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PATHOGENETIC ASPECTS OF PERIODONTITIS DEVELOPMENT IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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Annotation: Periodontitis and type 2 diabetes pose serious health challenges worldwide. Estimates suggest that up to 50% of the global population suffers from gum disease, and this figure is likely to increase in the future, driven by longer life expectancies, improved dental health, and an aging population. The global diabetes epidemic is one of the most significant public health challenges of the 21st century. Currently, there are approximately 537 million diabetics worldwide, and according to estimates by the World Health Organization and the International Diabetes Federation, this number will reach 643 million by 2030.

Keywords: hyperglycemia, diabetes mellitus, inflammation, oxidative stress, periodontitis, microbiota.

IKKINCHI TOIFA QANDLI DIABET BILAN OG'RIGAN BEMORLARDA PERIODONTITNI RIVOJLANISHINING PATOGENETIK ASPEKTLARI

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Abstract: Periodontit ham, 2-toifa qandli diabet ham jiddiy global sog'liq muammolarini anglatadi. Periodontal kasallik dunyo aholisining 50 foizigacha ta'sir qilishi taxmin qilinmoqda va bu ko'rsatkich kelajakda umr ko'rish davomiyligi, tabiiy tishlarning ko'proq saqlanib qolishi va aholining tez qarishi tufayli ortishi kutilmoqda. Qandli diabetning global epidemiyasi 21-asrning eng katta sog'liqni saqlash muammolaridan biridir. Bugungi kunda dunyo bo'ylab qariyb 537 million kishi qandli diabetga chalingan, Jahon sog'liqni saqlash tashkiloti va Xalqaro diabet federatsiyasining hisob-kitoblariga ko'ra, 2030-yilga borib bu raqam 643 millionga ko'payadi.

Kalit so'zlar: giperglikemiya, diabetes mellitus, yallig'lanish, oksidlovchi stress, periodontit, mikrobiota.

ПАТОГЕНЕТИЧЕСКИЕ АСПЕКТЫ РАЗВИТИЯ ПАРОДОНТИТА У БОЛЬНЫХ САХАРНЫМ ДИАБЕТОМ 2 ТИПА

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Аннотация: Пародонтит и сахарный диабет 2 типа представляют собой серьезные вызовы для здравоохранения во всем мире. По данным оценок, до 50% населения земного шара страдают от заболевания десен, и эта цифра, вероятно, будет расти в будущем, чему способствуют увеличение продолжительности жизни, лучшее сохранение зубов и старение населения. Глобальная эпидемия диабета – одна из важнейших проблем общественного здоровья XXI века. На сегодняшний день насчитывается около 537 миллионов диабетиков по всему миру, и, по расчетам Всемирной организации здравоохранения и Международной федерации диабета, к 2030 году их число достигнет 643 миллионов.

Ключевые слова: гипергликемия, сахарный диабет, воспаление, окислительный стресс, пародонтит, микробиота.

Introduction: Diabetes mellitus is a general term for a group of metabolic disorders characterized by impaired blood glucose regulation due to defects in insulin secretion, action, or both [6]. Scientific evidence indicates that long-term hyperglycemia can lead to damage, impairment, and failure of various organs and systems over time. The most common chronic complications in patients with diabetes are vascular in nature and can be either macro- or microvascular. Macrovascular complications, such as cardiovascular, cerebrovascular, and peripheral atherosclerosis [7], include lesions of large blood vessels, the main pathological substrate of which is atherosclerotic plaque. Cardiovascular disease is the leading cause of disability and mortality in patients with diabetes. It is estimated that approximately 32% of patients with diabetes suffer from some form of cardiovascular disease, and approximately 50% of deaths in this population are related to these conditions [8]. Microvascular complications affect the smallest blood vessels, capillaries, and precapillary venules. One of the key manifestations is microangiopathy—thickening of the capillary basement membrane caused by the deposition of glycogen, mucopolysaccharides, and glycoproteins. This leads to the development of diabetic retinopathy, nephropathy, and neuropathy, which can cause varying degrees of renal failure and visual impairment [9]. Although many people with type 2 diabetes suffer from periodontitis, the factors contributing to the development of this disease in this group remain poorly understood. However, advances in periodontology allow for a better understanding of the role of inflammation and destructive processes in periodontal tissues in various systemic diseases. In this regard, periodontitis is increasingly considered a risk factor for the development or exacerbation of common diseases, including difficulties in achieving adequate metabolic control in diabetes. Although the mechanisms of the relationship between diabetes and periodontitis at the cellular level are not yet fully understood, oxidative stress is believed to play an important role in this process [12].

