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Диагностическая значимость провоспалительных цитокинов при планировании дентальной имплантации у пациентов с общесоматическими патологиями

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АННОТАЦИЯ

Введение. Современный этап развития дентальной имплантологии позволяет провести полноценную стоматологическую реабилитацию даже в сложных клинических ситуациях. Однако существует ряд затруднений, которые не всегда позволяют обеспечить высокую успешность имплантологического лечения в случаях некоторых общесоматических патологий, имеющих проявление в виде системного воспаления и являющихся относительным противопоказанием к имплантации. К значимым общесоматическим патологиям относят хроническую обструктивную болезнь легких, атеросклероз, инсулиннезависимый сахарный диабет, остеопороз и др., при них создается риск острого воспалительного ответа организма на хирургическое имплантологическое вмешательство. Также риск непрогнозируемых осложнений возрастает по причине недостаточной широты лабораторного диагностического спектра для планирования дентальной имплантации, который включает в себя биохимический анализ крови, коагулограмму, реакции на наличие специфических инфекций и вирусных заболеваний. Указанного перечня диагностических данных не всегда достаточно для полноценного прогноза успешности планируемого лечения у пациентов, имеющих осложненный общесоматический или стоматологический статус. Кроме этого, часто не учитывается явление взаимосвязанности стоматологических хронических заболеваний и общесоматических патологий, имеющих в ряде случаев общие этиопатогенетические факторы, т.к. без должной диагностической широты они остаются незамеченными и нередко ведут к сложно купируемым осложнениям в различные сроки после завершения лечения. Развитие технологий хирургической и ортопедической стоматологии позволяет полноценно оказать стоматологическую помощь пациентам даже с различными патологиями органов и систем. Но в данном случае важное место должна занимать расширенная лабораторная диагностика, нацеленная на выявление факторов хронического системного воспаления, сосудистого риска, бактериальных угроз, например, оценка ряда интерлейкинов, фактора некроза опухоли, С-реактивного белка.

Заключение. Совокупность клинических, лабораторных и инструментальных диагностических методов позволит адекватно оценить риск неудач лечения и выстроить прогностическую тактику комплексной терапии, тем самым снизить вероятность непрогнозируемых осложнений при дентальной имплантации у пациентов с различными общесоматическими патологиями.

Ключевые слова: *дентальная имплантация; системное воспаление; общесоматическая патология; биохимический анализ крови; интерлейкины; фактор некроза опухоли; С-реактивный белок*

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Diagnostic Significance of Proinflammatory Cytokines in Planning Dental Implantation in Patients with General Somatic Pathologies

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ABSTRACT

INTRODUCTION: The current stage of development of dental implantology permits to perform a complete dental rehabilitation even in complicated clinical situations. However, there are some difficulties which prevent achievement of a high success of implantological treatment in certain somatic pathologies that manifest in the form of systemic inflammation, and present relative contraindications for implantation. Important general somatic pathologies include chronic obstructive pulmonary disease, atherosclerosis, non-insulin-dependent diabetes mellitus, osteoporosis, etc., they are associated with the risk of acute inflammatory response of an organism to surgical implantological intervention. The risk of unpredictable complications also increases because of insufficiently wide laboratory diagnostic spectrum for planning dental implantation that includes a biochemical blood test, coagulogram, reaction to the presence of specific infections and viral diseases. This list of diagnostic data is not always sufficient for a complete prognosis of success of planned treatment in patients with a complicated general somatic or dental status. Besides, the interrelation between dental chronic diseases and general somatic pathologies which in some cases have common etiopathogenetic factors, is often not taken into account, but without the adequate diagnostic range they often remain unnoticed and lead to persistent complications in different periods after completion of treatment. Development of technologies of surgical and orthopedic dentistry permits to provide full dental care to patients even with different pathologies of organs and systems. But in this case, of importance is extended laboratory diagnostics aimed at identification of factors of chronic systemic inflammation, vascular risk, bacterial threats, for example, evaluation of some interleukins, tumor necrosis factor, C-reactive protein.

