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Clinical and Pathogenetic Relationship Between Nephropathy and Diabetic Foot Syndrome

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Abstract: Diabetic nephropathy and diabetic foot syndrome are among the most severe and disabling complications of diabetes mellitus, determining the severity of systemic disorders and an unfavorable prognosis. Modern research indicates the presence of a common pathogenetic basis for these conditions, including chronic inflammation, endothelial dysfunction, microcirculation disorders and activation of fibrotic processes. In this work, data on 32 patients with various degrees of diabetic foot syndrome according to the Wagner classification, who simultaneously showed signs of diabetic nephropathy, are considered. The analysis showed that more severe forms of foot syndrome are associated with a pronounced decrease in the glomerular filtration rate and a high degree of albuminuria, which indicates progressive kidney damage in this category of patients. The data obtained emphasize the need for a comprehensive assessment of target organ damage in patients with diabetes mellitus, which is important both for the prognosis and for the choice of management tactics. Particular attention is paid to the role of chronic renal failure as a factor in the deterioration of reparative processes and a predisposition to purulent-necrotic complications of the lower extremities.

Keywords: Diabetes mellitus, diabetic nephropathy, diabetic foot syndrome, chronic renal failure, severity of complications.

Introduction: Diabetes mellitus is a chronic multi-organ disease accompanied by vascular, metabolic and inflammatory disorders, which over time lead to the development of severe complications. The most significant among them are diabetic nephropathy and diabetic foot syndrome, which significantly reduce the

quality of life, aggravate the course of the underlying disease and increase the risk of disability. Diabetic nephropathy remains the leading cause of end-stage renal disease, especially in patients with long-term type 2 diabetes mellitus, and is accompanied by persistent changes in the glomerular apparatus, the development of proteinuria, a decrease in the glomerular filtration rate, and the formation of fibrosis [1, 2].

Diabetic foot syndrome is formed against the background of a combination of peripheral neuropathy, micro- and macroangiopathy and infection, and is the leading cause of non-traumatic amputations of the lower extremities worldwide [3, 4]. The course of this complication is exacerbated in patients with concomitant renal dysfunction, since chronic uremia, anemia, and decreased immune reactivity contribute to the progression of ulcerative-necrotic changes and a slowdown in reparative processes [5]. Current studies indicate that the presence of diabetic nephropathy increases the risk of purulent complications and amputations in patients with diabetic foot syndrome, while the severity of renal damage correlates with the severity of foot damage and the prognosis [6, 7].

Despite the obvious clinical conjugation of these conditions, many aspects of their pathogenetic relationship are not fully understood, and the issue of risk stratification in patients with combined complications remains a subject of discussion. Given the high prevalence of combined foot and kidney damage in patients with long-term diabetes, it seems relevant to study the clinical and functional relationships between these conditions.

The purpose of this work is to analyze the severity of diabetic nephropathy in patients with diabetic foot syndrome of varying severity and to discuss the pathogenetic mechanisms of their mutual burden.

METHODS

This study is based on the analysis of data from 32 patients diagnosed with type 2 diabetes mellitus hospitalized in the surgical department of the multidisciplinary clinic of Tashkent State Medical University between January 2022 and December 2024 for complicated forms of diabetic foot syndrome. All patients at the time of inclusion in the analysis had signs of diabetic nephropathy of varying severity, which made it possible to study the clinical and functional relationship between the severity of renal damage and the degree of foot syndrome.

Among the examined patients, there were 19 men (59.4%) and 13 women (40.6%) aged 48 to 72 years, the mean age was 61.2±6.4 years. The average duration of diabetes mellitus at the time of inclusion was 11.7±3.2 years. The diagnosis of diabetic foot syndrome was established on the basis of clinical examination, instrumental examination, assessment of ulcerative-necrotic changes, palpation data of peripheral arteries and ankle-brachial pressure index. Classification of severity was used according to the Wagner system: stage I was diagnosed in 6 patients (18.8%), stage II - in 10 patients (31.3%), stage III - in 9 patients (28.1%), stage IV - in 7 patients (21.8%).

