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Correlation Between Extracutaneous Microvascular Complications and Diabetic Foot Ulcers in Patients with Type 2 Diabetes Mellitus

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ABSTRACT

Background: Diabetes is a metabolic disease that is taking an epidemic proportion around the world. The occurrence of microvascular complications and diabetic foot ulcer is associated with an increased mortality and morbidity incidence, which is the most serious complication of this disease, which significantly reduce the quality of patient life. **Objective.** The aim of the study was to determine the correlation of extracutaneous microvascular complications with diabetic foot ulcer in patients with type 2 diabetes. **Method.** The study was prospective, and included 160 patients with type 2 diabetes. It was conducted at the University Clinical Center of the Republic of Srpska in the period from January 2016 until December 2019. The respondents were adults, of both sexes, suffering from type 2 diabetes, in whom complications of this disease are present. Glycemic control was established based on a target HbA1c value of 7%. **Results**. Of the 160 patients in the study, 53.8% were men and 46.2% were women. The average age of the patients was 70.11%±10.05 years. Extracutaneous microvascular complications were present in 85 patients (53.1%); of which 30.2% had well-regulated glycemia (HbA1c≤7.0%), while 61.5% (p<0.001) had unregulated glycemia (HbA1c≥7.0). Polyneuropathy was present in 23.3% of patients with HbA1c≤7.0%, while 41.0% of patients had HbA1c≥7.0% (p<0.043). Nephropathy with HbA1c≤7.0% was present in 36.8% of cases compared to patients with HbA1c≥7.0 in whom the prevalence was 36.8% (p<0.004). Out of total, 25.6% had retinopathy with HbA1c≤7.0%, while in 41.9% of patients with HbA1c≥7.0% (p <0.067). Diabetic ulcer foot was present in 13 patients with HbA1c≥7 (11.1%) compared to patients with HbA1c≤7.0% where there was no occurrence of this complication 0.0% (p<0.021). At the same time, 5.6% of patients had a diabetic foot ulcer with polyneuropathy (p=0.010), 4.4% had neuropathy (p=0.058) and 5.6% had retinopathy (p=0.014). **Conclusion:** The high incidence of extracutaneous microvascular complications and diabetic foot ulcer in patients with type 2 diabetes requires a multidisciplinary approach of medical professionals that includes prevention of risk factors and good regulation of glycemia.

Key words: Diabetes mellitus, microvascular complications, diabetic ulcer foot.

1. BACKGROUND

Diabetes mellitus is a chronic noncommunicable disease that is taking epidemic proportions in the world today. Chronic exposure to hyperglycemia results in a negative impact on the microvascular structure, which leads to the development of diabetic nephropathy, retinopathy and neuropathy with a large impact on the quality of life and overall life expectancy of the patient (1-2). Microvascular complications in diabetics not only cause blindness, renal failure, and non-traumatic amputations, but are also a significant predictor of cardiovascular complications (3). The burden of diabetes is mainly attributed to morbidity and mortality associated with microvascular and macrovascular complications (4). One of the complications of diabetes is the development of a diabetic foot ulcer, which is marked as one of the most common causes of morbidity in diabetics. It occurs as a consequence of peripheral vascular disease and remains asymptomatic for a long period. Therefore, annual screening of diabetic foot and measures for its care are important in the early identification of high-risk diabetics (5). Strong predictors that indicate the development of diabetic foot ulcer in the patient is the presence of other microvascular complications such as diabetic nephropathy, retinopathy and elevated body mass index (5). Scientific studies indicate that poor regulation

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Variables	All patients		Group I		Group II		p-value
			(HbA1c <7.0%)		(HbA1c >7.1%)		
	N=160		N=43 (26.9%)		N=117 (73.1%)		
Age, mean (SD)	70.11	10.05	71.6	8.87	69.56	10.43	0.256
Gender (N, %)							
Male	86	53.8%	25	58.1%	61	52.1%	0.592
Female	74	46.2%	18	41.9%	56	47.9%	
Obesity, BMI >25, (N, %)							
Yes	91	56.9%	15	34.9%	76	65.0%	0.001
No	69	43.1%	28	65.1%	41	35.0%	
Duration of diabetes, mean (SD)							
<1 year	12	7.5%	4	9.3%	8	6.8%	
1-9 years	50	31.3%	21	48.8%	29	24.8%	0.006
9-19 years	63	39.4%	15	34.9%	48	41.0%	
>20 years	35	21.9%	3	7.0%	32	27.4%	
Therapy (N, %)							
Insulin dependents (ID)	93	58.1%	18	41.9%	75	64.1%	0.018
Insulin independents (II)	67	41.9%	25	58.1%	42	35.9%	

Table 1. Characteristics of respondents in study. n (%)- total number (percentage) of patients, X- mean, SD- standard deviation

of glycemia may be associated with the pathogenesis of vascular damage (oxidative stress, endothelial damage, inflammation) leading to the development of micro and macrovascular complications (8). On the other hand, studies show that strict glycemic control as a standard in clinical approach can improve long-term outcomes, or postpone the development of microvascular complications, and thus improve the quality of life of patients (9-10).

