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DIABETIC NEPHROPATHY AND DIABETIC FOOT SYNDROME: PATHOGENESIS, CLINICAL RELATIONSHIP AND MODERN APPROACHES TO TREATMENT

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Abstract: Diabetic nephropathy and diabetic foot syndrome are one of the most severe and clinically significant complications of diabetes mellitus, determining the quality of life and life expectancy of patients. Their pathogenesis is formed against the background of chronic hyperglycemia, activation of pro-inflammatory and fibrotic cascades, microcirculation disorders and endothelial dysfunction, which forms common links in the lesion of the renal and peripheral vascular systems. The mutual aggravation of diabetic nephropathy and diabetic foot syndrome is due to the cross-involvement of immune mechanisms, disruption of reparative processes and worsening of the prognosis in the presence of terminal chronic kidney disease. Early detection of early stages of nephropathy, including subclinical albuminuria, as well as assessment of neuroischemic forms of foot lesions, are crucial to prevent complications and optimize management tactics. In recent years, integrative approaches to therapy, including the use of metabolically active and nephroprotective drugs, local immunomodulatory agents, as well as the participation of multidisciplinary teams in comprehensive prevention and treatment, have become of particular importance. The presented review summarizes current information on the pathogenesis, clinical relationship and effective directions of therapy for these complications of diabetes mellitus.

Key words: diabetic nephropathy, diabetic foot syndrome, microangiopathy, inflammation, complications of diabetes mellitus.

INTRODUCTION

Diabetes mellitus remains one of the most pressing medical and social problems of our time, the progressive course of which is accompanied by the development of severe microvascular and macrovascular complications that significantly affect life expectancy and the level of disability of patients. Among such complications, a special place is occupied by diabetic nephropathy and diabetic foot syndrome, united not only by the commonality of pathogenetic mechanisms, but also by the high frequency of mutual combination, which aggravates the clinical course and therapeutic prospects. Diabetic nephropathy is the leading cause of terminal chronic kidney disease and occupies a dominant position in the structure of diseases requiring renal replacement therapy, including hemodialysis and transplantation. At the same time, diabetic foot syndrome remains the main cause of non-traumatic lower limb amputations, which makes these two complications key determinants of prognosis in patients with long-term diabetes mellitus [2, 6, 8].

Modern studies emphasize the presence of a direct pathogenetic relationship between the

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progressive decrease in glomerular filtration, the level of albuminuria and the risk of ulcerative-necrotic lesions of the foot. The mechanisms of this relationship include systemic endothelial dysfunction, chronic inflammation, fibrosis activation, impaired tissue regenerative capacity, and deterioration of immune reactivity, especially pronounced during the transition of diabetic nephropathy to the stage of chronic renal failure [3, 5, 12]. It has been established that the presence of nephropathy more than doubles the risk of purulent-necrotic complications in the foot area, and the combination with diabetic angioneuropathy is accompanied by an unfavorable clinical course and a high probability of septic complications [7, 9].

In the context of the growing epidemiological burden of diabetes mellitus, early detection of risk factors, timely diagnosis of the initial stages of nephropathy and minimal signs of trophic changes in the foot area, as well as the integration of interdisciplinary approaches to treatment are crucial. The purpose of this article is to systematize modern ideas about the pathogenetic relationship between diabetic nephropathy and diabetic foot syndrome with an emphasis on the common links of damage to vascular and immune regulation, as well as to analyze current prevention and therapy strategies against the background of metabolic decompensation and impaired tissue repair [1, 4, 10, 13].

MAIN PART

Pathogenesis of diabetic nephropathy

Diabetic nephropathy develops as a result of prolonged exposure to hyperglycemia on the structures of the nephron, which triggers a cascade of disorders at the molecular, cellular and tissue levels. The key pathogenetic links in this case are the activation of the renin-angiotensin-aldosterone system, endothelial dysfunction, oxidative stress and chronic inflammation, which form progressive damage to the glomerular apparatus of the kidneys. In the early stages, hyperfiltration is observed due to dilatation of the adductor arterioles and a decrease in the resistance of the vascular bed, which leads to an increase in intraglomerular pressure and accelerated damage to the basement membrane [4, 6].

Gradually, membrane thickening and expansion of the mesangial matrix develop, accompanied by infiltration of immune system cells and the release of pro-inflammatory cytokines such as interleukin-6, tumor necrosis factor alpha, and transforming growth factor beta, which enhances fibrosis and reduces glomerular filtration capacity. An important role is also played by the accumulation of glycation products that bind to receptors on the cells of the renal epithelium and induce a prolonged inflammatory response that supports the activation of macrophages and the formation of reactive oxygen species [3, 7, 11].

