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Risk factors of peripheral occlusive arterial disease in patients with diabetic retinopathy due to type 2 diabetes

Фактори ризика периферне оклузивне артеријске болести код пацијената са дијабетском ретинопатијом изазваном дијабетесом тип 2

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SUMMARY

Introduction/Objective Diabetic retinopathy, peripheral vascular disease, and other diabetic complications may lead to a lowering of quality of life, significant comorbidity and mortality.
The aim of the study was to analyze the risk factors of peripheral occlusive arterial disease in patients suffering from diabetic retinopathy due to type 2 diabetes.

Methods We analyzed 63 patients having diabetic retinopathy (33 patients without and 30 patients with peripheral occlusive arterial disease). All the patients were asked for demographic data, medical history, physical findings, laboratory and vascular status.

Results Patients having confirmed peripheral occlusive arterial disease suffered from diabetes significantly longer (32.67 *vs*. 9.71 years, t = 12.834, p < 0.001), were more often smokers (23:13, χ^2 = 8.92, p < 0.05), had ischemic heart disease significantly more frequently (24:10, χ^2 = 15.643, p < 0.001), used statins more frequently (21:14; χ^2 = 4.84, p < 0.05), had claudications (25:4, χ^2 = 32,075, p < 0.001), depilations (30:9, χ^2 = 35,240, p < 0.001), thinned atrophic foot skin (30:12, χ^2 = 28.64, p < 0.01), foot ulcers (10:1, χ^2 = 10.013, p < 0.01), significantly higher HbA1c values (9.31:7.17, t = 5.250, p < 0.001), as well as glycemic control (11.60:8.20, t = 4.913, p < 0.001).

Conclusion It has been shown that the duration of type 2 diabetes, smoking, poor regulation of blood glucose levels and HbA1c significantly contributes to the development of diabetic retinopathy in patients having peripheral artery occlusion.

Keywords: Type 2 diabetes; diabetic retinopathy; peripheral occlusive arterial disease; risk factors

САЖЕТАК

Увод/Циљ Тип 2 диабетес је метаболичко обољење. Дијабетска ретинопатија, периферна васкуларна болест и друге компликације могу довести до лошег квалитета живота, значајног морбидитета и морталитета. Циљ је анализа фактора ризика стенозантно-оклузивне болести периферних артерија код болесника са дијабетском ретинопатијом изазваном тип 2 дијабетесом.

Методе Анализирали смо 63 пацијента са дијабетском ретинопатијом: 33 болесника без и 30 пацијента са стенозантно-оклузивном болести периферних артерија. Код свих пацијената су испитивани демографски подаци, анамнеза, лабораторијске анализе, физикални знаци и васкуларни статус

Резултати Болесници са оклузијом периферних артерија значајно дуже су боловали од дијабетеса (32.67 према 9,71 годину, t = 12.834, p < 0.001), чешће су били пушачи (23:13, χ^2 =8.92, p < 0.05), чешће су имају срчану исхемијску болест (24:10, χ^2 = 15.64, p < 0.001), чешће су узимали статине (21:14; χ^2 = 4.84, p = 0.028). имали су учесталије клаудикације (25:4, χ^2 = 32,075, p < 0.001), знаке периферне исхемијске болести и улцерације прстију (10:1, χ^2 = 10.013, p < 0.01). Код њих су утврђене значајно више вредности *HbA1c* (9.31:7.17, t = 5.25, p < 0.001) и гликемије (11.60:8.20, t = 4.913, p < 0.001). Код болесника без испољених знакова оклузије периферних артерија утврдјене су повишене вредности укупног (6.02:4.32, t = 7.151, p < 0.001) и ЛДЛ холестерола (3.64:2.86, t = 3.185, p < 0.01).

Закључак Код болесника са оклузијом периферних артерија испољени су фактори ризика: дужина трајања тип 2 дијабетеса, пушење, повишене вредности *HbA1c*, учесталија исхемијска болест срца и нерегулисане вредности гликемије.

