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ANALYSIS OF RISK FACTORS THAT INFLUENCE MICROVASCULAR AND MACROVASCULAR COMPLICATIONS IN PATIENTS WITH DIABETES MELLITUS TYPE 2

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Type 2 diabetes mellitus is the most common form of the disease and represents a condition of chronic hyperglicemia caused by peripheral tissue abnormalities. The consequences of diabetes mellitus type 2 are numerous complications than increase disease mortality and morbidity. The aim of this study is to analyze the influence of certain risk factors on micro- and macrovascular complications appearing in hospitalized patients with type 2 diabetes mellitus.

The patients hospitalized at the Metabolic Unit of the Internal Clinic, Clinical Center of Kragujevac, with type 2 diabetes mellitus were enrolled in this cross-sectional study. Demographic and laboratory data of the patients were obtained from their patient histories. Statistical processing was made using the binary logistic regression test with statistical significance cut-off set at $p < 0.1$.

The study involved 193 patients with type 2 diabetes mellitus, 89 females and 104 males, with the average body mass index of 27.08, and aged 60 years on the average. Statistically significant risk factors that can contribute to the chronic complications of diabetes mellitus are patient age, disease duration, body mass index, level of cholesterol, triglycerides and smoking status.

According to numerous epidemiological studies, diabetes mellitus is going to be the most common disease of the modern world. It is therefore important to educate people as to the reduction of risk factors for the onset and progression of complications of the disease. *Acta Medica Medianae 2017;56(1):64-70.*

Key words: *type 2 diabetes mellitus, micro and macrovascular complications, risk factors*

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Introduction

Diabetes mellitus (DM) is a condition of chronic hyperglycemia, which occurs as the consequence of an absolute and/or relative lack of insulin, i.e. the lack of insulin action. Hyperglycemia characteristic for diabetes is the result of reduced consumption of glucose and/or its increased production. Diabetes occurs due to complex interactions of different factors, mainly genetic and environmental ones (1).

Type 2 diabetes mellitus (DM2) is the most frequent form of the disease, the complications of which can be viewed as acute and chronic ones. Among the acute diabetes complications the following conditions are listed: ketonuria, diabetic ketoacidosis, lactic acidosis, hyperglycemia, hyperosmolar nonketogenic condition and hypoglycemic coma. Among the chronic diabetes complications there are microangiopathic ones (retinopathy, nephropathy, polyneuropathy) and macroangiopathic ones (arterial hypertension, coronary heart disease, cerebrovascular disease, peripheral macroangiopathy, diabetic foot, and susceptibility to infections) (2, 3).

Complications occur as the result of poor sugar level regulation, lack of physical activity and inadequate compliance with certain dietary regimes, necessary with these patients. An increased risk of complications is seen in people with diagnosed diabetes who are overweight, have lipid profile imbalances, and have increased creatinine values (4).

The purpose of this research was to analyze the frequency of certain risk factors and presence

of microvascular and macrovascular complications in the population of patients diagnosed with DM2.

MATERIAL AND METHODS

We carried out our cross-sectional study of the patients diagnosed with DM2, who were hospitalized at the Metabolic Unit of the Clinic for Internal Medicine, Clinical Centre in Kragujevac. The study enrolled 193 patients of both sexes who were treated in the hospital from the beginning of 2015 till the end of August 2015.

The criteria for inclusion in the study were as follows: diagnosed DM2 and diagnosed hypertension which was pharmacologically treated, regardless of the fact whether those were the patients with newly discovered DM2 or the patients diagnosed with it a certain time ago. This study did not enroll those with renal failure who required a dialysis treatment, patients with acute infections, nor those with incomplete medical documentation (i.e. those without all the values for the biochemical parameters that were followed up). The necessary information about the patients were obtained from their medical histories and were related to: gender, age, duration of DM, body mass index, diagnosis of hypertension, family history of DM and cardiovascular diseases, alcohol consumption and smoking status, values of glycosylated hemoglobin, total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides, results of diagnostic tests undertaken in order to detect chronic complications of diabetes that indicate their presence in the microvascular and macrovascular bed. The body mass index was calculated using the standard formula (weight in kilograms/height in meters squared, kg/m^2).

