destructive processes of local macrophages and osteoclasts.

Contrary to these hypotheses, Dennison and Van Dyke [18] claim that macrophages and their altered functions are mainly responsible for the pathogenesis of a periodontal lesion. Namely, according to them macrophages represent the effectory cells that manage the activities of osteoclasts and osteoblasts. An adequate production of one of the key Th2 cytokines, IL-4, inhibits the activation of macrophages, the presence of antigenes, production of proinflammatory cytokines necessary for triggering an adaptive immune response and increases the apoptosis of macrophage, resulting in the delay in onset of periodontal lesion. Interferon (IFN)-γ key Th1 cytokine has the opposite effect.

Peri-implantitis is a result of an unregulated inflammatory response of the host to antigene bacterial determinants from dental plaque. The basis of peri-implantitis consists of an interactions complex that is established between bacterial products, host cells and locally produced biological active factors. The degree and outcome of the destructive processes is determined by the nature of inflammatory response at the local level.

The capability of immune effectory cells to produce and release cytokines in response to stimulation of biological agents is a good strategy for monitoring the condition of peri-implant tissues. Because of this, the research of cytokines local production on the region of inflammation gives relevant data on the state of peri-implant tissues in relation to the monitoring of production of cytokines in peripheral blood. The balance between stimulatory and inhibitory cytokines, together with the regulation of expression of their receptors and signal cascades determine the level of peri-imiplant tissues destruction. Namely, the local balance of these mediators, which reflects the local activity of cells that produce them, determine the level of tissue destruction.

Cytokines that are present in peri-implant tissues can be diagnosed by measuring their concentrations in peri-implant fluid (PICF). This fluid fills the peri-implant sulkus and cytokines present in it, reflecting physiological interaction of gingival epithelium and local leukocytes on the microorganisms of dental plaque and oral flora [19]. Microorganisms are capable of synthesizing detrimental products that damage epithelium and connecting tissue cells and extracellular content.

Periotron is a device that precisely collects and determines the volume of peri-impant fluid. Cytokines are mostly detected by commercial cytokine kits (ELISA test). However, some other immunological essays for simultaneous detection of multiple cytokines from small samples have recently been developed.

Over the last ten years, the role of cytokines as useful diagnostical indicators that might represent an important addition to clinical parameters has been considered, and which might indicate the presence or absence of peri-implant disease, or indicate the treatment result that, in same cases may include the need for additional medical procedures.

Increased level of proinflammatory cytokines and chemokines significantly correlates with the level of inflammation [20, 21].

Local production of cytokines can depend on the interaction of specific microorganisms with gingival tissue, but also on the function of residential and infiltrating cells. In these complex events, one of the earliest one is the increase in production of IL-1β by gingival macrophages, which then induces, among other things, the secretion of IL-8. These two cytokines direct the selective migration of polymorphonuclear and monocytes from the gingival blood vessels, which are locally activated by the action of bacterial lipopolysacharide. Activated cells further produce different mediators, out of which the most impotrant are IL-1β, IL-6 and IL-8. The progression of gingival inflammation is probably the consequence of IL-1β and IL-6 activities, which cause an important tissue damage by the activation of osteoclasts and induction of collagen synthesis and fibroblasts [22]. In Figure 1 cells involved in the inflammatory response are presented.

