Autonomic neuropathy, cardivascular form - a risk factor for progression of complications of diabetes mellitus type 2

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Abstract: The article gives information about autonomic neuropathy, cardivascular form - a risk factor for progression of complications of diabetes mellitus type 2.

Keywords: diabetes mellitus, cardiovascular disease, cardiovascular autonomic neuropathy, microvascular complications, colorectal cancer

Introduction. Diabetes mellitus (DM) is a common and disabling endocrine pathology [1]. The increase in incidence exceeds 50% over 5 years; by 2045, the number of patients with diabetes worldwide will reach 783 million people [2]. The most dangerous complication of diabetes remains diabetic foot syndrome (DFS), which is the main cause of non-traumatic amputations of the lower extremities [3, 4]. Despite the efforts of the entire medical community, the survival rate of patients with DFS with non-healing ulcers and after foot surgery does not exceed 50% over 5 years and is comparable to the survival rate of patients with colorectal cancer [5]. The main cause of death in patients with DFS remains cardiovascular pathology. Another complication, cardiovascular autonomic neuropathy (CAN), is an independent risk factor for cardiovascular disease and cardiovascular mortality in patients with diabetes [6, 7]. CAN consists of a disruption of the innervation of not only the heart, but also the central and peripheral vessels. Damage to the innervation of peripheral vessels (neurocirculatory regulation) underlies the pathogenesis of the development and progression of all microvascular complications of diabetes [8, 9]. Cases of aggressive course of CAN (progressive course) increase the risk of cardiovascular mortality in patients with diabetes. However, data on the impact of CAN progression over time on other microvascular complications of diabetes, especially among different groups of patients and patients with diabetes, are scarce and contradictory [10-12].

Purpose of the study: to determine the features of the course and evaluate the impact of progression of CAN on the development of other complications of diabetes in patients with diabetes and postoperative wounds over 2 years of observation.

To achieve this goal, an observational (observational) prospective study was performed with a follow-up period of 2 years.

Materials and methods

Criteria for inclusion of patients in the study:

1) age from 35 to 75 years;

2) CD2;

3) neuropathic form of SDS;

4) previous surgical interventions for SDS;

5) open postoperative wounds on the feet.

Exclusion criteria from the study:

1) non-diabetic neuropathy;

2) diseases of the arteries of the lower extremities (ankle-brachial index (ABI) <0.9);

3) poorly controlled diabetes (HbA1c ≥ 10%);

4) acute complications of diabetes (ketoacidosis, hyper-/hypoglycemic coma, lactic acidosis);

5) chronic complications of diabetes in severe stages (diabetic retinopathy requiring laser coagulation of the retina, diabetic nephropathy with an estimated glomerular filtration rate (eGFR) ≤ 30 ml/min/1.73 m2);

6) atrial fibrillation or the presence of an artificial cardiac pacemaker;

7) chronic heart failure FC III-IV;

8) COPD, as well as other chronic diseases in the stage of decompensation.

Patient examination

All patients received surgical treatment of purulent-necrotic complications of SDS in the department of purulent surgery of the Samarkand city hospital.

Information about the onset of development and duration of diabetes, chronic complications, and surgical interventions performed on the feet was taken from the medical documentation. Anthropometric, laboratory and instrumental examinations were carried out initially at the time of inclusion in the study with open postoperative wounds, as well as after 2 years of follow-up. The results of treatment of postoperative wounds (healing time), as well as cases of repeated hospitalizations and operations over 2 years of observation were taken into account.

From the laboratory examination, the work included data on HbA1c, serum lipid spectrum, creatinine and eGFR.

Study of cardiac autonomic innervation

To assess the presence and severity of CAN, 5 standard cardiovascular tests (CVT) were performed. Parasympathetic innervation was examined using the Valsalva test and the deep breathing test. Sympathetic innervation was assessed by changes in blood pressure during tests with a dynamometer, passive orthostasis, and cold vasoconstriction was also determined by photoplethysmography. The results of each test are assigned 0 points in the case of normal values, 0.5 points in the case of borderline values, and 1 point in the case of pathologically altered values (Table 1).

Table 1.