The reference values of variables were set on the basis of recommendations of the World Association of Diabetologists: normal values of glycosylated hemoglobin were all the values below 7%, with total cholesterol the values below 5.1 mg/dl, LDL cholesterol <2.6 mg/dl; HDL cholesterol levels >1.04mg/dl; TG < 1.7 mg/dl (5).

The statistical analysis was performed using the software package SPSS 18.0 for Windows and binary logistic regression testing. The statistical significance cut-off was set at $p < 0.1$. Using descriptive statistics, the analysis of patients' demographic data was performed. Chi-squared test was used to test the difference in complication occurrence between the genders. To test for the differences between numerical characteristics, we used the independent samples t-test where the statistical significance cut-off was set at $p \leq 0.05$.

Results

The patient data was collected by examining the medical records and were classified as demographic and biochemical data, as shown in Tables 1 and 2. The average age of hospitalized male patients was 58.41±11.80 years (± standard deviation). The average age of hospitalized female patients was 61.04±9.87 years. There was not any statistically significant difference in age between men and women ($t = 1.681$; $df = 191$; $p = 0.94$).

Table 1. Demographic data of patients

Demographic data		
Gender (%)	male	89 (46,11)
	female	104 (53,89)
Average BMI		27,08 ± 5,17
Cigarette smoking (%)	yes	71 (36,79)
	no	122 (63,21)
Alcohol consumption (%)	yes	11 (5,70)
	no	182 (94,30)
Age		59,83 ± 10,85
CVS-history[1] (%)	yes	67 (34,72)
	no	126 (65,28)
DM-history[2] (%)	yes	70 (36,27)
	no	123 (63,73)

[1]– CVS-history – positive family history of cardiovascular disease
[2]– DM-history – positive family history of diabetes mellitus

Table. 2. The values of biochemical parameters

Biochemical parameters	Minimum	Maximum	Mean ± SD[1]
HbA1c (%)	4,5	16,9	9,58 ± 2,43
Total cholesterol (mmol/l)	2,15	14,7	5,48 ±1,63
LDL cholesterol (mmol/l)	1,09	7,06	3,52 ± 1,19
HDL cholesterol (mmol/l)	0,31	2,3	1,06 ± 0,39
Triglycerides (mmol/l)	0,49	13,76	2,17 ± 1,61

SD[1] - standard deviation

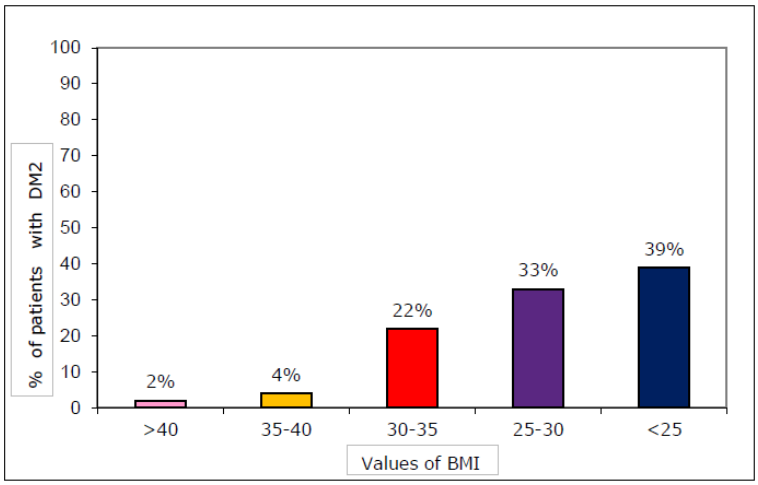
By way of retrospective review of data about the hospitalized patients, we obtained the answer to the question which risk factors were in correlation with diabetes-related complications. With the statistical test of binary logistic regression, it was established that peripheral vascular disease was in correlation with the patients' age, presence of obesity and high total cholesterol. In cerebrovascular disease, in addition to the factors of age and obesity, cigarette smoking and elevated levels of total cholesterol had a considerable impact on the development of this complication. For the onset of coronary heart disease as the leading cause of death among people with diabetes, the major risk factors were the patients' age, use of tobacco, and duration of diabetes.