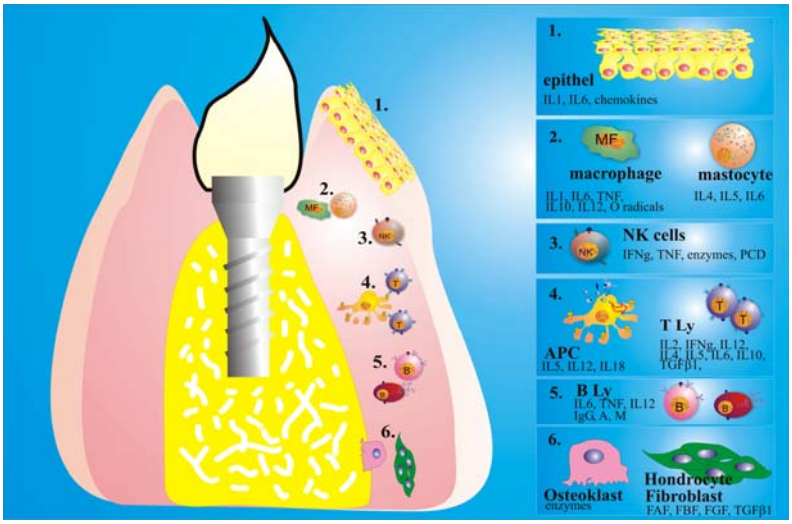

Fig. 1 – Cells involved in the inflammatory response

Proinflammatory cytokines and chemokines are very expressed in the peri-implant tissue in the early stages of inflammation when an implant is inserted. Panagakos et al. [22] and Salcetti et al. [23], by determining the values of IL-1β in the fluid of peri-impant sulkus, showed that concentration of this cytokine is increased by the progression of peri-implantitis. Most of the authors showed that tissue inflammation is proportionally connected with the increased level of different inflammatory mediators, which are, therefore, considered as adequate markers of inflammation. The results of Curtis et al. [24] show that there is a significantly lower level of concentration of proinflammatory cytokines in healthy tissue around implant compared to the advanced stage of peri-implantitis.

Chemokines and cytokines provide a complex network of signals that can activate or suprime an inflammatory response.

The clinical study performed in the Military Medical Academy monitored the levels of the following 4 cytokines: IL-1β, IL-8, tumor necrosis factor (TNF)-α and macrophage inflammatory protein-1 alpha (MIP-1α) [21]. Proinflammatory cytokines IL-1β and TNF-α are significant in immune response to microbial antigenes, whereas different levels of concentration of chemokines IL-8 and MIP-1α, can affect the migration of leukocites and together with TNF-α and IL1-β regulate the onset, course and outcome of inflmammation.

The research showed that the concentrations of proinflammatory cytokines and chemokines were singificantly higher in the patients with peri-implantitis in relation to the ones with perimucositis and the healthy ones. With the progression of peri-implantitis, the concentrations of all the researched cytokines in PICF were increased, but there were also individual differences in the level of the increase production of mediators of the inflammation. There has been a positive and statistically significant correlation between the levels of IL-1β and MIP-1α, TNF-α and MIP-1α as well as MIP-1α and IL-8 in PICF.

Proinflammatory cytokines (IL-1β, TNF-α) are important mediators of inflammatory host responses to the infection and other inflammatory stimuli and therefore have an important role in natural immunity and inflammation. IL-1β is a proinflammatory cytokine in certain concentration present in healthy peri-implant tissue and its value shows the real level of inflammation of peri-implant tissues. This local parameter of immune reactivity can be used for evaluation of the states of peri-implant tissues. It regulates degradation of the connective tissue and modulates the reparative activity by the induction of the endothel cells by proliferation of fibroblasts and hemotaxis of neutrophils in inflammated gingiva. Concentrations of IL-1β in PICF are increased in the early stages of peri-implantitis with the tendency of further increase with the progression of the disease [22, 25, 26].

IL-1β and TNF-α act synergically including stimulation of bone resorption [27].

The levels of IL-1β in PICF were approximately three times higher in patients with the evident peri-implantitis compared to healthy controls [25]. Also, the values of IL-1β showed a positive correlation with clinical parameters of the disease.

A significantly increased level of IL-1β in PICF have been detected in regions with failed dental implants compared to the level of this cytokine in PICF with successful control implants [23, 24, 28].

Murata et al. [29] have analysed the levels of osteocalcin, deoxipiridinolin and IL-1 β as the markers of bone metabolism in PICF in patients with peri-implantitis. The volume of PICF as well as the levels of IL-1ß in regions with peri-implantitis were significantly higher than in regions with mucositis or with helthy gingiva. The conclusion of this study is that IL-1β was an effective marker for evaluation of periimplant inflammation.

