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Influence of glucose levels on exercise test results in patients with coronary artery disease and type 2 diabetes mellitus

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There is a significant relationship between the level of glycated hemoglobin (HbA1c) and the risk of developing macrovascular and microvascular complications. The aim of this study was to examine the influence of glucose levels on the exercise stress test results in patients with coronary artery disease and type 2 diabetes mellitus. The study included 90 participants treated at the Military Hospital Niš.

All the participants were divided into three groups: Group I: 40 patients with confirmed coronary artery disease and type 2 diabetes mellitus (CAD and type 2 DM); Group II: 30 patients with coronary artery disease (CAD); Group III: 20 participants without signs of coronary disease, diabetes or glucose intolerance. All the participants underwent ECG, echocardiographic examination and a physical exercise stress test.

The performed T-test showed statistically significantly higher values of systolic and diastolic blood pressure before exercise, maximum systolic pressure, and systolic pressure one minute after exercise, in the group of patients with CAD and type 2 DM. On the other hand, maximum diastolic blood pressure, heart rate recovery time, the heart rate reserve used, blood pressure drop, exercise duration

and the maximum power in W had stasticially significantly lower values. The concentration of fasting morning glucose showed a stronger positive correlation with the exercise duration, while the other parameters did not show such an association.

The patients with coronary artery disease and type 2 diabetes mellitus exhibit reduced physical capacity compared to the expected values, even at satisfactory levels of glycemic control. The analysis showed that fasting morning glucose is a significant factor that negatively affects the exercise stress test results.

Keywords: coronary artery disease, type 2 diabetes mellitus, exercise stress test

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Uticaj nivoa glukoze na rezultate testa opterećenja kod bolesnika sa koronarnom bolešću i dijabetesom melitusom tipa 2

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Postoji značajna veza između nivoa glikoziranog hemoglobina (HbA1c) i rizika za nastanak makrovaskularnih i mikrovaskularnih komplikacija. Cilj rada bio je ispitati uticaj nivoa glukoze na rezultate testa opterećenja kod bolesnika sa koronarnom bolešću i dijabetesom melitusom tipa 2. Istraživanjem je obuhvaćeno 90 ispitanika lečenih u Vojnoj bolnici Niš.

Svi ispitanici su podeljeni u tri grupe: I grupa: 40 bolesnika sa dokazanom koronarnom bolešću i dijabetesom melitusom tipa 2 (KB i DM tipa 2); II grupa: 30 bolesnika sa koronarnom bolešću (KB); III grupa: 20 ispitanika bez znakova koronarne bolesti, dijabetesa i intolerancije glikoze. Kod svih ispitanika urađen je EKG, ehokardiografski pregled i test fizičkim opterećenjem.

Urađen T-test je pokazao statistički značajno veće vrednosti sistolnog i dijastolnog pritiska pre opterećenja, maksimalnog sistolnog, i sistolnog pritiska nakon jedne minute, u grupi bolesnika sa KB i DM tipa 2, dok su vrednosti maksimalnog dijastolnog krvnog pritiska, vreme oporavka srčane frekvence, upotrebljena rezerva srčane frekvence, pad krvnog pritiska, trajanje testa opterećenja i maksimalna

snaga u W imale statistički značajno niže vrednosti. Koncentracija jutarnjih vrednosti glikemije ima značajniju pozitivnu povezanost sa trajanjem testa opterećenja. Ostali parametri nisu pokazali ovakvu jačinu veze.

Bolesnici sa koronarnom bolešću i dijabetesom melitusom tipa 2 pokazuju smanjen fizički kapacitet u odnosu na očekivane vrednosti, čak i pri zadovoljavajućem nivou glikoregulacije. Analiza je pokazala da je jutarnja glikemija značajan faktor koji negativno utiče na rezultate testa fizičkog opterećenja.

Ključne reči: koronarna bolest, dijabetes melitus tipa 2, test fizičkim opterećenjem

Introduction

High levels of glycated hemoglobin (HbA1c) are associated with an increased risk of macrovascular and microvascular complications, both in the general population and in individuals with type 2 diabetes mellitus (1, 2).