Regarding microvascular changes, age was also positively correlated with the occurrence of complications. People with diabetes are predisposed to nephropathy, often leading to severe

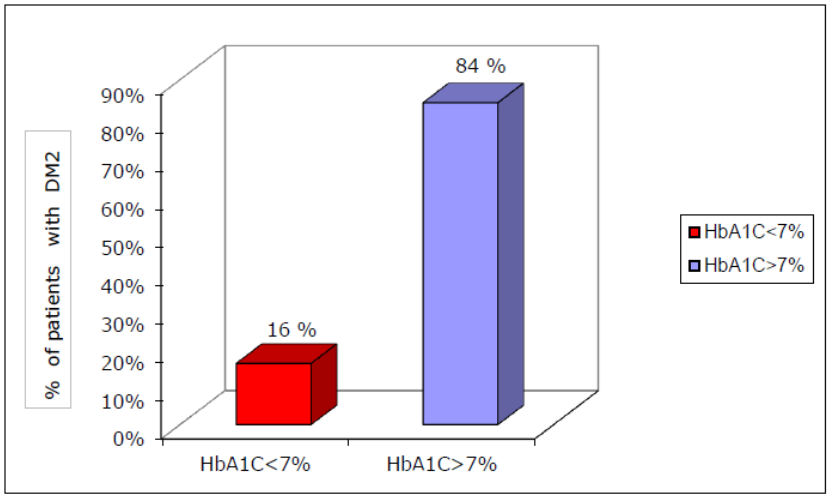
Table 3. "p" values of binary logistic regression for risk factors that influence the development of complications in DM

	Microvascular complications "p" value			Microvascular complications "p" value		
Risk factors	PVD	CVD	IHD	Retinopathy	Nephropathy	Neuropathy
Age	0.000*	0.000*	0.004*	0.000*	0.001*	0.016*
Length of disease	0.455	0.739	0.078*	0.064*	0.705	0.317
Cigarette smoking	0.133	0.004*	0.003*	0.051*	0.007*	0.171
BMI	0.050*	0.003*	0.001*	0.974	0.066*	0.018*
Total cholesterol	0.010*	0.128	0.547	0.345	0.187	0.874
LDL cholesterol	0.120	0.031*	0.627	0.310	0.080*	0.779
Triglycerides	0.396	0.861	0.338	0.192	0.572	0.039*

"p" value of <0.1 indicates a statistically significant association between risk factors and complications in DM2
PVD – Peripheral vascular disease
CVD – Cerebrovascular disease
IHD – Ischemic heart disease



Graphic 1. The values of BMI in patients with DM2



Graphic 2. The values of glycosylated hemoglobin in patients with DM2

renal insufficiency that requires dialysis treatment. Statistical data analysis demonstrated the influence of obesity and use of cigarettes in the occurrence of this complication. The occurrence of polyneuropathy, which accompanies diabetes and is one of the causes of invalidity in diabetics, is in correlation with increased values of triglycerides and body mass index (Table 3).

Of 193 patients enrolled in this study, 163 had glycosylated hemoglobin above 7%, while 114 patients were obese, meaning that the body mass index was over 25, out of which 49 patients were

with the index over 30.

Graphic 1 illustrated obesity as an important factor in the occurrence of other numerous complications. In Graphic 2 you can see the proportion of patients with glycosylated hemoglobin above 7%, which was used as an indicator of average blood sugar levels in the preceding three months.

Using the Chi-squared test it was found that there was a statistically significant gender difference in the occurrence of ischemic heart disease – the disease was more prevalent in our female patients ($\chi^2 = 7.732$; df = 1; p=0.005).

Discussion

Diabetes is a serious health problem, and a rapidly increasing prevalence of this disease has caused global concerns. It is known that in 2010 from type 2 diabetes suffered as many as 285 million people worldwide, and it is anticipated that the number of the affected will increase to 438 million by 2030 (6). This increase is primarily due to population aging, excessive nutrition, obesity and sedentary lifestyle. According to the data of the World Health Organization and the International Diabetes Federation, around 600,000 people suffered from diabetes in Serbia in 2010, which represented 8.2% of the population; nevertheless, at least half of the people with type 2 diabetes do not have their disease diagnosed and do not know of their illness. The number of people with type 2 diabetes is much higher than the number of those with type 1 diabetes (6).