Cardiovascular test values and scoring system

Cardiovascular tests	Normal values (0 points)	Borderline values (0.5 points)	Pathological values (1 point)
Valsalva test, conv. units	⩾1.41	1.40-1.20	⩽1.19
Deep breathing test, per minute	⩾15	14-11	⩽10
Test with a dynamometer, mm Hg. Art.	⩾15	14-11	⩽10
Cold vasoconstriction,%	⩾36	35-25	⩽24
Passive orthostasis test, mm Hg. Art.	⩽10	19-11	⩾20

The method for diagnosing the presence and severity of CAN using a CVT score has been developed by many researchers [13, 14]. According to the latest expert recommendations, early stage CAN (CAN 1) is verified if⩾1 point, confirmed form of CAN (CAN 2) - in cases⩾2 points, and severe CAN (CAN 3) - with identified symptomatic and/or asymptomatic orthostatic hypotension [14].

Diabetic Sensorimotor Neuropathy Study

To assess the presence and severity of diabetic sensorimotor neuropathy (DSMN), a clinical neurological examination was performed with filling out the Neuropathic Dysfunctional Score (NDS) scale. According to this scale, DSMN is verified if there are 4 points or higher, which correlates with the results of electroneuromyography, which is a reference method for studying lesions of sensorimotor fibers [15].

Statistical data processing

A sufficient number of observations was established using evidence-based formulas using sample size tables to achieve 80% power ($\alpha = 0.05$, two-sided). The type of distribution of variable values was assessed by constructing distribution histograms and calculating the Kolmogorov-Smirnov criterion. All data are presented as mean ± SEM for normally distributed quantitative variables, as mean ± 95% confidence interval (CI) for non-normally distributed variables, and as percentages for qualitative bipolar variables. The difference between quantitative characteristics in dependent samples with a normal distribution was calculated using the Student t-test; with a non-normal distribution, the Wilcoxon test was used. To compare qualitative variables between groups, χ^2 with Yates' correction (for small groups), Fisher's test was used.

Odds ratios (OR) for the progression of microvascular complications of DM and unsatisfactory treatment of DM depending on the nature of the development of CAN were determined using logistic regression analysis. To identify threshold values of quantitative values, the method of classification trees was used. A p value <0.05 was considered statistically significant in all cases. The STATISTICA v.13 software package was used. (Statsoft, USA).

Results

Baseline characteristics of patients with DFS

A total of 94 patients with DFS (38.3% men and 61.7% women) discharged for outpatient treatment after surgery were included in the study. Baseline characteristics of patients are presented in Table. 2.

Table 2.

Baseline characteristics of patients with diabetic foot syndrome (n = 94)

Parameter		Meaning
age		57.0 ± 0.93
Gender (m/f)		38.3/61.7%
Duration of T2DM, years		10.7 ± 0.92
Age at onset of T2DM < 40 years, n (%)		27 (28.7%)
History of minor amputations, n (%)		20 (21.3%)
Previous surgical treatment	autopsy, n (%)	46 (48.9%)
	amputation, n (%)	48 (51.1%)
Diabetic retinopathy (yes/no, %)		36.2/63.8%
IHD, n (%)		52 (55.3%)
GB, n (%)		83 (88.3%)
Insulin therapy, n (%)		23 (24.5%)
Statins, n (%)		50 (53.2%)
VAT, point		10.5 ± 0.50
KW, point		2.1 (95% CI 1.8-2.3)
CH 2-3, n (%)		54 (57.4%)
BMI, kg/m²		29.4 ± 0.51
HbA1c,%		8.3 ± 0.20
obchs, mmol/l		5.2 ± 0.13
LDL cholesterol, mmol/l		3.3 ± 0.11
HDL cholesterol, mmol/l		1.2 ± 0.05
TG, mmol/l		1.8 ± 0.10
eGFR, ml/min		94.5 ± 3.37

Note. T2DM - type 2 diabetes mellitus, IHD - coronary heart disease, HD - hypertension, VDS - neuropathic dysfunctional score scale, CVT - cardiovascular tests, CAN - cardiovascular autonomic neuropathy, BMI - body mass index, HbA1c - glycated hemoglobin, bHc - total cholesterol, LDL cholesterol - low-density lipoprotein cholesterol, HDL cholesterol - high-density lipoprotein cholesterol, TG - triglycerides, eGFR - estimated glomerular filtration rate.