The concentration of intracellular glucose in endothelial cells reflects the extracellular environment (3). There are numerous pathogenic mechanisms through which hyperglycemia induces acute changes in intracellular metabolism (activation of the polyol pathway, activation of the diacylglycerol-protein kinase C, increased oxidative stress), as well as cumulative long-term changes in the structure and function of macromolecules (through the formation of AGE products). When tissues do not require glucose uptake into cells (such as the kidneys, retina, nerves and blood vessels), hyperglycemia activates the polyol pathway, resulting in the formation of sorbitol (4). Aldolase is the first and rate-limiting enzyme in the polyol pathway, reducing the aldehyde group of glucose to sorbitol.

Several experimental and clinical studies indicate a relationship between increased activity of the polyol pathway and the development of chronic diabetic complications. The target organs affected by diabetic complications show varying sensitivity to damage depending on the degree of gene expression for aldose reductase (5). Aldose reductase uses NADPH in the conversion of glucose to sorbitol, leading to the cellular depletion of NADPH (4). The reduction of NADPH is necessary for the function of many endothelial enzymes, including NO synthase and the cytochrome P450, as well as for the antioxidant activity of glutathione reductase. High ATP consumption during the operation of the polyol metabolic pathway may lead to increased demands for EDRF production (6).

Another glucose-induced alteration in cellular metabolism responsible for endothelial dysfunction is the activation of the protein kinase C (PKC). Hyperglycemia causes de novo synthesis of diacylglycerol, leading to PKC activation, especially the β isoform. The presence of this pathway has been demonstrated in all vascular tissues involved in diabetic complications. The consequences of PKC activation are diverse, as it is involved in various cellular functions (7). It contributes to impaired responses of endothelium-dependent agonists via the activation of phospholipase A2, the increased production of arachidonic acid metabolites, and the inhibition of Na^+/K^+-ATPase. The adverse effects of elevated glucose levels include the acetylcholine-induced relaxation impairment in the rabbit aorta and rat arteries, which can be

improved by PKC inhibitors. Furthermore, glucose-induced vasoconstriction via prostanoids was prevented by PKC inhibition (8).

Impaired acetylcholine-induced relaxation was improved after chronic insulin therapy, but not after short-term insulin administration, even when glucose levels were normal (9). Acute exposure to high glucose concentrations in humans induces endothelial dysfunction similar to that observed in diabetic animals (10).

Glycemic control is a predictor of both microvascular and macrovascular complications, although the relationship is relatively weak, particularly in type 2 diabetes. Numerous studies have found a correlation between HbA1c concentration and the degree of endothelium-dependent vasodilation (11).

The exercise stress test is the first-line diagnostic option in the algorithm for evaluating chest pain suspected to be of coronary origin. Gianrossi et al. observed high sensitivity and specificity of the exercise stress test for coronary artery disease in the general population, although with wide variability (12). To date, there is no higher level of clinical evidence regarding the diagnostic value of the exercise stress test in asymptomatic patients with type 2 diabetes mellitus. Moreover, due to wide variability in diagnostic values among studies, there is still a lack of systematic understanding of how different factors contribute to the sensitivity and specificity of the exercise stress test in detecting the asymptomatic coronary artery disease in diabetic patients (13).

The aim of this study was to examine the influence of glucose levels on the results of the exercise stress test in patients with coronary artery disease and type 2 diabetes mellitus.

Materials and methods

The study included 90 participants, of whom 70 were patients with coronary artery disease treated at the Military Hospital Niš, and 20 were healthy individuals. The patients with the following conditions were excluded from the study: valvular heart disease, cerebrovascular disease, an implanted pacemaker, chronic liver or kidney disease, malignant diseases, or any other conditions that could affect the characteristics of the coronary artery disease in the examined patients.

All the participants were divided into three groups according to the presence of diabetes and signs of glucose intolerance:

Group I: 40 patients with confirmed coronary artery disease and type 2 diabetes mellitus (CAD + type 2 DM).

Group II: 30 patients with coronary artery disease (CAD) without diagnosed diabetes or signs of glucose intolerance, which was confirmed by an OGTT test.

Group III: 20 subjects without signs of coronary artery disease, diabetes or glucose intolerance.

For all patients, a detailed medical history was taken, followed by venous blood sampling from the cubital vein before the start of therapy. The lipid parameters were determined: total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides.