The development of diabetes and subsequent complications are closely linked to an imbalance between oxidative stress and cellular antioxidant defense. Elevated plasma free radical concentrations are one of the main consequences of hyperglycemia in diabetic patients. Non-enzymatic glycolysis, which produces advanced glycation end products (AGEs), is accompanied by the formation of oxygen free radicals (O2 -, H2O2, OH˙). Furthermore, non-enzymatic glycolysis, which affects extracellular and intracellular superoxide dismutase (SOD) and other antioxidant enzymes, reduces their effectiveness. AGEs bind to receptors on the surface of endothelial cells, macrophages, and neutrophils, stimulating the generation of free radicals and increased cytokine production by monocytes and endothelial cells. A direct relationship was also found between the degree of metabolic control in diabetic patients, the amount of superoxide anion radical (O2 •−) released by neutrophils, and the severity of periodontal tissue damage. These data indicate that oxidative stress may play a key role in the progression of periodontitis in people with diabetes [15].

These findings are supported by animal studies. In particular, Ohnishi et al. [2] found significantly higher concentrations of hydrogen peroxide (H2O2) in the plasma of mice with experimentally induced diabetes compared to healthy controls, as well as increased alveolar bone resorption, which accompanies the development of diabetes. When adding an antioxidant (N-acetylcysteine) to the diet of diabetic mice, the authors recorded a decrease in plasma H2O2 levels and cessation of alveolar bone resorption.

Available evidence suggests that the prevalence and risk of more extensive periodontal damage are increased in diabetes. For example, Nascimento et al. found that diabetes nearly doubles the odds of periodontitis onset and progression. Furthermore, a meta-analysis of epidemiological studies by Zheng et al. found that periodontitis occurs in 68% of patients with diabetes, which is almost double the rate recorded for systemically healthy individuals (36%). Furthermore, a study by Wu et al. found that the periodontal health of patients with type 2 diabetes was significantly worse than that of individuals without diabetes: periodontal pocket depth was 0.61 mm greater, attachment loss was 0.89 mm greater, and there were fewer remaining natural teeth [14]. However, not all patients with diabetes are at equal risk of developing periodontitis. The degree of metabolic control is considered to be an important risk factor for periodontal damage, as hyperglycemia is a major cause of the characteristic complications of diabetes. For example, an analysis of data from the National Health and Nutrition Examination Survey for the period 2009–2014 confirms this, and Eke et al. found that in the United States, individuals with poor glycemic control have a higher risk of developing periodontitis compared to systemically healthy individuals. The severity of periodontal tissue destruction is believed to be largely determined by the degree of diabetes control, as more severe periodontal damage is typically observed in patients who have failed to achieve adequate metabolic control compared to those who

maintain it [13]. For example, Lim et al. found a significantly higher incidence of periodontal pockets ≥ 5 mm deep, and Aoyama et al. reported worse mean CAL (clinical attachment level) and BOP (bleeding on probing) scores in patients with poor diabetes control compared to those with good control.

Most existing studies examining the relationship between diabetes mellitus and periodontitis are based on data on T2DM, as its prevalence worldwide is higher and the age of disease onset is typically later. These factors combined increase the likelihood of co-occurrence of T2DM and periodontitis. Many studies examining the relationship between T2DM and periodontitis have demonstrated that deterioration of periodontal tissues and an increased risk of periodontitis are directly associated with higher levels of glycosylated hemoglobin. Although this relationship is not linear, hyperglycemia is associated with an increased likelihood of periodontitis and subsequent tooth loss [11].