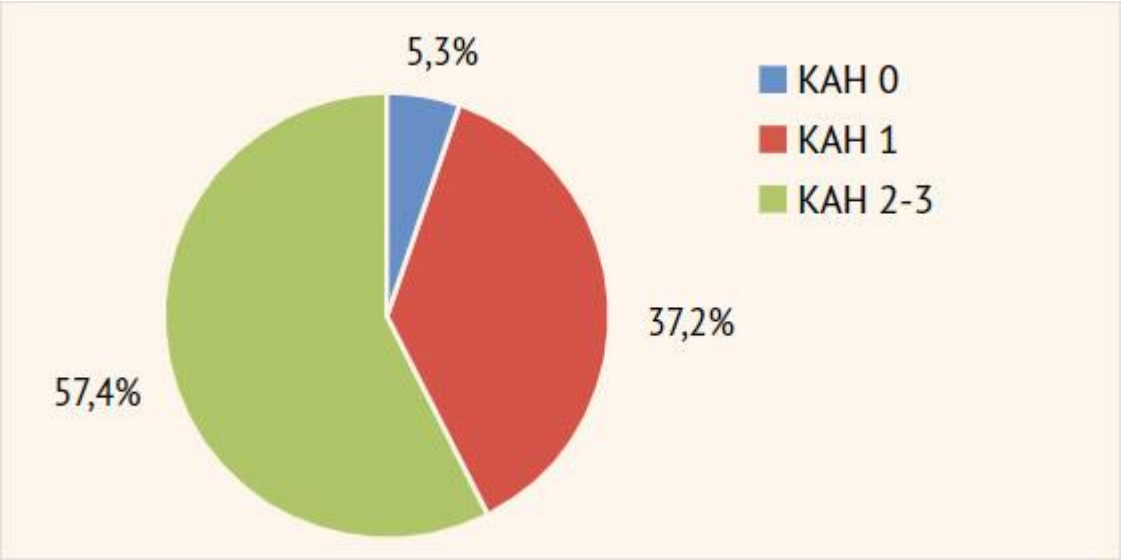
As can be seen from table. 2, all patients underwent surgery, including amputations within the foot in 51.1% of cases (48/94), after which the patients were

discharged for outpatient treatment. However, more than 20% of patients (21.3%; 20/94) had a history of repeated surgical interventions on the feet (minor amputations). The average duration of T2DM was 10.7 years; at the time of diagnosis of diabetes, 28.7% (27/94) of patients were under 40 years of age. 24.5% (23/94) of people received insulin therapy or combination therapy with insulin and oral hypoglycemic drugs.

All patients initially had microvascular complications of diabetes. Thus, all patients suffered from DSMN of predominantly moderate severity (10.5 ± 0.50 points on the VAT scale), confirmed (severe) CAN (CAN 2-3) was diagnosed in 57.4% (54/94) of patients. In addition, diabetic retinopathy was detected in 36.2% (34/94) of cases, a decrease in eGFR less than 60 ml/min was noted in 9.6% (9/94) of patients. Macrovascular complications (CAD) occurred in 55.3% (52/94) of patients.

The distribution of patients according to the severity of CAN is presented in Fig.1.

Figure 1. Prevalence of cardiovascular autonomic neuropathy among patients with diabetic foot syndrome after surgical treatment



CAN 0 - no cardiovascular autonomic neuropathy; KAN 1 - early stage; KAN 2 - confirmed stage; KAN 3 - severe form, cases of clinical and/or asymptomatic orthostatic hypotension

From Fig. 1 shows that only 5.3% (5/94) of patients with DDS were not diagnosed with CAN. In most cases (57.4%; 54/94), patients suffered from a confirmed or even severe form of CAN (CAN 2-3).

It should be noted that the metabolic parameters of DM patients at the time of inclusion in the study did not meet the target values. Thus, the average level of HbA1c was 8.3%, total cholesterol 5.2 mmol/l, LDL cholesterol 3.3 mmol/l, TG 1.8 mmol/l.

Characteristics of patients 2 years after the start of the study

All patients with DFS received outpatient treatment in accordance with accepted international and domestic standards until the wound defect of the feet healed by secondary intention. In the presence of a relapse of the purulent-necrotic process, the patients were hospitalized in a surgical hospital for repeated operations. All cases of repeated operations, as well as the development of Charcot foot, were taken into account during two years of observation.