Methods for assessing glycemic control

The fasting blood glucose was determined from capillary blood samples after 12 hours of fasting, using a single-channel analyzer AXON from the company Bayer. The glucose levels were expressed in mmol/l.

The daily glucose profile was determined by taking 5 capillary blood samples throughout the day, which includes fasting in the morning, at noon and in the evening, as well as 2 hours after breakfast and lunch. Glycemia was determined using the specified analyzer. The glucose values were expressed in mmol/l. The mean blood glucose (MBG) value was obtained by calculating the arithmetic mean of all five measurements and it was expressed in mmol/l.

In the group of patients without diabetes, an OGTT was performed. The patients who showed glucose intolerance or a diabetic profile were not included as a part of Group II or III.

The HbA1c values were determined through a Dimension Expand analyzer by using the reagents from the company Dade Behring, with the normal values 3.9–5.7% (it is recommended that HbA1c < 6.1%).

The test was performed in an optimally heated room. After breakfast, coronary dilators and beta-blockers were withheld prior to testing. The test was carried out on a bicycle ergometer and analyzed by computer. The protocol began with a load of 25 W for three minutes, followed by an increase of 25 W for every three minutes until the test was terminated. During the exercise test, the blood pressure values (sisTA pre, dijTA pre) and the heart rate (SF pre) were recorded before exercise, at maximum exertion (sisTA max, dijTA max, SF max) and one minute after the exercise (sisTA/1min, dijTA/1min, SF/1min). Based on these data, the double product was calculated as an indicator of O_2 consumption. The double product was calculated as the product of heart rate and the systolic blood pressure, divided by 1,000 (DP pre, DP max, DP/1min). The maximum workload was recorded in W, as well as the presence of symptoms during the test, the ST-segment changes (dynamics, localization) and

the test duration. In addition, the heart rate recovery (HRR) and the proportion of heart rate reserve used (HR reserve) were calculated.

All the patients underwent ECG and echocardiographic examination. During the echocardiographic examination, the following parameters were registered: EDD- left ventricular end-diastolic dimension in mm, ESD- left ventricular end-systolic dimension in mm, Ss-Septum thickness in systole in mm, Sd-Septum thickness in diastole in mm, PWs-Back wall thickness in systole in mm, PWd-Back wall thickness in diastole in mm, EF-Ejection fraction, FS-shortening fraction.

Results

The characteristics of the examined groups are presented in Table 1.

Table 1.

Of the total number of patients examined, 49 (55%) were female and 41 (45%) were male. The mean age of the patients was 58.8 ± 6.49 years, with no statistically significant difference in age between the sexes.

Examination of lipid status included determination of LDL, HDL and total cholesterol concentrations, as well as triglyceride concentrations (Table 2).

Table 2.

The performed Student's T test did not show a significant difference in the values of total cholesterol, LDL and HDL cholesterol, but triglycerides were statistically significantly higher in the group of CAD patients with DM type 2 (Table 2).

Echocardiographic parameters of left ventricular systolic function (Sd, EDD, PWd, Ss, ESD, PWs, EF, FS) were examined and the results are shown in Table 3.

Table 3.

The examined parameters of systolic function Sd, EDD, PWd, Ss, PWs had statistically significantly higher values, while EF and FS had statistically significantly lower values in the group of patients with CAD and DM type 2.

The exercise test parameters in patients with CAD depending on the presence of DM are shown in Table 4.

Table 4.

The performed T-test revealed statistically significantly higher values of sisTA pre, dij TA pre, sisTA max and sisTA/1min in the group of patients with CAD and type 2 DM, while the parameters DP max, HRR, HR reserve, the TA drop, the exercise test duration and the maximum workload in W, had statistically significantly lower values.

The relationship between the glycoregulation parameters and the exercise test parameters in the group of patients with CAD and type 2 DM is shown in Table 5.

Table 5.

The conducted analysis demonstrated that only the fasting morning glucose concentration shows a significant positive correlation with the exercise test duration, while the other parameters did not exhibit such an association.

Discussion

The fact that ergometry is a non-invasive and relatively inexpensive method providing valuable clinical, diagnostic and prognostic information, has made it, over the past two decades, an important clinical tool for assessing the cardiovascular and overall mortality risk (14).