Against the background of these processes, podocyte damage occurs, loss of intercellular contacts and the development of proteinuria, which is one of the early and reliable signs of diabetic nephropathy. With the progression of the disease, capillary density decreases, ischemia of the renal parenchyma and irreversible sclerosing of nephrons develop, which leads to a decrease in the glomerular filtration rate and the transition to the stage of chronic renal failure. In the late stages, electrolyte disorders increase, intoxication increases, and systemic inflammatory reactions are activated, exacerbating immune deficiency and increasing the risk of infectious complications, including lesions of the subcutaneous tissue and purulent processes in the foot [5, 9, 14].

Thus, diabetic nephropathy is not only an isolated kidney lesion, but also an important factor determining systemic changes in diabetes mellitus, which requires a comprehensive pathogenetic approach to

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therapy and prevention, especially in the presence of associated complications, such as diabetic foot syndrome [2, 10, 13].

Pathogenesis of diabetic foot syndrome

Diabetic foot syndrome is formed against the background of a long course of diabetes mellitus and is the result of a complex interaction of neuropathic, angiopathic, immune and metabolic factors that consistently disrupt the integrity of tissues, microcirculation and the regenerative potential of the skin and subcutaneous fat. The basis of the pathological process is diabetic peripheral neuropathy, which develops as a result of chronic hyperglycemia and ischemia, leading to damage to Schwann cells, axonal degeneration and impaired conduction of nerve impulses. Loss of sensitivity contributes to microtraumatization, and disturbance of autonomic innervation causes dry skin, cracks, and increased susceptibility to secondary infection [4, 7, 12].

Along with the neuropathic component, angiopathy plays a key role in the development of diabetic foot syndrome, manifested by thickening of the basement membrane, a decrease in the vasodilator response and a violation of the rheological properties of the blood. This leads to a critical decrease in tissue perfusion and hypoxia, in which all phases of wound healing are disrupted, from chemotaxis and angiogenesis to proliferation and remodeling. The resulting ischemia reduces the activity of fibroblasts and macrophages, inhibits collagen synthesis, and inhibits capillary growth, which contributes to the formation of chronic ulcerative-necrotic defects [3, 8, 14].

Immune disorders in diabetic foot syndrome include decreased neutrophil activity, impaired phagocytosis, and deficiency of local cytokine regulation, which makes it difficult to limit infection and contributes to the progression of purulent processes. Microbial wound seeding, biofilm formation, and the presence of multidrug-resistant microflora are of particular importance, especially in patients with concomitant chronic renal failure, which is confirmed by a number of clinical observations [2, 9, 11]. Against this background, tissue necrosis increases, spreading through the fascial spaces, leading to the formation of phlegmon, osteomyelitis and, in severe cases, the need for amputation.

Thus, diabetic foot syndrome is a multifactorial complication formed at the intersection of neurogenic, vascular and immune disorders, aggravated in combination with other diabetic complications, in particular, nephropathy. These features require early detection of foot lesions, assessment of the degree of ischemia, and aggressive complex therapy with the participation of a multidisciplinary team [5, 6, 10, 13].

The relationship between diabetic nephropathy and diabetic foot syndrome

Diabetic nephropathy and diabetic foot syndrome, despite the difference in the localization of clinical manifestations, have common pathophysiological mechanisms, which is confirmed by numerous epidemiological and clinical studies. The presence of diabetic nephropathy significantly increases the likelihood of trophic ulcers of the lower extremities, especially in cases of decreased glomerular filtration rate and the presence of macroalbuminuria, which is associated with worsening tissue perfusion, decreased immune reactivity, and impaired detoxification function of the kidneys [3, 6, 8]. At the same time, patients with diabetic foot syndrome often show latent or undiagnosed signs of renal dysfunction, including increased creatinine, decreased concentration function, and signs of microalbuminuria, which reflects the

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systemic nature of vascular and metabolic damage [1, 5, 11].

The common links in the pathogenesis are generalized endothelial dysfunction, hyperactivation of pro-inflammatory cascades, oxidative stress, and dysregulation of vasoactive substances, primarily nitric oxide, endothelin, and angiotensin II. Reduced expression of vascular endothelial growth factor, activation of type 1 T-helper cells, and suppression of angiogenesis exacerbate the course of both forms of complications, creating conditions for persistent ischemia, necrotic changes, and chronic wound infection [4, 7, 13].