The mean healing time for postoperative wounds was 14.3 (95%; CI 10.8-17.7) weeks. In 26.6% (25/94) of patients, the wounds did not heal and repeated surgical treatment was required (opening, revision of wounds, excision of necrotic tissue, amputation within the foot).

The following were considered unsatisfactory results of treatment for SDS:

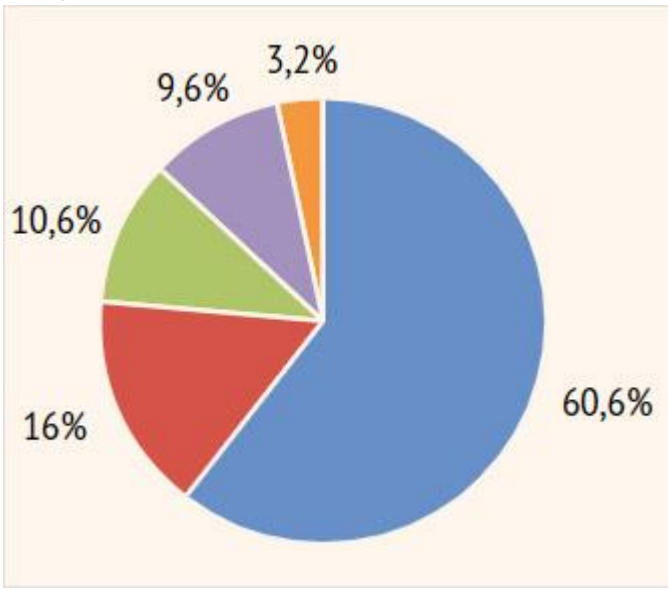
1) cases of prolonged healing of postoperative wounds (more than 24 weeks),

2) relapse of the purulent-necrotic process with repeated surgical interventions, including amputations at the level of the feet,

3) diagnosis of Charcot foot for two years after inclusion in the study.

Thus, the results of treatment for SDS over two years were unsatisfactory in 39.4% (37/94) of patients. The distribution of patients according to the results of treatment for SDS is presented in Fig. 2.

Figure 2. Distribution of patients according to the results of treatment of diabetic foot syndrome over two years of observation (n = 94)



As shown in Fig. 2, repeated operations (amputations at the foot level, necrectomy) were required in 26.6% of patients (25/94), including due to unhealed postoperative wounds (13 patients). In another 9 patients (9.6%; 9/94), postoperative wounds healed for more than 24 weeks, which was interpreted as chronicity of the inflammatory process, and the treatment result was assessed as unsatisfactory. Charcot foot developed in 6 patients during two years of observation, including in three patients (3.2%; 3/94) with a good previous result of conservative therapy.

Changes in the main laboratory parameters, data from laboratory and instrumental studies of patients with DFS after 2 years are presented in Table. 3.

Table 3.

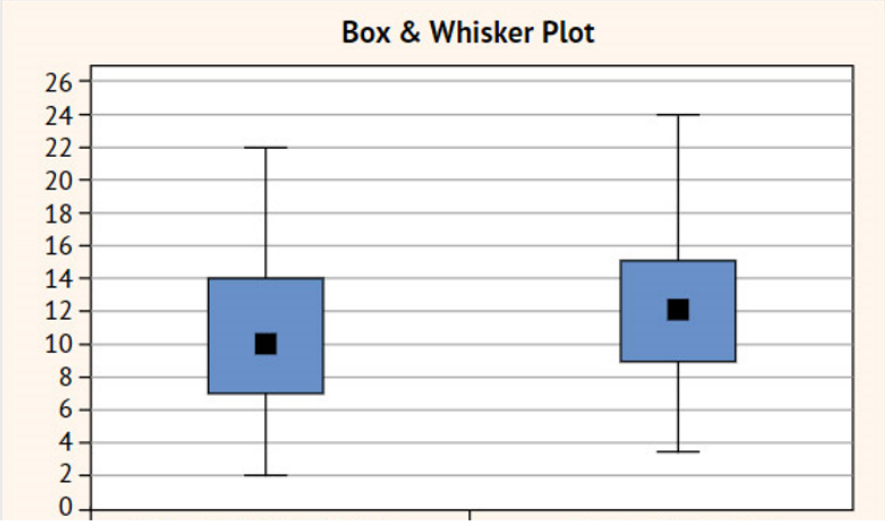
Changes in characteristics of patients with diabetic foot syndrome after two years (n = 94)