2. OBJECTIVE

The aim of our study was to determine the correlation of extracutaneous microvascular complications with diabetic foot ulcer in patients with type 2 diabetes mellitus.

3. PATIENTS AND METHODS

The study was prospective, and included 160 patients with type 2 diabetes mellitus. It was conducted at the University Clinical Center of Republic of Srpska (UCC RS) in Banjaluka, in the period from January 2016 to December 2019 at the Skin and Venereal Diseases Clinic of the UCC RS. This study was approved by the Ethics Committee of the UCC RS.

The respondents were adults, of both sexes, suffering from type 2 diabetes mellitus. They were referred for hospital treatment or were treated as outpatients referred by a family doctor and other internal medicine and surgical branches of medicine. All patients underwent glycemic control based on HbA1c (%). In accordance with the American Diabetes Association (ADA) recommendations for target values of HbA1c 7%, good glycemic control, respondents were divided into two groups.

Group I consisted of respondents with good glycemic control, HbA1c<7.0%, while Group II consisted of respondents with unregulated glycemic values, HbA1c>7.1%. Body mass index (BMI) and anamnestic data related to the time (years) of diabetes and the therapy they use (insulin-dependent / independent therapy) were determined. In the clinical study, this study used relevant laboratory analyzes of blood and urine, and in addition to examinations by endocrinologists, it also used consultative examinations by other specialists in order to confirm the diagnosis of microvascular complications.

Statistical analyses were carried using IBM Statistics SPSS 22 software package. The data were described by mean values and standards deviations (SD) for continuous variables and incidence, and percentage for categorical variables. The differences between subgroup mean values were analyzed by the t-test and the one-way analysis of variance (ANOVA) depending on the number of groups. The chi-squared test was used to determine whether there was a significant difference between incidences of categorical variables. The p-values lower than 0.05 were considered as significant.

4. RESULTS

In a study of 160 adult patients diagnosed with type 2 diabetes mellitus, with various microvascular complications and diabetic foot ulcer, there were 86 men and 74 women (53.8% and 46.2%) whose average age was 70.11±10.05 years. According to HbA1c values, respon-

dents were divided into two groups, group I with well-regulated glycemic values (HbA1c <7.0%) and group II with unregulated glycemic values (HbA1c> 7.1%).

In Group I, 43 respondents (26.9%) had well-regulated glycemic control. The average age in this group was 71.6±8.87 years. In group II, 117 respondents (73.1%) had unregulated glycemic control. The average age of the respondents in this group was 69.56±10.43 years. There were 15 (34.9%) obese patients (BMI> 25 kg/m^2) in group I, while there were 76 (65.9%) obese respondents in group II, which is a statistically significant difference (p=0.001) (Table 1). The correlation of obesity with microvascular complications was not statistically significant except in retinopathy where 41.8% of respondents with this complication had a BMI> 25 kg m^2.

There were 93 patients on insulin therapy (58.1%), 41.9% of respondents had good glycemic control, while 64.1% of respondents had unregulated glycemic control, which is a significant statistical difference (p=0.018). The majority of respondents with unregulated glycemic control values (27.4%) had been diagnosed with diabetes mellitus more than 20 years ago compared to well-controlled glycemia (7.0%), which is a statistically significant difference (p=0.006) (Table 1).