The presence of complications influences both quality of life and life expectancy (with the reduction of 8 to 10 years). The presence of risk factors contributes to faster development of complications – the factors have a synergistic effect in the development of comorbidities (7, 8). The key pathophysiological processes in type 2 diabetes are insulin resistance, beta-cell dysfunction, hyperglycemia, and increased concentration of free fatty acids. The risk factors for DM2 are positive family history of DM, obesity (>20% of desirable body weight or BMI > 27 kg/m2), age over 45 years, previously identified glucose intolerance syndrome or syndrome of elevated fasting glucose, information about gestation diabetes or the data about the delivery of a child weighing over 4 kg, hypertension (>140/90 mmHg), total cholesterol increased > 4.5 mmol/l, LDL cholesterol >2.6 mmol/l, HDL cholesterol <0.9 mmol/l, and/or triglycerides >1.7 mmol/l and the polycystic ovary syndrome (9, 10).

The importance of this disease is reflected in the occurrence of complications that lead to disability and increased morbidity and mortality rates. Diabetes is the most common cause of blindness. Diabetic retinopathy is explained via a series of pathophysiological mechanisms. High levels of glucose on one hand contribute to increased levels of glutamate, a neurotransmitter, which if found in excess in presynaptic spaces may have a toxic effect on photoreceptor cells, while on the other hand, damage to endothelial cells of precapillary retinal arterioles, mediated by prooxidative free radicals, may lead to fine ischemic lesions of the vascular bed, and a loss of functional cell structures (11).

This model of endothelial damage may be associated with diabetic nephropathy through several mechanisms. Namely, endothelial damage by reactive oxygen radicals leads to the aging of endothelial cells, which can be an early sign of development of vascular lesions, which further may lead to glomerular sclerosis (12); 20-25% of patients with terminal renal failure are diabetics. These patients have a 15 to 20 times higher risk of having a foot amputation than non-diabetic patients.

Atherosclerosis, together with the coronary artery disease, is the cause of death in approximately 70% of patients suffering from diabetes. Lipid profile imbalance in the presence of endothelial dysfunction in patients with DM, tends to promote atherosclerotic plaques in the coronary circulation. In the presence of uncontrolled hypertension, that could lead to an acute coronary syndrome (13-15).

Cigarette smoking is an important risk factor for the development of diabetes type 2. It is known that nicotine and many toxins from the tobacco smoke, such as polycyclic aromatic hydrocarbons, oxidants and thiocyanate, lead to insulin resistance. The harmful effect of nicotine, which on one hand causes a disturbance of endothelial homeostasis and reduction of the regenerative power of endothelial cells, on the other hand affects further the occurrence of microvascular and macrovascular complications in patients with DM (16-18), all of which was confirmed in this study as well.

In the obese, the sensitivity of beta-cells to the increase of glucose concentration in the blood is reduced over time, and besides that, the number of target tissue insulin receptors (of the body's own and exogenous insulin) is reduced as well.

It is well known that obesity is associated with the development of other diseases, such as DM, ischemic heart disease and some types of cancer. The reason why obesity causes insulin resistance lies in the fact that adipose tissue serves not only as an energy depot, but has also a secretory function in the production of cytokines, hormones and proteins that affect the function of cells throughout the body. Adipocytes secrete TNFα which on one hand increases the level of free fatty acids, thus leading to the loss of tissue sensitivity to the presence of insulin, and on the other induces the production of glucose by the liver. Endocrine function of adipose tissue is reflected as well in the production of leptin, a hormone the increased concentration of which affects the onset of insulin resistance because it leads to the changes of insulin receptors through their phosphorylation (19). Studies show that weight reduction significantly contributes to the reduction of particularly cardiovascular disease in people

with type 2 diabetes, and also affects better regulation of blood glucose levels (20, 21).