Parameter	Originally	After 2 years	p-value
BMI, kg/m²	29.5 ± 0.51	30.6 ± 0.6	0.0000
Diabetic retinopathy, n (%)	34 (36.2%)	34 (36.2%)	
VAT, points	10.5 ± 0.50	11.9 ± 0.6	0.0005
KW, points	2.1 (95% CI 1.8-2.3)	1.9 (95% CI 1.6-2.2)	0.7791
eGFR, ml/min	94.5 ± 3.37	91.9 ± 4.6	0.2716
HbA1c,%	8.3 ± 0.20	8.0 ± 0.22	0.0655
obchs, mmol/l	5.2 ± 0.13	5.3 ± 0.19	0.8219
LDL cholesterol, mmol/l	3.4 ± 0.11	3.2 ± 0.17	0.2717
HDL cholesterol, mmol/l	1.2 ± 0.05	1.3 ± 0.05	0.9407
TG, mmol/l	1.8 ± 0.10	1.9 ± 0.13	0.0595
Unsatisfactory results of treatment of SDS, n (%)		37 (39.4%)	
Progression of DN, n (%)		28 (29.8%)	
Progression of CAN, n (%)		21 (22.3%)	

Note. DFS - diabetic foot syndrome, DN - diabetic nephropathy, VDS - neuropathic dysfunctional score scale, CVT - cardiovascular tests, CAN - cardiovascular autonomic neuropathy, BMI - body mass index, HbA1c - glycated hemoglobin, THC - total cholesterol, LDL cholesterol - lipoprotein cholesterol low density, HDL cholesterol - high density lipoprotein cholesterol, TG - triglycerides, eGFR - estimated glomerular filtration rate.

After 2 years of follow-up, no significant changes were registered in the main metabolic parameters, as well as in eGFR and CBT scores in patients with DFS. No new cases of diabetic retinopathy were identified either. However, a significant progression of DSMN was noted according to the VAT scale scores (Fig. 3).

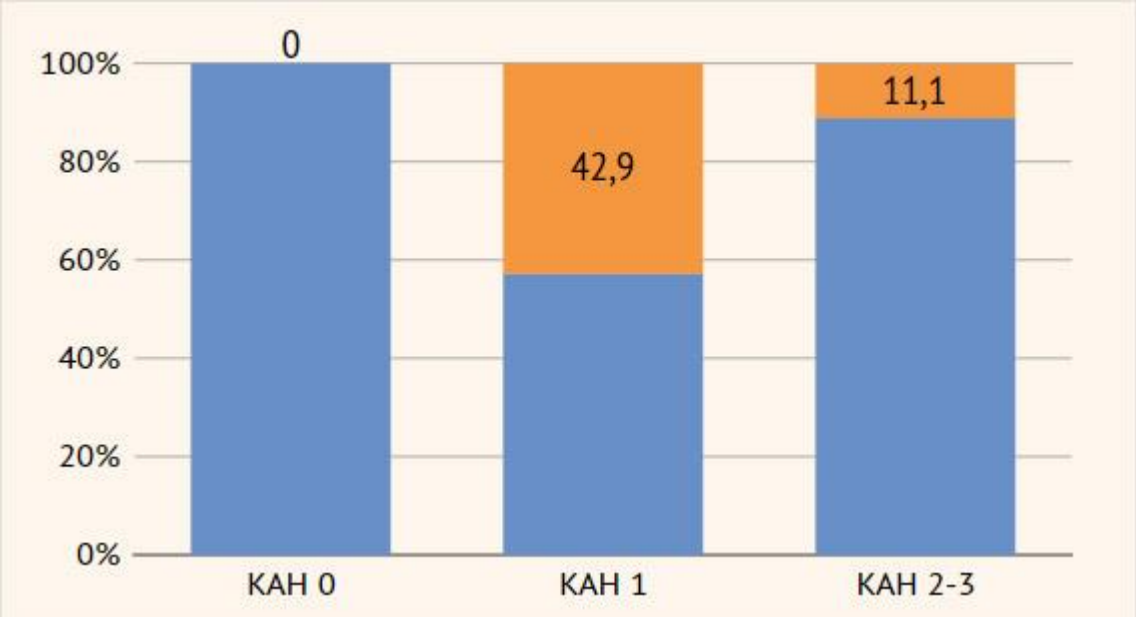
Figure 3. Changes in the severity of diabetic sensorimotor neuropathy in patients with diabetic foot syndrome after two years of observation