Variables Extracutaneous microvascular complications (N, %)	All patients N=160		Group I (HbA1c <7.0%) N=43		Group II (HbA1c ≥7.1) N=117		p value
Yes	85	53.1%	13	30.2%	72	61.5%	0.001
No	75	46.9%	30	69.8%	45	38.5%	
Polyneuropathy							
Yes	58	36.3%	10	23.3%	48	41.0%	0.043
No	102	63.7%	33	76.7%	69	59.0%	
Nephropathy							
Yes	49	30.6%	6	14.0%	43	36.8%	0.004
No	111	69.4%	37	86.0%	74	63.2%	
Retinopathy							
Yes	60	37.5%	11	25.6%	49	41.9%	0.067
No	100	62.5%	32	74.4%	68	58.1%	
Diabetic foot ulcer							
Yes	13	8.1%	0	0.0%	13	11.1%	0.021
No	147	91.9%	43	100.0%	104	88.9%	

Table 2. Prevalence of extracutaneous complications and diabetic foot ulcer in patients with type 2 Diabetes mellitus

Extracutaneous microvascular complications			Diabetic foot ulcer Yes	Diabetic foot ulcer No	Total
Polyneuropathy	Yes	Count	9	49	58
		% of Total	5.6%	30.6%	36.3%
	No	Count	4	98	102
		% of Total	2.5%	61.3%	63.7%
Nephropathy	Yes	Count	7	42	49
		% of Total	4.4%	26.3%	30.6%
	No	Count	6	105	111
		% of Total	3.8%	65.6%	69.4%
Retinopathy	Yes	Count	9	51	60
		% of Total	5.6%	31.9%	37.5%
	No	Count	4	96	100
		% of Total	2.5%	60.0%	62.5%
Total		Count	13	147	160
		% of Total	8.1%	91.9%	100.0%

Table 3. Correlation of diabetic foot ulcer with extracutaneous microvascular complications

Examining the presence of extracutaneous microvascular complications in patients with type 2 diabetes mellitus in our study, out of a total of 160 respondents, 85 respondents (53.1%) had microvascular complications. Of these, in group I 30.2% of respondents had well-regulated glycemia (HbA1c<7.0), while in group II, 61.5% of respondents had unregulated glycemic values (HbA1c>7.1%) which is a statistically significant difference (p=0.001). Polyneuropathy was present in a total of 58 respondents (36.3%); in group I, in well-regulated glycemia in 23.3% of patients and in group II in 41.0% of patients, which is of statistically significant difference (p=0.043). Out of total, 49 respondents or 30.6% had nephropathy. In group I there were 14.0% of respondents, and in group II 36.8% of respondents with HbA1c>7.1% and nephropathy, which is a statistically significant difference (p=0.004). Retinopathy was present in 60 respondents or 37.5%, in group I there were 25.6% of respondents, and in group II 41.9%, which was not statistically significant difference (p=0.067). A total of 13 respondents (8.1%) had diabetic foot ulcer in our study; in group I there was no occurrence of this complication (0.0%) while in group II all 13 patients were in the group with unregulated glycemic values or 11.1%, which is a statistical significance (p=0.021) (Table 2).

In our study, the total number of respondents with diabetic foot ulcer was 13. The simultaneous appearance of this complication and polyneuropathy was present in 9 cases or 5.6% (p=0.010), which is statistically significant. The simultaneous appearance of diabetic foot ulcer and neuropathy was present in 7 cases or 4.4% (p=0.058), which is not statistically significant. Of the 13 respondents with diabetic foot ulcer, 9 (5.6%) had retinopathy at the same time, which is statistically significant difference (p=0.014) (Table 3).

5. DISCUSSION

Type 2 diabetes mellitus is a metabolic disease of chronic character and a large part of the burden of this disease is caused by its complications, which are divided into two groups: macrovascular (heart disease, stroke) and microvascular complications (polyneuropathy, nephropathy, retinopathy) (11). Microvascular complications are the leading cause of blindness, renal failure, and lower limb amputation in patients of all ages, including children and adolescents (12–13). Our study showed that extracutaneous microvascular complications were statistically significantly more common in elderly respondents with poorer glycemic control (HbA1c>7.1%) and were positively correlated with the duration of diabetes, which is consistent with the results of other scientific studies (9, 13-14).

Diabetic polyneuropathy, associated with neuropathic pain, diabetic foot ulcers, and autonomic dysfunction, is associated, like diabetic nephropathy, with a significant risk of mortality and reduced quality of life. In our study, the prevalence of polyneuropathy was 61.5%.

In diabetics, 30-40% of patients with HbA1c>7.1% and hypertension will develop diabetic nephropathy or chronic renal failure, which is a significant public health problem and lead to high treatment costs (15-16). Studies show that an important risk factor that contributes to the development of chronic microvascular complications, including this, is oxidative stress, which can adversely affect the action of acidic growth factor in fibroblasts, which has a protective effect against it, as well as strong angiogenic activity (17). In our study, the prevalence of nephropathy was in 36.8%.