Кључне речи: *diabetes mellitus* тип 2; дијабетска ретинопатија; периферна оклузивна артеријска болест; фактори ризика

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disease due to lack of insulin activity or its inadequate activity. There is also an interaction of inheritance and the environmental and risk

factor impact [1, 2]. Diabetes type 2 (T2DM), is a result of a decreased function of *β*-cells and/or resistance to insulin effect. T2DM makes 90–95% of diabetics. Several genetic and acquired factors are involved in etiopathogenesis of DM: gluconeogenesis and glycogenolysis followed by hyperglycemia and decreased cellular glucose disintegration manifested by characteristic signs of ischemia. Complications of DM may be acute (ketoacidosis, hyperglycemic coma) and chronic (retinopathy, nephropathy, neuropathy, peripheral vascular, coronary and cerebrovascular disease).

Retinopathia diabetica (RD) is a microvascular chronic complication of DM primarily affecting precapillary arterioles, capillaries and postcapillary venules [3,4]. DM is one of the main causative agents of blindness in active working population. Although hyperglycemia is known to be significantly associated with RD, pathophysiological mechanisms have not been entirely clarified [4,5]. Clinically, RD can be classified as: *Retinopathia diabetica non proliferativa* (RDNP) with *mild*, *moderate* and *severe* stages and *Retinopathia diabetica proliferativa* (RDP). The most frequent complications of T2DM are known and they represent the major risk factors [3] for the onset and development of RD. RD is a progressive disease with characteristic signs: microaneurysms, dot-and-blot hemorrhage, soft (*cotton wool*) and hard exudates as well as changes in the caliber of blood vessels and retinal reperfusion [4]. The elevation of retinal ischemia stimulates the production of vasoproliferative factors.

Peripheral arterial occlusive disease (POAD) is a condition most frequently caused by atherosclerosis, but other diseases may be of etiological importance. POAD is a major cause of lower extremity amputation, and is also related to higher probability of suffering from ischemic heart condition and cerebrovascular disease. DM, smoking, hypertension and hyperlipidemia are the main etiological factors of POAD. Furthermore, other risk factors are also important (age, DM duration, obesity, co-morbid states and complications of DM) [3, 6]. The diagnosis of POAD is established based on history of illness, clinical findings, doppler finding and

arteriography. In patients with DM, due to calcification and non-elasticity of arteries, there may be found unreal and falsely increased levels of doppler ankle-brachial index (ABI) [7,8]. POAD is treated with revascularization (endovascular or surgical procedures) and medicamentous administration.

The purpose of the study was to analyze the incidence of risk factors for the development of POAD in patients with confirmed diagnosis of RD who suffered from T2DM.

METHODS

The total number of the subjects (63) was divided into two groups: the study group (SG) of 30 patients with POAD and the control group (CG) of 33 patients without POAD. The study was conducted at the Clinic of Eye Diseases, University Clinical Center of Serbia (UCCS) and the Outpatients' Department of the Clinic of Vascular and Endovascular Surgery, UCCS.

The diagnosis of RD was established on the basis of indirect biomicroscopy by using the Volk®, Super vitreo fundus lens. The changes in the eye fundus were evaluated. They included microaneurysms, dot-blot hemorrhage, flame hemorrhage, soft and hard exudates in RDNP as well as newly formed blood vessels (*neovascularization of papillary disk* and *neovascularization elsewhere*) in RDP.

The diagnosis of POAD was established based on the existence of at least one symptom or sign of peripheral vascular disease and reduced ABI. The ABI measurements in the patients suffering from RD were done on Elcap Vaso Lab 1.000 apparatus, by stick probe of 8 MHz in the Clinic of Vascular and Endovascular Surgery, UCCS. The highest level of the indices obtained was the reference ABI level. The patients who had normal ABI levels (0.91 to 1.40) with no symptoms and signs of peripheral angiopathy belonged to the group with no signs of POAD (CG), whereas the patients with ABI levels below 0.91 were in the group with the signs of POAD (SG).

Demographic data, history of illness (T2DM duration, smoking, hypertension, ischemic heart condition, cerebrovascular disease, claudication, the use of drugs), physical exam finding (body mass index, i.e. BMI, ischemic thinned skin, depilation and ulceration), laboratory findings (blood cell count, total LDL, HDL cholesterol, triglycerides, glycemia, glycated hemoglobin i.e. HbA1C, creatinine, urea, liver enzymes and C reactive protein ie. CRP) were evaluated followed in all the patients.

All the subjects submitted their written informed approval for the participation in the clinical study upon reading short protocol and the purpose of the study. The Ethical Committee of the UCCS (1040/28) gave approval for the conduction of this study.