When analyzing the results, it turned out that in some patients with DMS there was a progression of not only DMS, but also other microvascular complications of diabetes, although no significant differences in the average values of instrumental and laboratory parameters were detected. Thus, a decrease in pGFR by more than 20 ml/min after 2 years of the study, regarded as progression of diabetic nephropathy, was recorded in 29.8% (28/94) of patients, and a deterioration in GFR values by more than 1 point - in 22.3% (21/94) cases (Table 3).

A decrease in CVT values by more than 1 point is interpreted as progression of CAN. Such an aggressive course of CAN was observed mainly in patients with an initially early (functional) stage of the complication (Fig. 4).

Figure 4. Progression of cardiovascular autonomic neuropathy in patients with diabetic foot syndrome after two years of study



CAN 0 - no cardiovascular autonomic neuropathy; KAN 1 - early stage; KAN 2 - confirmed stage; KAN 3 - severe form, cases of clinical and/or asymptomatic orthostatic hypotension

Thus, in more than 40% of patients with DDS with an initially functional stage of CAN (42.9%; 15/35), the disease developed aggressively and over 2 years of observation turned into a confirmed or even severe form, while in patients with confirmed/severe form of CAN (CAN 2-3), such a development occurred only in 11.1% of cases (6/54).

Progression of T2DM complications over two years of follow-up

The next stage of the study was a comparative analysis of the main parameters studied among patients with a stable course of CAN (or even regression) and in patients with progression of CAN. Factors associated with the aggressive development of CAN in patients with DFS were identified.

Among these factors were:

- age of onset of T2DM is younger than 40 years,
- unsatisfactory results of treatment for DBS for 2 years,
- decrease in eGFR by more than 20 ml/min over 2 years of study,
- progression of DSMN by more than 2 points on the VAT scale.

Thus, the age of onset of T2DM younger than 40 years increased the risk (odds ratio - OR) of a further aggressive course of CAN in patients with T2DM by more than 5 times (5.1; 95% CI 1.3-20.8; p = 0. 0190). It should be noted that neither the dynamics of anthropometric parameters nor changes in metabolic parameters influenced the development of CAN in the study group of patients over 2 years of observation.

Using the statistical method of logarithmic regression, odds ratios (OR) of progression of other complications of diabetes were also determined depending on the nature of the course of CAN (Table 4).

Table 4.

Odds ratio for progression of diabetes complications in patients with aggressive cardiovascular autonomic neuropathy during two years of follow-up

Parameter	OS	95% CI	p-value
unsatisfactory results of treatment of SDS	40	6.0-268.5	0.0001
decrease in eGFR > 20 ml/min	22.4	3.4-147.4	0.0009
increase in VAT scale points > 2	14.6	3.0-70.5	0.0006

Note. OR - odds ratio, CI - confidence interval, DM - diabetes mellitus, eGFR - estimated glomerular filtration rate, NDS - neuropathic dysfunction score, DFS - diabetic foot syndrome.

The presented table shows that the risk of an unsatisfactory result of treatment for SDS increased 40 times in cases of CAN progression over 2 years of observation. The risk of progression of other microvascular complications of diabetes (DSMN and diabetic nephropathy) also increased by 22.4 and 14.6 times, respectively.

Discussion

It is known that the risk of developing cardiovascular diseases and death is 5-7 times higher in patients with type 2 diabetes than in persons without diabetes [16, 17]. Among other risk factors for cardiovascular pathology, CAN, a common but often ignored complication of diabetes, is associated with early disability and mortality of patients [7, 18]. Clinical manifestations of CAN, such as silent myocardial infarction, cardiac arrhythmias, postural hypotension, and sudden death, are often irreversible and fatal. According to the literature, the prevalence of CAN is 17-66% in patients with T1DM and 31-73% in patients with T2DM [9, 14]. The large scatter is due to both the heterogeneity of patient groups and differences in the criteria used to diagnose CAN [9, 14, 18].