Diabetic retinopathy, as a common complication of diabetes, remains the leading cause of blindness among the working-age population. For decades, diabetic retinopathy was considered only a microvascular complication, but the microvascular structure of the retina is closely related and guided by neurons and glia, which are affected even before clinically visible vascular lesions and visual field problems in patients (18). Therefore, early detection of diabetic retinopathy is crucial in the prevention of irreversible visual impairment. In our study, the prevalence of retinopathy was 41.9% in the group with poor glycemic regulation, or HbA1c>7.1%.

The average age of the respondents in our study, in total sample, was 70.11±10.05 years and in most respondents the glycemic control was poor, HbA1c>7.1%. These results are consistent with other scientific studies showing that the incidence of microvascular complications is significant in the elderly with poorer glycemic control (19-20).

In our study, 56.9% of the total number of respondents were obese (BMI> 25 kg/m^2). There were statistically significantly more obese respondents with unregulated HbA1c values>7.1% compared to obese respondents with HbA1c<7.0% (34.9%) and only in the case of retinopathy it was shown that of the total number of respondents with BMI>25 kg/m^2, 41.8% of them have this microvascular complication, which is in line with the results of other scientific studies showing that obesity and poor glycemic control are significant risk factors for microvascular complications including diabetic foot ulcer (21-23).

In our study, 58.1% of the respondents were on insulin therapy. The majority of respondents (64.1%) had statistically significantly unregulated glycemic values of HbA1c>7.1% compared to respondents with HbA1c <7.0% and this is positively correlated with the duration of diabetes and age of the respondents, which is in accordance with the results of other scientific studies showing that in addition to the duration of diabetes, the development of chronic complications in unregulated glycemia of insulin-dependent patients leads to significant impairment of physical and mental health of patients and death (24-26).

In diabetics, macrovascular and microvascular complications greatly contribute to an increased risk of developing diabetic foot ulcers and consequent lower limb amputations (27). Zafar et al. find in their study that the prevalence of diabetic foot ulcer is relatively high in diabetics with diabetes longer than ten years, which is confirmed by other scientific studies (28-30). In our study, diabetic foot ulcer was statistically significantly more prevalent in respondents with unregulated glycemic values (in 11.1% of respondents). Other studies also confirm that risk factors for the development of diabetic foot ulcers include poor glycemic regulation and peripheral neuropathy, smoking, previous history of ulcers, foot deformities, diabetic nephropathy (especially in hemodialysis patients) and previous amnesia amputations (31). The results of the study show that the success rate of treatment and healing of ulcers / wounds is higher in patients with better regulated HbA1c values (32).

The results of our study show that the simultaneous appearance of diabetic ulcer on the foot and some of the microvascular complications is statistically significant. Namely, the results show that respondents with diabetic foot ulcer also have polyneuropathy in a statistically significant percentage ($p = 0.010$). Abdissa et al state that the connection between these two complications is conditioned by diabetic polyneuropathy, which causes loss of protective feeling of pain, loss of pressure perception and damage to microcirculation (33). Scientific studies also show that peripheral occlusive disease is a risk factor for the development of these complications in 15% of cases, as well as neuropathic and dystrophic tissue that is particularly susceptible to infections and injuries, especially in the elderly (34-35). The concomitant association of diabetic ulcer and nephropathy in our study was not statistically significant ($p = 0.058$) as confirmed by other studies that also found no association of diabetic foot ulcer with diabetic renal dysfunction, including other risk factors such as hypertension, serum creatinine, microalbumins, proteins in urine, HbA1c (36).

On the other hand, Rastogi et al. point out that prevalent nephropathy and incidental amputation after the development of diabetic foot ulcer are an indicator of increased mortality in patients and not glycemic control or previous coronary artery disease (37). The results of our study show that diabetic retinopathy is statistical-

ly significantly associated with diabetic foot ulcer and strongly predicts the occurrence of ulcers in the same patient (p=0.014). Recent scientific studies have identified certain genetic factors (single nucleotide variants) that are involved in the pathology of the development of diabetic retinopathy, although their precise mechanisms remain unclear (38). The results of other scientific studies show that the incidence of proliferative diabetic retinopathy is 3.9 times higher in patients with chronic diabetic foot ulcer in older males (14, 39).

6. CONCLUSION

There is an increased risk of extracutaneous microvascular complications, especially polyneuropathy and retinopathy, which may cause increased mortality in patients with type 2 diabetes mellitus who have had unregulated HbA1c glycemic values for many years and who have a diabetic foot ulcer. Adequate preventive examinations and better metabolic control of diabetes can lead to a reduction in the development of these complications and an improvement in the quality of patient's life.

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