Diabetic nephropathy was confirmed on the basis of two criteria: the presence of persistent albuminuria (≥ 30 mg/day) and a decrease in the glomerular filtration rate according to the CKD-EPI formula. Depending on the degree of renal failure, the patients were divided into three subgroups: 12 patients (37.5 %) with preserved renal function (glomerular filtration rate ≥ 60 ml/min/1.73 m^2), 13 patients (40.6 %) with moderate decrease (glomerular filtration rate 30–59 ml/min/1.73 m^2) and 7 patients (21.9 %) with a pronounced decrease in filtration capacity (glomerular filtration rate < 30 ml/min/1.73 m^2).

Laboratory studies included serum creatinine, glomerular filtration rate, daily proteinuria, glycosylated hemoglobin (HbA1c), C-reactive protein levels, and leukocyte count. To assess the relationship between the severity of diabetic nephropathy and the stage of diabetic foot syndrome, Spearman's correlation coefficient was used. To assess the statistical significance of the differences between the subgroups, the Mann–Whitney U-test for quantitative traits and the Pearson χ^2 test for qualitative traits were used. The significance level was assumed to be $p < 0.05$.

Data processing and visualization were carried out using the Statistica v.12.5 and SPSS v.25.0 packages. All data were previously anonymized, the study was performed without interference in the treatment process and did not require the approval of the ethics committee.

RESULTS

The analysis of the distribution of patients by the severity of diabetic foot syndrome depending on the level of decrease in the glomerular filtration rate revealed a clear clinical and functional relationship between the severity of renal damage and the stage of local destructive changes in the foot area. In the group with preserved renal function (glomerular filtration rate ≥ 60 ml/min/1.73 m^2), patients with grade I-II diabetic

foot syndrome predominated, while in patients with moderate to severe decline, grade III-IV glomerular filtration rate according to the Wagner classification was more common.

Table. Distribution of patients by degree of diabetic foot syndrome and glomerular filtration rate (n = 32)

The degree of diabetic syndrome стопы (Wagner)	glomerular filtration rate (**ml/min**)			
	≥ 60	**30–59**	**< 30**	**TOTAL**
I degree	5 (41,7 %)	1 (7,7 %)	0 (0 %)	6 (18,8 %)
II degree	5 (41,7 %)	4 (30,8 %)	1 (14,3 %)	10 (31,3 %)
III degree	2 (16,6 %)	5 (38,5 %)	2 (28,6 %)	9 (28,1 %)
IV degree	0 (0 %)	3 (23,0 %)	4 (57,1 %)	7 (21,8 %)
TOTAL	12 (100 %)	13 (100 %)	7 (100 %)	32 (100 %)

Based on the data obtained, it was found that severe forms of diabetic foot syndrome (III-IV degree) prevailed in patients with a glomerular filtration rate of <30 ml/min/1.73 m², which indicates an adverse effect of pronounced nephropathy on the course of local purulent-necrotic processes. In this category of patients, deeper ulcerative defects, slow granulation dynamics and frequent involvement of bone structures in the process were recorded, which increased the need for surgical interventions, including amputations.

Correlation analysis showed the presence of a statistically significant inverse relationship between the level of glomerular filtration rate and the degree of diabetic foot syndrome ($r=-0.67$, $p<0.01$), which confirms the clinical and pathogenetic relationship between progressive nephropathy and aggravation of local lesions of the extremities. There is also a tendency to increase the level of C-reactive protein and neutrophilia in patients with stage III-IV diabetic foot syndrome and severe renal failure, which reflects the systemic inflammatory load.

DISCUSSION

Diabetic nephropathy is one of the most serious microvascular complications of diabetes mellitus, leading to chronic kidney disease and end-stage renal disease. According to various studies, up to 40% of patients with diabetes mellitus develop diabetic nephropathy during their lifetime [1].

The pathogenesis of diabetic nephropathy involves a complex interplay of metabolic and hemodynamic factors. Chronic hyperglycemia leads to activation of the polyol pathway, increased formation of advanced glycation end products (AGEs), and activation of protein kinase C, which contributes to inflammation and fibrosis of renal tissue [2]. In addition, activation of the renin-angiotensin-aldosterone system (RAAS) increases intraglomerular pressure, contributing to the progression of nephropathy [3].