A recent review systematically summarized the evidence on the bidirectional association between T2DM and periodontitis and found that T2DM increased the incidence of periodontitis by 34% (RR = 1.34; 95% CI, 1.11–1.61). Patients with T2DM had 0.89 mm greater clinical attachment loss, 0.61 mm greater periodontal pocket depth, 2.01 fewer remaining teeth, and 2.22 greater tooth loss than participants without T2DM. The two diseases each contributed to the increased incidence of the other and were associated with disease severity [8]. Stöhr et al. also conducted a systematic review and meta-analysis of existing studies, summarizing data from 15 observational studies including 295,804 participants and over 22,500 confirmed cases. The results showed that diabetes is associated with an increased risk of periodontitis development and progression in adults compared with individuals without diabetes mellitus (SRR = 1.24; 95% CI, 1.13–1.37). Therefore, patients with diabetes need to be aware of their increased risk of periodontal disease [8,9]. Another clinical study also confirmed that patients with T2DM have more severe tooth loss, and more than 95% of patients with T2DM had some periodontal tissue damage of varying degrees. These results can serve as a basis for the development of collaborative and comprehensive approaches to diabetes treatment. A study conducted in an Italian population showed that a family history of T2DM, poor glycemic control, and C-reactive protein (CRP) levels can be effective predictors of the onset and progression of severe periodontitis. A 1-unit increase in serum HbAlc increased the odds of severe periodontitis by approximately 60%, and the risk was higher in T2DM patients with higher baseline glycosylated hemoglobin levels [4].

Thus, the onset, duration, and severity of hyperglycemia play an important role in the development of chronic periodontitis. Hyperglycemia promotes an inflammatory response in periodontal tissues, both directly and indirectly, through advanced glycation end products (AGEs) and their receptor (RAGE), which can alter the function

of leukocytes and fibroblasts, stimulate the production of proinflammatory cytokines, and increase the RANKL/OPG ratio, ultimately leading to osteoclast activation and alveolar bone resorption [7].

Periodontitis is a condition caused by a bacterial infection that leads to inflammation and destruction of the tissues that support the teeth. Although over 500 species of bacteria can contribute to the development of dental plaque, Porphyromonas gingivalis, Tannerella forsythia, Prevotella intermedia, and Aggregatibacter actinomycetemcomitans have been identified as the primary causative agents of periodontitis. However, the extent of destruction caused by these microorganisms is determined by their interaction with the host immune system, which, in turn, is influenced by genetic and environmental factors. Diabetes is reported to be a key environmental risk factor for the development of periodontitis [14].

Periodontitis results from the interaction between the reconstituted inflammatory/immune response of the periodontal host and the dysbiotic challenge of the periodontal microbiota, characterized by a chronic destructive and progressive inflammatory reaction that is driven by Gram-negative bacteria in bacterial plaque as part of microbial dysbiosis [11,12]. It is a chronic multifactorial inflammatory disease that affects the supporting tissues of the entire periodontium and can lead to periodontal attachment loss, periodontal pocket formation, alveolar bone resorption, and ultimately tooth loss if left untreated [13]. Periodontitis affects approximately 45–50% of adults, and among people over 65 years of age, the incidence of this disease exceeds 60% [14]. Severe periodontitis is the sixth most common disease among 291 global diseases studied and is estimated to affect an average of 11.2% (ranging from 5% in Oceania to 20.4% in Latin America) of the global adult population. In recent years, numerous epidemiological and experimental studies have demonstrated that periodontitis can influence overall health through various molecular mechanisms and is independently associated with most chronic systemic diseases, including diabetes mellitus. Thus, severe periodontitis represents a significant social, economic, and health problem, increasing global health costs and social inequalities, and significantly impacting the public health system [9]. Existing studies confirm the existence of a bidirectional relationship between periodontitis and diabetes: they mutually increase the risk of developing each other and are associated with the severity of the disease. Diabetes mellitus is one of the major risk factors for the development of periodontitis, and the incidence or risk of periodontitis progression in patients with uncontrolled diabetes has been shown to increase by 86% compared to patients without diabetes or with well-controlled diabetes.