The obtained data were collected in the tabular questionnaire and analyzed by the methods of descriptive and analytic statistics. The methods of descriptive statistics used were central tendency rates, relative numbers and variability rates. The methods of analytic statistics, for the estimation of statistical significance, included student t-test for numerical features, $\chi 2$ test for attributive features and Fisher's test of accurate probability. The value $p \leq 0.05$ was used as borderline value of statistical significance whereas the value $p \leq 0.01$ as borderline value of high statistical significance. The data collected were analyzed in a tabular form by applying the program IBM SPSS Statistics 20.

RESULTS

Complete study results of both groups are shown in Table 1.

Demographic Data

The majority of the patients were males (60.3%). The variability in distribution of patients according to gender was not significant. The obtained results of demographic studies indicated that SG and CG groups were statistically comparable.

Medical history data

The patients with the confirmed diagnosis of POAD suffered from T2DM significantly longer. The patients in SG were more frequently smokers than in CG. Hypertension occurred within approximate values in both groups. The use of antihypertensive drugs was approximately equally present in both groups. Statins were used more by SG than CG group. SG patients were found to be suffering from ischemic heart condition more frequently than CG patients. Among the studied patients, there was none who had a positive history of cerebrovascular disease. Most SG patients complained of claudication, so high significance was proven in the studied group.

Physical exam finding

There was no difference in BMI values. Peripheral ischemic changes (ischemic loss of hair on the foot and lower extremities, atrophic, thinned skin and ischemic foot ulcerations) were significantly more frequent in the patients having the manifested POAD.

Laboratory findings

Erythrocyte, leucocyte and platelet counts and hemoglobin concentration were similar in the studied groups. There was no difference in HDL cholesterol levels between the studied groups. However, the total and LDL cholesterol levels were significantly lower in the SG patients than in the CG ones. The difference in blood triglyceride concentration was not noticed between study groups. The average glycemia levels were significantly higher in the SG patients than in the CG ones. The HbA1c levels were higher in the SG patients than in the CG ones. There was no statistical difference in the average urea and creatinine blood levels of the studied groups. The differences of basic liver enzyme concentration were not significant in both groups. The CRP levels were within reference values in both groups, but statistically significant difference was determined between the studied groups.

SG patients had ABI index values from 0.59 to 0.68. All CG subjects had ABI over 0.92, but below 1.40.

DISCUSSION

RD is common cause of the vision loss in the patients 20–64 years old and one of the most frequent microangiopathic complications of T2DM [9]. The prevalence of RD is around 24.5% of patients with the found of DM and around 10.7% of patients with undiagnosed DM [10]. RD may occur in every patient suffering from T2DM so RD can be prevented by the control of glycemia and elimination of other risk factors [3].

T2DM is followed by the higher risk of POAD, cardiovascular and cerebrovascular diseases. These conditions frequently require hospitalization of patients and may be accompanied by acute complication, leg amputation and lethal outcome [1,2]. DM and POAD are approximately even between genders [3]. There were no significant differences in RD and POAD in the patients according to gender [9]. This study showed that RD occurred slightly more frequently in males than females (38:25), but were no significancy. Magri et al. had similar findings with the ratio of 98:83 [11]. However, Cherchi et al. studied sex distribution of RD in 20611 patients with T2DM showed that there was higher prevalence of RD in males in spite of less present risk factors. This meant that the male sex could represent a separate risk factor for the RD onset [9].

Leley et al. think that around 50% of T2DM patients develop RD in older age due to reduced retinal blood flow and microglial alterations. This makes retina more vulnerable to oxidative and ischemic alterations leading to RD progression [12]. Our patients were of older age (over 70 years), and there were no significancy between SG and CG as found by other authors [11]. However, most studies show that RD occurs in patients younger than 70 [13].

Such findings suggest that our patients are diagnosed and treated of RD and POAD later than patients in more developed countries.

Duration of T2DM was significantly different in our studied groups: SG (32.67±2.09) vs. CG (9.71±9.59), so this difference was highly significant. Such findings indicate that RD can be diagnosed in the period of 10 years from the onset of T2DM. That shows also that clinically manifested POAD occurs significantly later during T2DM. The duration of T2DM strongly affects the onset of POAD. Other authors find that the duration of T2DM over 10 years is very important factor for progression of POAD and its complications [14]. Duration of diabetes and systemic risk factors affect the seriousness of RD clinical finding. Studying the severity of RD in diabetics under 25 y..o (161) and over 25 y.o (493), Parameswarappa et al. showed that younger patients suffering from T2DM had more chance to develop threatening RD in spite of the presence of similar risk factors [15].We suggest that there is necessity of monitoring and treating of arterial pressure, glycemic status and other possible diabetic complications in these patients to decrease the risk of threatening RD and POAD [2,15].