CONCLUSION: A complex of clinical, laboratory and instrumental diagnostic methods will permit to adequately evaluate risk for treatment failure and construct a prognostic tactics of complex therapy, thereby reducing the probability for unpredictable complications in dental implantation in patients with different somatic pathologies.

Keywords: *dental implantation; systemic inflammation; general somatic pathology; biochemical blood test; interleukins; tumor necrosis factor; C-reactive protein*

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ECO•VECTOR

ABBREVIATION LIST

CRP — C-reactive protein
CVS — cardiovascular system
DI — dental implantation
DM — diabetes mellitus
hs — high sensitive
IL — interleukin
MFR — maxillofacial region
TNF-α — tumor necrosis factor-α
VEGF — vascular endothelial growth factor

INTRODUCTION

A modern protocol of planning dental implantation permits to exactly predict success of treatment in almost any clinical situation [1]. However, a number of general somatic factors not taken into account in preparation for the operation, give a certain percent of failures in treatment. Later, it may be manifested in the failure of osseointegration, peri-implantitis, implant rejection reactions. These complications can unpredictably emerge in the clinically favorable, at first sight, conditions for osseointegration [2]. Some parameters of the general somatic condition of a patient are not included in the protocol of obligatory examinations before the operation, but, nevertheless, they may be an important characteristic that can point out a key risk factor for failure of implantation.

The process of osseointegration of the implant is a certain structural and functional type of connection between the bone tissue and the implant surface, which ensures its biological stability. The essence of the biological stability of the implant is the formation of new bone tissue and its restructuring (remodeling) in different periods of the implant functioning. However, subtle morphological osteogenic processes can be disrupted by the local or systemic inflammatory factors. In case of a local inflammatory focus, identification of a factor that can affect the successful bone implant integration, is a simple diagnostic task, because modern radiation and other physical diagnostic methods permit to accurately visualize the picture and consequences of inflammatory foci in the maxillofacial region (MFR). A more threatening complication is a systemic inflammatory reaction, which starts at the level of organ systems, being a general somatic pathology. In this case, there are a lot more causes and initiators for the development of such a complication than for local inflammation within the MFR. Often, it is impossible to suspect a general somatic factor of potential complications in routine dental practice due to the insufficient width of the laboratory diagnostic spectrum for planning dental implantation (DI), which includes biochemical blood analysis, coagulogram, reactions to the presence of specific infections and viral diseases [3].

At the stage of taking history and on suspicion of systemic pathologies, the patient may be referred to additional diagnostics, including determination of the level of C-reactive protein (CRP) and proinflammatory cytokines (interleukins (IL), tumor necrosis factor-α (TNF-α)), analysis of the leukocyte formula; however, these examinations are not included in the list of obligatory procedures. In addition, in the available literature, it is not possible to find specific diagnostic protocols and clinical recommendations for planning DI in cases of existence of some underlying somatic pathologies, including chronic systemic inflammation. Often, many general somatic conditions that potentially threaten with the development of the acute phase of inflammation are considered a contraindication for DI, however, there exists a certain percentage of patients who need this modern type of treatment. In this case, the operation can also be performed, but with due consideration of an expanded clinical, instrumental and laboratory diagnostic protocol, which will permit to adequately assess the risk of treatment failure and construct a prognostic tactics of comprehensive therapy.

Systemic inflammatory processes can be identified by determination of the level of certain markers. One of these is CRP, which is a protein of the acute phase of inflammation. In this condition, its concentration in blood plasma dramatically increases by on average 10-100 times. The amount of CRP also correlates with the dynamics of the inflammatory process, the extent of tissue damage. Another feature of CRP is its production by macrophages directly in the focus of inflammation, which is important for the local diagnosis of early postoperative inflammatory phenomena [4]. In this regard, from the point of view of laboratory diagnostics, CRP is one of the most sensitive parameters. Besides, in different injuries, the concentration of CRP can actively rise as early as within the first 6-8 hours, which is also true for surgical interventions in the head and neck performed with a different degree of invasion, especially in reconstructive surgeries in the MFR using endoprosthetics in combination with tooth extraction and, for example, with immediate DI. An increase in the concentration of CRP in such cases is a response of the body aimed at the cellular organization of the

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inflammation process, localization of the lesion and restoration of the functional ability of tissues of different morphology.