On the other hand, patients with periodontitis have poor glycemic control, an additional risk of insulin resistance, and a higher prevalence of diabetes-related complications [10]. Many studies have confirmed that periodontal therapy can reduce

the burden of periodontal inflammation, which,In turn, this has a positive effect on glycated hemoglobin levels in the blood. Therefore, it is necessary to screen patients with diabetes for periodontitis and vice versa.

However, because diabetes and periodontitis are comorbidities linked by complex interactions between the microbiome, inflammation, host immune response, oxidative stress, genetics, and other factors, the precise molecular mechanisms underlying this association, as well as the pathways by which diabetes influences the anatomical and physiological changes of periodontal tissues, remain poorly understood. Furthermore, there is a lack of interdisciplinary collaboration between endocrinologists and dentists in the management of patients with diabetes; studies show that only 30% of endocrinologists have ever referred their patients to a dental clinic for an oral health assessment. It is important that endocrinologists be aware of periodontitis and its impact on glycemic control and the risk of developing insulin resistance, and that patients with periodontitis be counseled about their increased risk of developing diabetes [10]. The aim of this study is to analyze the latest clinical data supporting the role of diabetes in increasing susceptibility to periodontitis from the perspectives of epidemiology, molecular mechanistic aspects, and potential therapeutic targets. This study also discusses possible molecular mechanistic factors, such as microbiome factors, inflammation, the host immune response, oxidative stress, periodontal tissue destruction, and epigenetic changes, with a particular emphasis on new data on the host inflammatory/immune response and oxidative stress. A better understanding of the intertwined pathogenesis of diabetes mellitus and periodontitis may enable physicians and dentists to facilitate timely diagnosis and optimal treatment of these two diseases.

In addition to the extent of periodontal tissue damage, the effectiveness of periodontal treatment also depends on the quality of metabolic control of diabetes. Studies indicate that patients with uncontrolled diabetes demonstrate a less pronounced positive response to periodontal therapy compared to those without the disease. However, periodontal treatment appears to be as effective in people with well-controlled diabetes as in healthy control patients [11]. However, some studies do not support this relationship, including the work of Kardesler and colleagues, who found no significant differences in probing depth (PD), clinical attachment level (CAL), and bleeding on probing (BOP) between patients with periodontitis and well- or poorly controlled diabetes. Such discrepancies are expected, since the extent of periodontal damage is influenced by numerous risk factors, primarily genetics, gender, age, socioeconomic status, and smoking, making it difficult to establish a clear link between periodontal tissue destruction and metabolic control of diabetes. In clinical practice, it is not uncommon to encounter patients with diabetes mellitus and poor glycemia who do not have obvious signs of periodontitis, while others, despite well-controlled diabetes, exhibit significant destruction of periodontal tissues [14]. It should also be

noted that the results of some studies do not support the influence of the degree of metabolic control of diabetes on the success of periodontitis treatment. Indeed, several studies show that in the short term, periodontal treatment is equally effective in patients with type 2 diabetes and in patients without diabetes, but periodontal disease relapse is more likely in the former group when glycemic control is inadequate [6].

It is important to note that comparison of results from different studies is difficult due to the inconsistent use of glycated hemoglobin (HbA1c) cutoff values to assess metabolic control in patients with diabetes. Although the American Diabetes Association established clear cutoff values in 2006 (HbA1c < 7% – good control, HbA1c ≥ 7% – poor control), these recommendations were not always followed. As a result, patients with the same HbA1c value (e.g., 8.0%) may be classified as having good metabolic control in one study and as having poor control in another, which undoubtedly affects the interpretation of the obtained data. The role of oxidative stress in the development of periodontitis has been substantiated by a number of authors, since patients with periodontitis, compared with healthy individuals, consistently exhibit higher levels of oxidative stress markers in saliva or blood, as well as reduced antioxidant potential.