Smoking is one of the most important risk factors for POAD in DM and atherosclerosis. However, the incidence of this risk factor is different in certain regions of the world [16]. In metanalysis of the risk of smoking in diabetics, Cai et al. [17] established that the risk for RD in diabetes type 1 was higher in smokers than non-smokers (risk ratio was 1.2; $p<0.001$). On the other hand, the risk for retinopathy in T2DM decreased in smokers compared to non-smokers (risk ratio was 0.92; $p<0.001$). Around the three quarters of our patients, suffering from POAD, had the smoking habit whereas non-POAD group counted less than half smokers. The observed difference was significant. Such data shows that in our population smoking is a highly prevalent risk factor for peripheral vascular disease in DM, so that more social effort and engagement on banning smoking is required.

Hypertension is an important risk factor for the development of POAD and RD in patients with T2DM [12]. Microvascular lesions were determined in RD (thickened capillary membrane, defect of blood-retinal barrier and pericyte loss) [18]. A multicentric study including 152.844 diabetics showed that there was correlation between hypertension and RD, but it was demonstrated that the higher prevalence of RD was also present with and without hypertension [19]. In our study, hypertension was found in over 60% of similar values of the studied groups, so the differences obtained were insignificant. High incidence of hypertension in DM and RD requires the application of antihypertensive drugs [11]. Our patients took all groups of antihypertensive drugs. The SG patients used statins more than the CG patients (21:14). The patients suffering from POAD used statins much more frequently than the patients having POAD. This is in contrast with the study of Magri et al. [11] in which it was shown that there was no significant difference between the studied groups. This suggests that our patients suffered more frequently from hyperlipoproteinemia than the patients in other populations. Nevertheless, one should be careful with prescribing statins because of their potential insulin-resistant effect [20].

It has been well known that T2DM is followed by a coronary disease [16,17,18]. Multiple regression analysis conducted by Kawasaki et al. [21] showed that RD was an important factor for the development of coronary complications with the following risk factors: increased triglyceride levels, smoking, age, T2DM duration, increased HbA1c level and female sex. In medical history, the incidence of ischemic heart disease in our subjects was significantly higher in SG (80%) than in CG (30.3%). Such finding may be the result of the difference in T2DM duraton as well as the possibility of asymptomatic presence of coronary disease in RD patients [6,8]. There were no history data of earlier cerebrovascular disease in our study. Carotid disease is known to be frequently asymptomatic, so the diagnosis requires duplex scan angiography [6,11], which was not used in this study.

Obesity and BMI in our patients is similar in all subjects (BMI from 25.0 to 29.9 kg/m^2) so there was insignificant difference in the studied groups. Other researchers had similar results [11].

Intermittent claudication represent one of the major complaints in the patients with POAD. Nevertheless, the presence of decreased claudication distances and the absence of pedal pulses is not sufficient for diagnosing POAD [7,8]. Our study showed that 25 patients in SG and only 4 in CG had claudication, which is a highly significance in the studied groups. It was established, by physical exam finding, that there was a significant difference in peripheral vascular state of our patient groups. The loss of hair, thinned skin and ulcerations were the result of low foot trophic and they may be significant signs of peripheral angiopathy. The study showed that these ischemic signs were more frequent in SG patients than in CG.

All our SG patients had decreased ABI. Decreased ABI is known to be present in patients with macroangiopathic alterations [11]. It is necessary to stress that the ABI finding in diabetics in advanced stages is of relative importance. Namely, in advanced atherosclerotic alterations due to DM, peripheral arteries become and uncompressible [7,11]. Careful interpretation of these findings is required [7] since in advanced stages of occlusive disease, in some diabetics, there may exist unreal high ABI values surpassing even 1.4 in spite of manifested critical ischemia. In advanced wall alterations, arteries may be uncompressible and ABI unmeasurable [7]. Such patients were excluded from our study [2].