Concentration of CRP can be evaluated by taking serum or blood plasma with further application of the method of radial immunodiffusion or highly sensitive immunoturbidimetry with latex enhancement, the latter method is mainly used for the determination of high sensitive (hs) CRP. In this case, the concentration of CRP is evaluated already at the level of 0.05 mg/l to 10 mg/l [4]. This type of examination is important not so much for making a diagnosis, but rather for determining the level of predictors of a particular pathology or groups of pathologies, which permits to obtain a quantitative parameter of the relative risk of developing the disease. Thus, even for non-extensive surgical intervention in the oral cavity, which may be a single tooth extraction or DI with a minimally invasive protocol, it is possible to preliminarily predict the peculiarities and severity of the body's inflammatory response. In case of dental interventions, one of the fundamental factors of successful treatment is the preserved volume of jaw bone tissue suitable for implantation and further prosthetics, CRP in this case can be a marker of the processes of mineralization and demineralization of bone tissue, which can also be a prognostic factor [4].

Besides changes in the concentration of CRP in the blood, it also appears in the oral fluid after production by hepatocytes in case of tissue damage or inflammation. CRP reaches maximal concentration in the oral cavity on average in 24 hours after synthesis. [5]. Thus, in an obtained sample of the oral fluid, concentration of CRP in it can be determined in immunoenzyme or turbidimetric analysis [4].

Other highly sensitive diagnostic markers are proinflammatory cytokines (IL, TNF-α): IL-1, IL-2, IL-6, IL-8, TNF-α [6]. The listed cytokines may increase systemically in the blood or locally, for example, in the oral fluid. Cytokines are antigen-nonspecific protection factors that provide a local immune inflammatory response. The pathogenetic role of proinflammatory cytokines in patients who underwent dental implant surgery is that when the balance of pro- and anti-inflammatory cytokines is disturbed, there is a risk of impaired osseointegration and the development of destructive processes in the peri-implantation zone [7]. Uncontrolled changes in the cytokine system indicate enhancement in inflammatory and destructive processes in the oral cavity and MFR [8]. In inflammatory phenomena, surgical interventions, or a systemic inflammatory reaction that has manifestations in the oral cavity, cytokines are produced by lymphocytes and macrophages, as well as due to the release of serum transudate and salivary gland secretion into the oral cavity. Besides the local determination of quantitative parameters of proinflammatory cytokines in chronic diseases of the dental system, for example, in chronic periodontitis, this laboratory diagnosis can also be useful in a relatively normal dental status, which can often be complicated by systemic inflammatory reactions of the body in somatic diseases or dermatological pathologies, as, for example, in lichen planus, vulgar pemphigoid, bullous pemphigoid, or in autoimmune diseases of the oral mucosa [9].

Concentration of CRP, as a rule, changes in chronic inflammatory states, and any new intervention can provoke an acute response of an organism, which may often happen in case of DI. For example, a chronic systemic inflammation is one of manifestations of chronic obstructive pulmonary disease and is characterized by inflammatory reactivity of endotheliocytes, as well as of cellular factors of connective tissue [10]. These patients have increased blood levels of CRP, neutrophils, IL-1, IL-2, IL-6, IL-8, TNF-α, which may influence the outcome of different interventions, prognosis for early complications [11] and the quality of DI performed. In the pathogenesis of such changes, a significant role is played by oxidative stress associated with production of excessive amounts of reactive oxygen species or oxygen radicals, which in turn, are one of the of factors of chronic systemic inflammation. With this, there is a wide spread of chronic pulmonary obstructive disease in the population including the category of dental patients.