Increased oxidative stress in the blood of patients with periodontitis may have a negative impact on their overall health. For example, Tomofuji et al. showed that lipopolysaccharide-induced periodontitis in experimental mice resulted in elevated serum hydrogen peroxide levels and oxidative DNA damage in the liver. Similarly, Ekuni et al. demonstrated that oxidative stress resulting from periodontitis may play a significant role in the progression of atherosclerosis. Their study found that periodontitis in experimental mice resulted in elevated lipid peroxidation markers in periodontal tissue and serum, as well as lipid accumulation in the aorta. Therefore, it can be hypothesized that periodontitis may have similar effects in patients with diabetes. Indeed, existing studies examining this relationship show that periodontitis exacerbates the already impaired oxidative status in patients with diabetes and is associated with beta cell dysfunction [7]. Specifically, Allen et al. found that patients with diabetes and periodontitis have higher levels of markers of oxidative protein damage in the blood, reduced β-cell function, and higher HbA1c values compared to patients with diabetes and a healthy periodontium. Although the pathogenetic mechanisms underlying the development of periodontitis in people with diabetes are not yet fully understood, vascular changes in the gums, immune mechanisms, collagen metabolism disorders, and a specific microbiological composition in periodontal pockets have been discussed in the scientific literature [5].

According to existing data, the risk of developing periodontitis among patients with type 2 diabetes is higher than in the general population and is associated with the degree of metabolic control. Furthermore, existing studies indicate that untreated

periodontitis can negatively impact metabolism, thereby increasing the likelihood of systemic health complications. Furthermore, periodontal therapy may help reduce HbA1c [4].

Given these findings, it is crucial to better understand the relationship between diabetes and periodontal disease and share this knowledge not only with healthcare professionals but also with patients with diabetes. In particular, oral and periodontal hygiene should be recognized as an integral part of diabetes management, which should be performed by an endocrinologist in conjunction with a dentist. Even if periodontal disease is not suspected, diabetologists should refer all their patients for periodontal examination, and dentists should be aware of their glycemic status. If intraoral examination does not lead to a diagnosis of periodontitis, patients with type 2 diabetes should be regularly monitored for any changes in oral health. Those diagnosed with periodontitis should undergo periodontal therapy immediately. In any case, all patients with type 2 diabetes should be educated about the importance of oral health, as this will ensure their compliance with treatment protocols and follow-up [1,2].

Continued research and active dissemination of the findings are expected to contribute to the development of effective preventative strategies that can be routinely implemented in clinical practice. The ultimate goal of this comprehensive approach is to limit the damage caused by increased oxidative stress in diabetes and identify the most beneficial forms of adjuvant antioxidant therapy for the treatment of diabetic complications.

Conclusions

Diabetes is recognized as a major factor in the severity and progression of periodontitis, and its severity is associated with poor glycemic control. Because this relationship is bidirectional, as advanced periodontitis can undermine adequate glycemic control, it is clear that patients with diabetes should be aware of the increased risk of developing periodontitis and its potential negative impact on metabolic control, which, in turn, will increase the risk of diabetic complications. Therefore, it is essential to incorporate periodontal health into diabetes treatment protocols, necessitating multidisciplinary treatment of patients with type 2 diabetes and periodontitis. While treatment of periodontal infection in people with diabetes is undoubtedly necessary for maintaining oral health, it can also play a significant role in establishing and maintaining glycemic control, potentially delaying or even preventing the onset or progression of diabetic complications. A better understanding of the pathogenetic mechanisms linking diabetes and periodontitis should facilitate the development of new therapeutic approaches that will reduce the risk of complications associated with both conditions.

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