Changes in blood count in diabetics were described (increased leucocyte and platelet counts) [22], which was not shown in our study. This may be the result of insufficient number of subjects and study design. Our SG patients had significantly lower total and LDL cholesterol levels in comparison to CG patients. These, apparently, paradoxical data may be explained by the effect of the applied therapy of statins [21] which were significantly more frequently used in our SG (2/3 of patients) than CG (1/2 of patients). It is undisputable that statins have

significant metabolic effects reducing atherogenesis. Thus, these drugs are significantly more used in patients having POAD than in patients not having POAD [20], which was shown in our study. In the studied groups, the differences in triglyceride levels did not reach statistical significance.

In both studied groups, increase HbA1c levels were found, but the values were significantly higher in patients suffering from manifested POAD. These results thus suggest that the impaired glycorerulation was more manifested in patients having POAD than in patients not having POAD. In SG patients, increased glycemia levels were obtained and these differences were highly significant related to CG. This indicates that the glycemia levels are not affected by insulin that is hypoglycemics only, but statin therapy, antiaggregating therapy as well as adequately prescribed diet [23]. RD treatment is conducted also using other agents such as: corticosteroids, vascular endothelial growth factor (VEGF) agents, interleukin inhibitor, Rho-kinase inhibitors, neuroprotective agents, laser therapy. All this significantly influences metabolic and pathogenetic vascular processes in RD [24, 25, 26].

In our patients, there were insignificant changes in urea and creatinine levels in the studied groups. This indicates that our patients did not have the advanced or terminal renal insufficiency and that RD was not detected since we did not measure poteinuria. Elevated basic liver findings (ALP, GGT, ALT, AST) were not seen in both studied groups. It is known that patients with metabolic syndrome have 2-4 times higher risk for cardiovascular diseases, as well as 5-9 times greater chances of T2DM development [24]. Although our studies showed that disorders of the cholesterol and triglyceride metabolism had a significant atherogenic effect, but by basic liver enzyme findings it was not possible to prove hepatic insufficiency.

The increased level of CRP in blood of T2DM patients may be a significant risk factor for DM complications. Horn study showed that the increased CRP level was in correlation with RD, but not independent of other risk factors (HbA1c, BMI, albuminuria) [25]. Nevertheless,

it remains unclear to what measure CRP leads to retinopathy. Correlation between CRP and RD may be explained in that CRP has proangiopoietic effect and stimulates monocytes to produce vascular VEGF-A [23]. In our study, it was shown that CRP level was significantly higher in CG than in SG, so this difference was noticed to be highly significant. A possible explanation is that the patients having POAD used statins more frequently since it is known that they lead to the CRP level decrease [24].

T2DM is a chronic metabolic disease caused by glucose metabolism disorder due to the disorder of insulin synthesis or activity. The disease is more common in adult and elderly population, in both sexes, with the tendency of progression due to congenital factors and modern way of life (decreased physical activity, increase of obesity and changes in diet) [1]. It leads to progressive microangiopathic, macroangiopathic and neuropathic diseases [1,2,12,14]. RD is characterized by retinal impairment affected by several etiopathogenetic factors: synthesis of proinflammatory cytokines and chemokines, growth factor disorder, oxidative means and other factors which lead to the development of microaneurysms, retinal hemorrhage and ischemia by synthesis of vasoproliferative factors, increased permeability of retinal vessels and serum transudation. The manifestations are thinned retina, macular edema and loss of vision [26].

CONCLUSION

In patients suffering from RD, the following risk factors for the development of POAD were identified: T2DM duration, smoking habit, elevated glycemia level, increased HbA1c levels and more frequent occurrence of coronary disease. The patients having POAD had significantly more frequent findings of claudication, ischemic depilation, thinned skin and foot ulceration with significantly more frequent use of statins.

The patients suffering from RD who were not determined to have manifested POAD had significantly increased total cholesterol levels, elevated LDL cholesterol levels and increased CRP levels. They used statins less frequently in medical therapy.

The obtained results suggest that early detection and risk factor elimination is required as well as complex therapy for the patients suffering from T2DM, RD and POAD. With these measures, complications are decreased and the quality of life of these patients is promoted.