Another numerous group of patients where chronic systemic inflammation is noted, are patients with obesity, many of which fall into the most common risk groups: those with cardiometabolic syndrome, insulin resistance, endothelial dysfunction, disorders of fibrinolysis and many others [12]. Despite different severity of somatic diseases, such patients also need dental care with application of modern methods of treatment including DI.

According to the research data, the degree of obesity has certain correlations with loss of teeth which is noted in 31% of such patients [13]. One of the main pathogenetic mechanisms of development of chronic inflammation in patients with obesity is increase in the level of proinflammatory adipocytes secreting proinflammatory cytokines (adipokines), such as TNF-α and IL-6 [14] which stimulate production of CRP by the liver cells. This process may induce alterations in the immune response of an organism, and production of TNF-α in this case may stimulate production of osteoclasts. Besides, it is pointed out that overweight patients especially those with abdominal obesity and insulin resistance, practically always have systemic chronic inflammation [15], and metabolic dysregulations of the level of insulin are closely interrelated with metabolism in the bone tissue [16], which is a critical parameter in prognosis of successfulness of DI. Since the patients with obesity relatively often face the problem

of chronic periodontal diseases, they are also at risk of development of such complication after DI as peri-implantitis. This is associated with factors of metabolic disorders, increase in the level of peroxide oxidation products and reduction of antioxidant substance, which contributes to chronic inflammation and different kind of tissue destruction [17].

A problem of development of peri-implantitis and its association with obesity is also demonstrated by the results of different studies. Thus, in obese patients, more expressed changes in the dental status are observed, manifested in a tendency to alterations of the bone tissue in the implantation area in the form of resorption, as well as a tendency to clinical disorders in the gingival margin in the region of implants and their suprastructures, which found correlation with increase in the concentration of IL-1β and IL-6 in saliva [18]. Thus, this category of patients are also at risk of development of acute phase reactions and launching of destructive alterations in the bone tissue in case of surgical interventions, which should be taken into account in laboratory diagnostics of the patient at the stage of planning DI.

Patients with excessive weight often have other problems with metabolism, for example, diabetes mellitus (DM) in history. Uncompensated DM is considered an absolute contraindication for DI, however, compensated non-insulin-dependent DM is only a relative contraindication. Here, it has been established that with the adequate metabolic control, the successfulness of DI and the condition of tissue in the region of osseointegration of the implant in patients with DM are not inferior to those of healthy individuals [19]. An importance of monitoring patients with DM is associated with the role of insulin in metabolic processes in the bone tissue, in particular, with its ability to maintain the functional condition of osteoblasts, interrelation with tissue growth factors, ability to stimulate production of hyaluronic acid and collagen synthesis [20]. In management of this group of patients, special attention should be paid to metabolic and biochemical control which may also include determination of concentration of CRP in blood as a marker of systemic inflammation often accompanying patients with DM.

General somatic metabolic pathologies are also reflected in the periodontal diseases, for example, in those associated with DM [21]. These pathological periodontal alterations result from elevation of glucotoxicity level in blood and gingival fluid associated with a dramatic increase in the level of proinflammatory cytokines. In this context, the important role in the pathogenesis and diagnosis in patients with an interrelated dental and somatic pathology is played by IL-1, IL-6, TNF-α.

Patients with chronic periodontal diseases who are not at risk by the parameters of their general somatic status may also face situations of increased levels of markers of the acute phase of inflammation and proinflammatory cytokines, for example, IL-1ß, IL-6, IL-8, which can be isolated in examination of the gingival fluid. The main role in the pathogenesis of development of essential periodontitis or periodontitis associated with somatic pathology, is played by immunocompetent cells: neutrophils, lymphocytes, macrophages. Activation of the cellular defense system and the launch of the cytokine cascade, as a rule, occur in response to a microbial pathogenic factor represented by gram-negative periodontopathogenic obligate or facultative anaerobes of the 1st and 2nd order [22]. In addition, it was also found that in peri-implantitis not associated with systemic inflammation, the level of CRP, IL-1β, IL-6, IL-8, as well as of TNF-α in the gingival fluid and blood serum also tends to increase, which already evidences a local chronic inflammation [23]. Thus, cytokine markers are a universal tool permitting to pinpoint the key risk zones for the development of different dental pathologies and to predict probable inflammatory and destructive events during different surgical interventions in the MFR and oral cavity.