In clinical practice, it is noted that patients with a pronounced stage of nephropathy are much more likely to need amputations due to the severe course of purulent-necrotic lesions of the foot, and are also more likely to suffer from septic complications, including gangrene, phlegmon, and osteomyelitis, which is explained by a decrease in the functional activity of leukocytes and impaired metabolic detoxification [2, 10, 14]. In addition, the presence of diabetic foot syndrome in patients with renal failure complicates the selection of antibacterial and anti-inflammatory therapy, requires a revision of surgical treatment tactics and increases the frequency of adverse outcomes.

Thus, the relationship between diabetic nephropathy and diabetic foot syndrome is not only pathogenetic, but also clinical and prognostic, determining the severity of the patient's condition, the complexity of treatment and the need for early integration of diagnostic and therapeutic algorithms. Awareness of the unity of these processes serves as the basis for comprehensive screening and risk stratification, as well as a personalized approach to the prevention and treatment of complications of diabetes mellitus [9, 12, 15].

Risk Diagnosis and Stratification

Timely diagnosis of diabetic nephropathy and diabetic foot syndrome requires the integration of clinical, laboratory and instrumental methods aimed at detecting early signs of organ damage, determining the degree of functional impairment and predicting the risk of complications. For diabetic nephropathy, the priority remains to determine the level of albuminuria, which is considered a sensitive marker of initial changes in glomerular filtration. Along with this, clinical practice uses the assessment of the glomerular filtration rate by creatinine and, if necessary, by the level of cystatin C, which makes it possible to improve the accuracy of diagnosing subclinical forms of nephropathy and assess the dynamics of its progression [2, 5, 10].

Diagnosis of diabetic foot syndrome is based on the detection of signs of sensory, motor and autonomic neuropathy, clinical assessment of the skin condition, the presence of deformities, hyperkeratoses, ulcers and areas of necrosis, as well as measurement of the degree of ischemia by determining the ankle-brachial index. The use of modern severity scales, such as the Wagner system and the PEDIS classification, makes it possible to standardize the assessment of the wound process and determine the need for specialized intervention. An important diagnostic stage is the microbiological study of wound exudate, which makes it possible to identify the nature of the microflora and its sensitivity to antibacterial drugs, especially in the context of progressive renal failure, in which the spectrum of pathogens acquires multidrug-resistant features [3, 7, 12].

Risk stratification in patients with diabetes mellitus should take into account the presence and severity of nephropathy, the level of glycemic control, the duration of the disease, indicators of inflammatory activity, and history of previous ulcers, amputations,

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and infectious complications. A comprehensive assessment of these factors makes it possible to identify high-risk groups and initiate early preventive measures, including the use of nephroprotective drugs, correction of microcirculation disorders, and the use of local immunotherapy [4, 8, 13]. Currently, special attention is paid to the development of integral risk assessment models that make it possible to predict outcomes not only at the level of one organ, but also from the standpoint of systemic inflammatory and vascular status, which is especially important in patients with combined kidney and lower limb damage [1, 6, 9].

Thus, the success of the management of patients with diabetic nephropathy and diabetic foot syndrome directly depends on the accuracy and timeliness of diagnosis, as well as on the effectiveness of stratification approaches aimed at individualizing therapeutic strategies taking into account prognostic indicators.

Principles of complex treatment

Comprehensive treatment of patients with diabetic nephropathy and diabetic foot syndrome requires not only the correction of metabolic disorders, but also a systematic approach to pathogenetic therapy aimed at stabilizing the vascular bed, suppressing the inflammatory cascade, improving microcirculation and stimulating reparative processes. Glycaemic control remains the basic component of treatment, but modern data emphasize that achieving glucose targets is not enough to inhibit the progression of nephropathy and the development of trophic complications, especially against the background of already formed vascular changes [2, 5, 8].

In recent years, drugs with nephroprotective properties, including type II sodium-glucose cotransporter inhibitors and type 1 glucagon-like peptide receptor agonists, have become of particular importance, which not only improve the glycemic profile, but also help reduce blood pressure, reduce albuminuria and prevent fibrotic processes in the renal parenchyma. At the same time, the use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers remains pathogenetically substantiated, especially in the presence of proteinuria and a decrease in the glomerular filtration rate [4, 6, 13].