Curtis et al. [24] after their extensive research, come to a conclusion that the measurement of IL-1β in PICF as local parameter of immune reactivity, can be an important addition to clinical results in the diagnosis of peri-implantitis. Average values of cytokines of PICF were three times higher in relation to the values in the initial stage.

Many studies [22–24] have shown that IL-1β is present in: small, but detectable concentrations in gingival fluids around

clinically heatlhy implants; moderately high concentrations in samples of PICF of patients with early stages of peri-imiplantitis and high concentrations in the samples of PICF of patients with advanced peri-implantitis.

Based on the numerous studies it is possible to summarize the role of proinflammatory cytokines (IL-1β, TNF-α) in peri-implantitis: they enable migration of inflammatory cells into the tissue (they are included in the acute-phase response against the infection and pathogenesis of peri-implant destruction); they stimulate the processes of inflammation and tissue destruction; they induce and increase bone resorption; they stimulate the release of MMP that cause degradation of proteins of extracellular matrix and, apart from the local, affect the systemic manifestation of inflammation.

Unlike proinflammatory cytokines, hemokines belong to the family of chemotactic cytokines that stimulate and regulate migration of leukocytes from the blood into the tissues.

Inflammatory cells can release different chemokines and there is a proof that infection of specific bacteria and viruses can stimulate the cells of hosts to produce characteristic sets of immune cells.

As it has previously been emphasized, Th1, Th2 and Th17 play a significant role in the pathogenesis of peri-implantitis, but that role is still not well-known.

Activation of Th1 subpopulation cells through IL12 result in the production of IL-2 and IFN-γ. These cytokines stimulate predominatly the cell immune response mediated by the cytotoxic T-cells, macrophages and natural killer (NK) cells. On the other hand, activation of Th2 subpopulation cells is followed by the production of IL-4, IL-5, IL-6 and IL-10, which stimulates a predominantly humoral immune response and inhibits the cells immune response. Th17 is a new subtype of CD_4^+ T cells that is significant for the immunity to bacteria, but also for the pathogenesis of autoimmune processes. The level of IL-17, the most important representative of this type of cytokine, is increased during gingivitis and periodontal diseases [30]. So far it has not been investigated in peri-implantitis.

The relation of bacteria in dental plaque determines the direction of pathological mechanisms. If plaque accumulates on implant surface, the subepithelial connective tissue is infiltrated by the inflammatory cells. According to numerous studies [21, 29, 30], together with the progression of peri-implantitis, concentrations of all the examined cytokines in PICF are increased, but also that there are individual differences in the rate of increase in the production of these inflammatory mediators. Therefore, there is a difference in concentration of cytokines of PICF depending on the stage of peri-implantitis, which indicates the interaction of cytokines concentration and clinical parameters.

Many researchers tried to modify pathological responses by manipulating cytokine interaction within the targeted peri-implant tissue [31, 32]. The discovery of new cytokines and identification of new activities for the existing cytokines have significantly contributed to understending immunopathogenesis of peri-implant disease.

The detection of cytokines as valid biomarkers of pathological process, can be very effective because it provides more precise explanation of patophysiological mechanism of the disease itself. Also, evaluation of cytokine production can be for the benefit of monitoring the immune status of the organism.

Conclusion

The diagnosis and monitoring of many systemic diseases in medicine in most cases is based on laboratory analyses of biological fluids, secrets and tissues. Therefore, in the last ten years, research in the field of implantology have also been focused on the analysis of peri-implant fluids with the basic aim to identify potentially valid biochemical and immunological markers of the level of activity of inflammatory processes and/or to predict risk for the onset of peri-implant disease.

The results of the clinical research so far have shown that monitoring of the levels of proinflammatory cytokines and chemokines in peri-implant fluid can be used for monitoring of disease progression, as well as for its early detection.

The role and interaction of Th1, Th2 and Th17 cytokines in these processes are still less understood.

Monitoring of dynamics of local cytokine levels during peri-implantitis, together with research of gene polymorphism for these cytokines and other genes included in the inflammatory process, and the correlation with clinial parameteres can be valid means for the diagnosis, prognosis and application of new peri-implant treatment methods.

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