A borderline risk group of patients similar to the previous group with obesity, is a group with diseases of the cardiovascular system (CVS) which are in necessity for dental care due to chronic periodontal diseases, and also due to absence of teeth. Thus, 7.3% of the total amount of dental patients with chronic periodontal diseases have different forms of diseases of CVS [24]. Here, it is pointed out that patients with chronic periodontitis have a potentially higher risk of development of cardiovascular diseases [25]. This can be explained by the metabolic changes of the common nature in an organism, which create different risk factors for development of organ pathologies on the local and systemic levels, for example, the phenomenon of oxidative stress [26]. Thus, generalized periodontal diseases and cardiovascular diseases have the following common manifestations: metabolic syndrome including arterial hypertension, disorder in lipid metabolism [27]. As was said above, the course of periodontitis is characterized by active production of proinflammatory cytokines, with actively increasing concentration of IL-1β IL-6, TNF-α that can influence metabolism of lipids and provoke hyperlipidemia [27]. This is associated with increase in the level of CRP and fibrinogen, which conditions the development of systemic inflammatory response influencing the state of the vascular endothelium.

This creates the probability for development of endothelial dysfunction associated with the systemic inflammation affecting the state of the vascular endothelium [28, 29] and occurring in response to invasion of toxins and antigens produced by periodontopathogenic microorganisms. The pathogenetic factor of the cardiovascular system consists in increasing risk of

development of atherosclerotic diseases associated with the systemic inflammation [30]. Infectious threat of the periodontium and related elevation of the inflammation markers may be due to atherosclerosis (including the risk of myocardial infarction) and diseases of peripheral vessels. Thus, in examination of atherosclerotic plaques by immunoenzyme assay, periodontal bacteria were detected in their composition [31].

Currently, new integral parameters of the dental status are used that evaluate its connection with somatic pathologies. N. A. Yudina and L. I. Leus proposed a risk index for chronic oral sepsis, which can be used to summate the foci of chronic infection in the oral cavity and make a prognosis for the development of chronic oral sepsis with evaluation of its influence on the development of somatic pathologies [32]. According to the authors' data, in evaluation of the risk of oral sepsis and manifestations of somatic pathologies it was found that among the patients with high index values, the percentage of patients with somatic diseases, in particular, with cardiovascular diseases, was higher, and with the medium index values in the age group of 45–54 years, 10% of patients had pathology of CVS.

Thus, it is possible to trace the key general mechanisms of the pathogenesis of systemic pathologies, including cardiovascular diseases and chronic diseases of the dental system, especially of chronic dental odontogenic inflammatory processes, which undoubtedly require active surgical and orthopedic treatment. With this, the diagnostic role of the above described proinflammatory cytokines increases in the given case, since it permits to evaluate the risks of development of different comorbid complications often having an interrelated genesis.

Relative contraindications for DI include the primary or secondary osteoporosis. However, in cases when this pathology does not have any significant manifestations and signs of progression in the MFR, DI is possible, but in a somewhat limited amount, for example, with use of minimally invasive techniques. The development of secondary osteoporosis, according to statistical data, is in most cases associated with chronic diseases of the pulmonary system, including extrapulmonary manifestation of the obstructive pulmonary disease, as well as with DM, where the accumulation of glycation products decreases the activity of osteoblasts and increases that of osteoclasts leading to resorption of the bone tissues [20]. Moreover, it is pointed out that in such cases osteoporosis develops due to systemic inflammation being a manifestation of the above mentioned diseases with the active production of proinflammatory cytokines TNF-α and IL-6, provoking formation of osteoclasts [33], therefore there exists a certain relationship between the processes of bone remodeling and systemic inflammation. Here, DI is also conducted in patients at risk due to osteoporosis. Some large clinical studies refute the claims of osteoporosis directly affecting the failure of DI and the loss of implants [34, 35]. Thus, in this category of patients in case of secondary osteoporosis due to the underlying chronic inflammation, with the appropriate control of the proinflammatory cytokines, as well as of biochemical parameters of systemic inflammation, it is possible to form a fairly accurate prognosis for success of DI and long-term survival of implants.