As for the treatment of diabetic foot syndrome, the key area is infection control, including early administration of antibiotic therapy, taking into account the microbiological profile of the wound and the state of renal function. Local methods of exposure include the use of modern dressings with antiseptic, enzymatic and immunoactive properties, as well as the use of cytokine drugs aimed at modulating the inflammatory response and stimulating tissue granulation. In the presence of ischemia, revascularization procedures, including angioplasty and bypass grafting, are indicated, especially if the viable area of distal blood flow is preserved [3, 7, 11].

An integral component of treatment is surgical correction in conditions of purulent-necrotic complications, which includes timely sanitation of the foci of infection, necrectomy, reconstructive interventions and, if necessary, amputation. The results are significantly improved with the participation of a multidisciplinary team including an endocrinologist, a surgeon, a nephrologist, and a wound therapy specialist, which ensures the coordination of medical and local interventions adapted to the level of systemic disorders [1, 9, 10].

Thus, the principles of comprehensive treatment of diabetic nephropathy and diabetic foot syndrome include synchronous correction of the metabolic background, systemic and local anti-inflammatory therapy, vascular reconstruction and surgical

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intervention if necessary, which makes it possible to achieve a reduction in the frequency of complications and an improvement in the long-term prognosis.

Prognosis, complications and prevention

The combined course of diabetic nephropathy and diabetic foot syndrome significantly complicates the clinical prognosis, increasing the risk of death, disability and the need for expensive interventions. Against the background of progressive nephropathy, metabolic control deteriorates, the effectiveness of antibiotic therapy decreases and the likelihood of a complicated course of the wound process, including the formation of phlegmon, osteomyelitis and sepsis, increases. Patients with end-stage chronic renal failure have the most unfavorable course of diabetic foot syndrome due to a pronounced decrease in immune resistance, impaired regeneration, and angiopathy reaching a critical level [1, 3, 6].

The prognosis in this category of patients depends on the timely detection of early stages of nephropathy, early initiation of therapy aimed at inhibiting fibrosis, as well as on adequate local and systemic treatment of infectious complications. Amputations of the lower extremities in patients with diabetic nephropathy are associated with a high level of in-hospital mortality, and a significant proportion of such cases could be prevented with regular foot screening and preventive sanitation [4, 7, 11].

Prevention of complications requires a systematic approach based on glycemic control, blood pressure correction, reduction of albuminuria levels, the use of drugs with a proven nephroprotective effect, as well as the organization of specialized care for patients at risk of developing diabetic foot syndrome. Educational programs for patients, training in the rules of foot care, the use of orthopedic shoes and regular examinations with the participation of multidisciplinary teams are effective. In the presence of baseline nephropathy, special attention should be paid to the individualization of therapy regimens and dynamic observation with the determination of markers of inflammation, albuminuria, and signs of microcirculatory disorders [2, 8, 10].

Thus, the prognosis in patients with diabetic nephropathy and diabetic foot syndrome is closely related to the severity of vascular disorders, the degree of diabetes compensation and the completeness of therapeutic and preventive measures. A comprehensive and personalized approach to such patients allows minimizing risks and increasing the effectiveness of therapy in the early stages of the disease.

CONCLUSION

Diabetic nephropathy and diabetic foot syndrome are two of the most severe and prognostically significant complications of diabetes mellitus, the development of which is determined by a complex interaction of inflammatory, vascular and immune mechanisms. Both pathologies are closely related to each other both at the level of general pathogenetic cascades and from a clinical point of view, since the presence of one of these conditions significantly increases the risk of manifestation of the other, forming a vicious circle of mutual burden. Decreased filtration function of the kidneys, deterioration of tissue trophism and increased resistance of infectious agents exacerbate the clinical course and limit the effectiveness of traditional therapy regimens, which requires the introduction of personalized approaches and multidisciplinary treatment strategies.

Modern data confirm the importance of early diagnosis, risk stratification and the use of integrative methods aimed at both stabilizing metabolic processes and preventing the complicated course of ulcerative-necrotic

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processes in the foot area. Effective interaction between a nephrologist, endocrinologist, surgeon and wound therapy specialist ensures maximum coordination of treatment measures and makes it possible to adjust management tactics in a timely manner. Given the growing prevalence of diabetes and the high medical and social significance of its complications, the prevention of diabetic nephropathy and diabetic foot syndrome should remain a priority both for clinical practice and for scientific research in the field of endocrinology, vascular surgery and internal medicine.

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