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Table 1. Findings of risk factors for development of peripheral arterial occlusive disease (POAD) in type 2 diabetes mellitus patients with *retinopathia diabetica*

Feature	Study group (with POAD)	Control group (without POAD)	Analytic statistic	p value
No. of subjects	30	33	-	-
Male (n)	20	18	DF = 1; χ^2 = 0.965	0.326
Female (n)	10	15		
Age ($\overline{x}$ ± SD years)	71.17 ± 5.60	71.64 ± 5.80	DF = 62; t = 0.326	0.745
DM duration ($\overline{x}$ ± SD years)	32.67 ± 2.09	9.71 ± 9.59	DF = 61; t = 12.83	< 0.001
Smoking habit (n)	23	13	DF = 1; χ^2 = 8.920	0.003
Hypertension (n)	20	20	DF = 1; χ^2 = 0.249	0.618
Antihypertensive use (n): ACE inhibitors β blockers Inhibitors of calcium channels Diuretics	 17 20 11 8	 20 19 7 5	 DF = 1; χ^2 = 0.099 DF = 1; χ^2 = 0.542 DF = 1; χ^2 = 1.841 DF = 1; χ^2 = 1.320	 0.752 0.461 0.175 0.251
Statin use (n)	21	14	DF = 1; χ^2 = 4.840	0.028
Coronary disease incidence (n)	24	10	DF = 1; χ^2 = 15.64	< 0.001
Claudication incidence (n)	25	4	DF = 1; χ^2 = 32.07	< 0.001
BMI (kg/m^2)	27.31 ± 2.87	26.09 ± 2.52	DF = 61; t = 2.03	0.08
Ischemic leg depilation (n)	30	9	DF = 1; χ^2 = 35.24	< 0.001
Ischemic skin atrophy (n)	30	12	DF = 1; χ^2 = 28.64	< 0.001
Foot ulcerations (n)	10	1	DF = 1; χ^2 = 10.01	< 0.01
Erythrocyte count (x10^{12}/l)	4.865 ± 0.53	4.736 ± 0.53	DF = 61; t = 0.345	0.731
Leucocyte count (x10^9/l)	7.3 ± 1.66	6.9 ± 2.1	DF = 61; t = 0.812	0.423
Platelet count (x10^9/l)	281.01 ± 54.4	268.55 ± 49.36	DF = 61; t = 0.945	0.348
Hemoglobin level (g/l)	133.67 ± 16.78	138.24 ± 17.85	DF = 61; t = 1.020	0.308
Total cholesterol (mmol/l)	4.32 ± 0.50	6.02 ± 1.21	DF = 61; t = 7.151	< 0.001
HDL cholesterol (mmol/l)	1.14 ± 0.23	1.15 ± 1.24	DF = 61; t = 0.210	0.835
LDL cholesterol (mmol/l)	2.86 ± 1.05	3.64 ± 0.89	DF = 61; t = 3.185	0.002
Triglycerides (mmol/l)	1.88 ± 0.84	2.25 ± 0.99	DF = 61; t = 1.573	0.006
Glycemia (mmol/l)	11.60 ± 2.10	8.2 ± 3.22	DF = 61; t = 4.913	< 0.001
HbA1c (%)	9.31 ± 1.54	7.17 ± 1.68	DF = 61; t = 5.250	< 0.001
Urea (mmol/l)	7.08 ± 2.35	7.94 ± 2.28	DF = 61; t = 1.453	0.151
Creatinine (μmol/l)	79.40 ± 17.71	84.3 ± 16.63	DF = 61; t = 1.115	0.269
ALP (U/l)	77.94 ± 21.59	75.89 ± 11.80	DF = 61; t = 0.463	0.645
GGT (U/l)	24.433 ± 7.48	27.03 ± 8.97	DF = 61; t = 1.222	0.225
ALT (U/l)	30.993 ± 8.50	29.424 ± 8.87	DF = 61; t = 0.677	0.501
AST (U/)	20.333 ± 4.50	22 ± 3.52	DF = 61; t = 1.620	0.110
CRP (mg/l)	1.533 ± 0.205	3.127 ± 1.01	DF = 61; t = 8.330	< 0.001

$\overline{x}$ - mean value; SD – standard deviation; DF – degree of freedom; DM – *diabetes mellitus*; ACE – angiotensin converting enzyme; BMI – body mass index; HDL – high density lipoprotein; LDL – low density lipoprotein; ALP – alkaline phosphatase; GGT – gamma glutamyl transferase; ALT – alanine amino transferase; AST – aspartate amino transferase; CRP – C-reactive protein