Biochemical parameters of systemic or local inflammatory reaction are also actively evaluated in patients who need extensive surgical interventions in MFR, often together with DI. Indications for surgical interventions can be inflammatory and non-inflammatory diseases of MFR including oncological ones. A common problem requiring surgical treatment, is an oroantral fistula which can form in result of perforation of the bottom of the maxillary sinus during tooth extraction. This kind of maxillary defect may often be caused by other factors, including otorhinolaryngological ones, for example, maxillary sinusitis, perforated forms of which account for 42%–77% of all diseases of MFR [36]. Thus, the dynamics of postoperative period and probable inflammatory complications after surgical interventions for closure of oroantral fistula, were evaluated by the biochemical parameters of the oral fluid with determination of CRP level [37]. The laboratory analysis of the biochemical inflammation markers in the given surgical interventions performed by dental surgeons jointly with ENT doctors, permits to effectively evaluate the extent of lesion of the sinus mucosa and determine the amount of surgical interventions [37]. In the given case, the main diagnostic parameters are CRP and procalcitonin, obtained from the oral fluid and mixed saliva [38]. His permits to monitor the postoperative period for inflammatory complications with high sensitivity.

Another group of MFR pathologies is a group of pathologies of the oncological genesis which often require invasive surgical intervention. In this case, a detailed analysis of somatic status and of patient's history, as well as evaluation of the dynamics of the oncological disease are important for correct selection of the tactics of surgical, conservative and radiological treatment. From the point of view of the pathogenesis, carcinogenesis may be triggered by a progressive chronic inflammation. Here, of diagnostic significance are proinflammatory cytokines: TNF-α, IL-1β, IL-6, IL-8, which, along with their participation in the inflammation process, suppress cell apoptosis and launch proliferation, stimulate pathological neoangiogenesis through the vascular endothelial growth factor (VEGF), and metastasis of the neoplasm [39]. Insufficient depth of diagnosis and of differential diagnosis may result

in overlooking the true pathology. In such cases, a specialist pays attention only to clinical symptoms of the chronic inflammation, for example, peri-implantitis in the dental implant area or advanced generalized periodontitis, but lack of comprehensive data does not permit to adequately elicit the main cause, a form and stage of progression of pathology. These conclusions are reflected in some foreign scientific studies [40, 41].

CONCLUSION

Based on the above stated peculiarities of the factors of different systemic and organ pathologies, it is possible to trace the importance of comprehensive evaluation of different biochemical parameters of inflammation in planning dental implantation surgery and other kinds of dental treatment of the bone and soft tissues of the maxillofacial region.

The close relationship of markers of chronic inflammation, such as interleukins 1, 2, 6, 8, tumor necrosis factor-α, C-reactive protein, permit to identify the borderline key peculiarities of the pathogenesis of different general somatic and dental pathologies and, on this basis, to more accurately predict success of treatment. This confirms the value of the listed biochemical and immunological parameters of blood or mixed saliva at the stage of diagnosis in dental patients, a significant part of whom have underlying somatic diseases that can influence the success of dental treatment. Just as general somatic diseases have an impact on dental status, chronic inflammatory processes in the maxillofacial region and oral cavity can affect the overall health status.

In this connection, in planning comprehensive dental treatment, attention should be given not only to local dental symptoms, but also to general history data and data of laboratory diagnostics, which will permit to improve the quality of dental treatment and to timely identify pathological interinfluence of comorbid processes, to maintain the general status of the health of the population.

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