It is known that in patients with prediabetes and newly diagnosed T2DM, CAN occurs in up to 10% of cases, mainly in mild, initial forms [9]. In this work, we

examined the most severe group of patients who already have DSM, as well as DSM with repeated surgical interventions. It is in these patients that CAN of varying severity is diagnosed in the vast majority of cases (95%; 89/94).

The identification of forms (stages) of CAN is of fundamental importance, since the early stages of CAN are reversible, namely, confirmed/expressed ones are associated with a high risk of cardiovascular mortality [18]. In addition, multicenter studies on large populations of patients with a long follow-up period have shown that the presence of confirmed CAN is associated with the progression of both retinopathy and nephropathy in patients with diabetes [10, 11]. In a cohort of patients with DFS, it was demonstrated that orthostatic hypotension is a risk factor for death in the next five years after lower limb amputations [19, 20]. Cases of confirmed/pronounced CAN are also associated with prolongation of healing time of postoperative wounds in patients with DFS [12]. In this study, confirmed/severe forms of CAN occurred in 60% of patients (57.4%; 54/94). Perhaps this explains the unsatisfactory result of treatment of DFS in almost 40% of patients (39.4%; 37/94), which included all cases of protracted course of the wound process (chronization of inflammation), as well as repeated operations, amputations and diagnosed Charcot's foot.

Of particular interest is the progression of CAN over time in patients with diabetes.

In previous studies, a similar variant of the course of the disease over a long period of observation was identified in 10-20% of patients with diabetes. Data regarding the influence of metabolic factors on the nature of the course of CAN in the literature are contradictory. A connection has been established between the progression of CAN and early onset of T2DM (<40 years), HbA1c level more than 6.8%, TG more than 1.7 mmol/l, as well as a decrease in glomerular filtration rate [21]. It has been shown that the aggressive development of CAN is associated with both a high risk of death from cardiovascular pathology and the progression of other microvascular complications of diabetes, namely diabetic nephropathy. However, the significance of such progression (aggressive course) of CAN for different categories of patients with diabetes remains unclear [10, 11].

In our study, an aggressive course of CAN was detected in more than 20% of cases (22.3%; 21/94). The progression of the disease was not recorded over a long period of time, but after 2 years of observation. Therefore, patients with DDS should be considered at high risk for both the presence of clinically significant forms of CAN and its aggressive development.

A similar variant of the development of CAN in patients with DDS was associated with a young age (under 40 years) at diagnosis of T2DM, which is consistent with data from other studies [11, 21]. Indeed, there is information in the literature about the importance of the age of patients at the time of diagnosis of

T2DM for the prognosis of the course of the disease as a whole. Thus, early onset of T2DM is associated with a more aggressive development of diabetes, the need for early initiation of combination therapy with oral hypoglycemic drugs and insulin therapy to compensate for carbohydrate metabolism parameters, as well as a progressive course of micro- and macrovascular complications [11, 21]. This feature of the development of the disease in young patients once again emphasizes the heterogeneity of T2DM in general.

Considering the above-mentioned literature data, the lack of connection between the aggressive course of CAN and the parameters of carbohydrate and lipid metabolism in patients with DFS in our study requires clarification. In our work, the patients were homogeneous in terms of metabolic parameters, and the initial parameters and those determined after 2 years of observation were far from the target. The latter fact may explain the general trend towards progression of CAN (more than 20% of cases) among patients with DFS. In the literature, the influence of metabolic factors on the course of CAN has been shown on thousands of observations and over a long period of time, therefore, in smaller samples and over a short period of observation, the strength of the influence of these parameters may not be reliable.

An important result of our work is the demonstration of the influence of the aggressive development of CAN on the progression of diabetic nephropathy, DSMN, as well as the chronicity of the inflammatory process and the risk of repeated surgical interventions and amputations in patients with DMS.