In people with type 2 diabetes, it is known that in a large percentage there is a disorder of lipid metabolism. Increased level of blood lipids in itself constitutes a risk for ischemic heart disease, and in patients with diabetes there is a synergistic, adverse effect particularly on the occurrence of macrovascular complications. In the examined population of diabetics, a very poor regulation of lipids was observed, which was illustrated by the fact that the average value of total cholesterol was 5.48 mg/dl, while the recommended value by the American Diabetes Association is 5.1 mg/dl. The mean values did not match the recommended ones for other lipids as well, and they were 3.52 mg/dl for LDL cholesterol, 0.98 mg/dl for HDL cholesterol and 2.17 mg/dl for triglycerides (5).

The increased levels of total and LDL cholesterol in particular are independent risk factors for cardiovascular disease. Any reduction of LDL cholesterol by 1 mmol/L reduces the risk of cardiovascular disease by 36% (22).

Good glycemic control is certainly one of the most important goals in the prevention or at least postponement of the onset of late complications. Disease control is good if the value of glycosylated hemoglobin (HbA1C) is below 7%, and fasting and preprandial glucose below 7 mmol/l (23). Although the average value of glycosylated hemoglobin was significantly increased in the studied population of patients (9.58%), a correlation between this important risk factor and complications of diabetes was not found by means of the statistical test. Studies show that with each 1% lower HbA1C, the incidence of retinopathy is reduced by 13%. A strict control of glycemia has a significant impact on the delay and slowing down of progression of diabetic nephropathy.

This research did not examine additional risk factors which can substantially contribute to the development of complications in patients. This primarily relates to the sedentary lifestyle and inadequate nutrition, as well as the level of education. The impact of the aforementioned factors could not be investigated in this study because the necessary information could not be found in the medical histories of our patients.

Conclusion

The results of this research point to the fact that dyslipidemia, being overweight, as well as cigarette smoking, have a significant impact on the development of chronic complications. It is especially important to emphasize that one of the main objectives is to maintain good glycoregulation and blood pressure in the appropriate range. Therefore, continuous education of patients is necessary so that they can increase their awareness of the significance of elimination of as many as possible risk factors, with the aim of postponing the occurrence of complications and improving the quality of life of people with diabetes.

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ANALIZA FAKTORA RIZIKA KOJI UTIČU NA POJAVU MIKROVASKULARNIH I MAKROVASKULARNIH KOMPLIKACIJA KOD BOLESNIKA SA DIJABETESOM MELITUSOM TIP 2

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Dijabetes melitus tip 2 je stanje hronične hiperglikemije, a najčešće je posledica različitih abnormalnosti na nivou perifernih tkiva. Prisustvo ove bolesti je povezano sa nastankom velikog broja komplikacija koje utiču na povećanje morbiditeta i mortalitata. Cilj ovog istraživanja bio je da se utvrdi uticaj faktora rizika, koji u najvećoj meri doprinose pojavi mikrovaskularnih i makrovaskularnih komplikacija kod hospitalizovanih bolesnika obolelih od dijabetes melitusa tip 2.

Studija je sprovedena po tipu studije preseka, koja je uključila obolele od dijabetesa melitusa tip 2 koji su hospitalizovani u Metaboličkoj jedinici na Internoj klinici Kliničkog centra u Kragujevcu. Neophodne informacije o bolesnicima dobijene su iz istorija bolesti, a odnose se na demografske i biohemijske podatke. Za statističku obradu podataka korišćen je test binarne logističke regresije, a statistička značajnost je određena vrednostima za koje je $p < 0,1$.

U studiju je uključeno 193 bolesnika sa dijabetesom melitusom tip 2 (89 ženskog i 104 muškog pola), prosečnog indeksa telesne mase 27,8, a prosečne starosti 60 godina. Faktori rizika za koje je dokazano da su u značajnoj korelaciji sa nastankom hroničnih komplikacija kod dijabetesa tip 2 su: starost bolesnika, godine trajanja bolesti, indeks telesne mase, vrednosti LDL, HDL holesterola i triglierida, kao i pušenje cigareta.

S obzirom da epidemiološke studije ukazuju na to da će dijabetes postati značajno zastupljena bolest u savremenoj populaciji, veoma je važna organizovana edukacija stanovništva kako bi se povećala svest o redukciji faktora rizika koji utiču na nastanak i progresiju komplikacija. *Acta Medica Medianae 2017;56(1):64-70.*

Ključne reči: *dijabetes melitus tip 2, mikro i makrovaskularne komplikacije, faktori rizika*