Clinically, diabetic nephropathy is manifested by proteinuria, a decrease in the glomerular filtration rate, and an increase in blood pressure. Early diagnosis and control of risk factors such as hyperglycemia and hypertension are key in slowing the progression of the disease [4].

Diabetic foot syndrome is a complex multifactorial complication of diabetes mellitus, characterized by the development of ulcers, infections and, in severe cases, gangrene of the lower extremities. According to the World Health Organization, up to 15% of patients with diabetes face foot ulcers during their lifetime [5].

The pathogenesis of diabetic foot syndrome includes peripheral neuropathy, ischemia due to peripheral arterial disease, and immune dysfunction. Neuropathy

leads to a loss of sensation, which contributes to invisible injuries and the subsequent development of ulcers. Ischemia exacerbates wound healing, and immune dysfunction increases the risk of infections [6].

Clinical management of diabetic foot syndrome requires a multidisciplinary approach, including glycemic control, wound care, antibiotic therapy, and, if necessary, surgery. Early diagnosis and prevention are key in reducing the risk of amputations [7].

There is strong evidence of a strong relationship between diabetic nephropathy and diabetic foot syndrome. According to studies, a decrease in the glomerular filtration rate and the presence of proteinuria are associated with an increased risk of foot ulcers and amputations [8].

The mechanisms of this relationship include worsening of microcirculation, increased inflammation and reduced immune defense in patients with advanced nephropathy. These factors contribute to poor wound healing and increase the risk of infections in the foot area [9].

Thus, the presence of diabetic nephropathy in patients with diabetic foot syndrome requires special attention from clinicians. A comprehensive approach to treatment, including control of glycemia, blood pressure, and renal function, as well as timely intervention for foot lesions, is key in improving the prognosis for this category of patients [10].

CONCLUSION

The data obtained confirm the existence of a pronounced clinical and pathogenetic relationship between diabetic nephropathy and diabetic foot syndrome. It has been established that a progressive decrease in renal function, especially with a decrease in the glomerular filtration rate less than 60 ml/min/1.73 m², is associated with an aggravation of the course of diabetic foot syndrome and an increase in the incidence of III-IV degrees according to the Wagner classification. This confirms the thesis about the systemic nature of vascular and inflammatory damage to target organs in diabetes mellitus.

The pathogenetic proximity of these complications is explained by common links in the form of chronic inflammation, endothelial dysfunction, dysregulation of angiogenesis and a decrease in the immune response. In patients with nephropathy, there is a deterioration in reparative processes, a tendency to infections, and pronounced ischemia of the distal parts of the extremities, which leads to a complicated course of ulcerative-necrotic processes and increases the risk of surgical interventions. A particularly severe course is noted with a combination of albuminuria, a reduced level of glomerular filtration rate and a neuroischemic form of foot syndrome.

Thus, when managing patients with diabetic foot syndrome, it is imperative to take into account the state of renal function, including a dynamic assessment of glomerular filtration rate and albuminuria. The inclusion of nephrological assessment in the risk stratification algorithm allows not only to predict the severity of the course, but also to apply nephroprotective measures in a timely manner, thereby improving outcomes and reducing the frequency of amputations. The presented results emphasize the importance of an interdisciplinary approach and the need for early diagnosis of concomitant complications of diabetes mellitus.

Ethics Statement:

This study was carried out on the basis of a retrospective analysis of anonymized clinical data obtained as part of standard diagnostics and treatment. Experiments and interventions outside of clinical protocols were not carried out. The study complies with the Declaration of Helsinki of the World Medical Association and did not require separate approval from the ethics committee.

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Conflict of interest:

The author declares that there is no conflict of interest that could affect the interpretation of the data presented or the scientific objectivity of the conclusions.

Author's contribution:

Saitov D.N. - development of the research concept, data collection and analysis, preparation of the text of the article, editing and final approval of the manuscript.

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