Chronic inflammation in patients with DFS remains an unresolved problem to this day. On the one hand, hyperglycemia leads to inhibition of cellular and humoral immunity in patients with diabetes [22-24]. On the other hand, DSM of the lower extremities with a decrease in tactile and pain sensitivity causes an asymptomatic course of microtraumas [25]. Impaired microcirculation (microangiopathy) leads to damage to the barrier function of the skin and mucous membranes, a delayed response to microbial invasion, which impairs the healing of ulcers and postoperative wounds in patients with diabetes. Sympathetic vasodilation plays a protective role against infection by initiating an inflammatory response. Damage to the autoregulation of skin microcirculatory blood flow due to impaired innervation reduces the inflammatory response and contributes to the progression and chronicity of skin and soft tissue infections [25, 26].

Impaired vasodilation of the microcirculation in response to damage, as well as theft of the microcirculatory bed through the shunt system due to the same CAN, underlies functional ischemia of the lower extremities in patients with DFS [27]. There is evidence of an unfavorable prognosis for the preservation of the limb of an impaired sympathetic response, even after successful revascularization and restoration of the main blood flow in patients with DFS [28].

Our work is the first to show a 40-fold increase in the risk of chronic inflammation, delayed healing, and the need for repeated operations and amputations in patients with progressive damage to cardiovascular innervation. There are a few studies in the literature demonstrating the influence of peripheral innervation on the inflammatory process in patients with diabetes, but the results are contradictory [12, 26]. Our work clearly demonstrates the connection between the aggressive development of CAN in the next 2 years after surgery and the unfavorable outcome of conservative treatment of postoperative wounds in patients with DFS. On the one hand, this fact lifts the veil of mystery about the high mortality rate of patients with DFS after foot surgery or with non-healing foot ulcers in the next 5 years, even in the absence of a widespread atherosclerotic process. On the other hand, it has invaluable applied practical significance, dictating the need not only for the use of high-tech methods for healing postoperative wounds in such patients, but also for the active introduction of agents that slow down the progression of CAN [29]. It should once again emphasize the need for an integrated approach to the treatment of patients with DFS after surgical treatment by specialists dealing with both the problems of wounds and wound infections, and cardiac pathology [20, 30].

In our study, all cases of newly diagnosed Charcot foot in the examined patients were also classified as an unfavorable outcome. The development of neuroosteoarthropathy with subsequent persistent deformation of the osteoarticular apparatus of the feet contributes to the recurrent course of the wound process with repeated operations. On the other hand, repeated trauma to the foot, including surgical interventions on the foot, which indirectly lead to the activation of osteoclasts, increasing the local level of pro-inflammatory cytokines, is of great importance for the formation of neuroosteoarthropathy. A significant contribution to the development of neuroosteoarthropathy is made by sensorimotor neuropathy with the development of weakness of the musculo-ligamentous apparatus of the feet, dislocations and subluxations in the joints of the foot, and especially autonomic neuropathy, which contributes to the occurrence of arteriovenous shunts. The opening of arteriovenous shunts leads to an intensification of local blood flow with an increase in the local level of advanced glycation end products, an increase in the expression of the cytokine RANKL and, as a consequence, to the activation of osteoclasts and bone demineralization [31]. Similar mechanisms explain the high risk of developing neuroosteoarthropathy in patients with DFS both after foot surgery and with progression of CAN.

Conclusions. Can of varying severity was diagnosed among all patients with DFS after surgical treatment. The prevalence of confirmed (severe) forms of CAN reaches almost 60% of cases (57.4%; 54/94). The course of CAN in patients with SDS after surgical treatment often becomes aggressive. Progression of CAN over 2

years of follow-up was recorded in more than 20% of patients (22.3%; 21/94). Thus, patients with DFS after surgical treatment of the feet are at high risk of identifying confirmed/pronounced forms of CAN and their progression in the next 2 years. The aggressive course of CAN in patients with DDS after surgical treatment is associated with early onset of T2DM (younger than 40 years) against the background of non-target parameters of carbohydrate and lipid metabolism. This variant of the development of CAN increases the risk of progression of other microvascular complications of diabetes, namely DSMN (14.6 times) and diabetic nephropathy (22.4 times). The study for the first time revealed a pattern of mutual aggravation of cases of progression of CAN and unfavorable course of the wound process in patients with DFS after surgical treatment over a 2-year follow-up period. The risk of chronic wound healing and repeated surgical interventions, including foot amputations, in patients with the neuropathic form of DDS after surgical treatment with an aggressive course of CAN increases 40 times.

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