The study of the importance of lipid disorders in diabetes for the occurrence of endothelial dysfunction and the development of CAD was performed by comparing the values of lipid parameters between groups of patients with CAD and DM type 2 and patients with CAD without DM type 2 (Table 2). It was shown that only the triglyceride values were significantly higher in the CAD group with DM type 2 ($p<0.01$), while the values of the other lipid indicators did not show a significant difference between these groups of patients.

High values of total cholesterol and triglycerides are of great importance, with triglycerides being better predictors of CHD. The strength of triglycerides as a risk factor depends on their association with other parameters (hypertension, PAI-1 level, etc.)(15). Epidemiological studies find a positive correlation between serum lipid values and blood pressure, and some have shown a slight decrease in blood pressure after correction of lipid disorders (16).

Echocardiographic parameters indicated myocardial thickening and lower systolic function in patients with CAD and DM type 2 (Table 3). There are a number of explanations for the reduction of myocardial contractility in diabetics and lower exercise tolerance. Chronic abnormalities in myocardial metabolism of carbohydrates and lipids due to lack of insulin lead to a reduction in the activity of adenosine triphosphate, a decrease in the ability of the sarcoplasmic reticulum to take up calcium and

intracellular accumulation of toxic fatty acid intermediates. This leads to adenosine triphosphate depletion and increased myocardial oxygen consumption. This results in focal, progressive loss of myofibrils, transverse tubules and sarcoplasmic reticulum, and separation of the fascia atherens on the intercalary disc with myocytes, causing myocyte hypertrophy, loss and replacement into fibrosis, reducing myocardial contractility (17).

The exercise test duration showed a significant positive correlation with the fasting glucose levels (Table 5).

Adequate glycemic control is essential for the successful therapy of type 2 DM. It exhibits its negative effects on several levels, starting from its role in contributing to the development of endothelial dysfunction, an increased formation of advanced glycation end products (AGE products), an impaired myocardial energy metabolism (18), pulmonary function abnormalities (19) and the presence cardiovascular autonomic neuropathy (20). Despite that, the results regarding the impact of glycemic control on exercise test parameters in patients with type 2 DM remain inconsistent (13). In most cases, it is stated that hyperglycemia negatively affects the exercise test parameters related to the regulation of oxygen transport and utilization (19).

Brasard et al. (21) investigated the influence of glycemic control on the heart rate response during exercise testing in patients with type 2 DM. They found that in diabetic patients without CAD, higher HbA1c levels are associated with pulmonary dysfunction characterized by reduced maximal power during submaximal exercise, and that high fasting glucose values negatively affect the heart rate increase during exertion.

In our study, no significant correlation was found between glycemic control and either test duration or maximal achieved power. The literature data on the association between hyperglycemia and the exercise tolerance in patients with type 2 DM are conflicting. Five major studies found no association between glycemic control and exercise power (22), while two others did (23). The mechanisms by which chronic hyperglycemia can lead to reduced stress tolerance and maximal power in stress tests, have still not been thoroughly studied. Long-term hyperglycemia probably has an effect on the lung structure and function. This is justified by the findings that patients with type 2 DM have a high concentration of glycated proteins, such as collagen in the lungs, as well as thickened basement membranes and fibrosis (24). Also, an impaired response to hypoxic stimuli suggests disrupted peripheral chemoreflexes, often associated with dyspnea (25). Diabetes also negatively affects the type III and IV nerve fibers. This

could potentially disturb the feedback regulation of the mechanoreceptors that send important reflex signals to cardiovascular and respiratory vegetative centers supporting chronotropy, ventilation and the corresponding vasoconstrictive response during stress testing (26).

Low heart rate variability (HRV) is associated with diabetic neuropathy and ischemic heart disease. Moreover, diabetes is believed to precede HRV alterations, while HRV alterations precede the development of atherosclerosis and CAD (27).

Well-controlled patients with type 2 DM achieve higher maximal power in stress testing and a higher peak heart rate compared with the poorly controlled patients with type 2 MD. At the same time, this finding persists even when comparing non-diabetic patients or diabetic patients with CAD (28).

The conducted T-test confirmed statistically significantly higher values of the exercise test parameters (sisTA pre, dijTA pre, sisTA max and sisTA/1min) in the group of patients with CAD and type DM, while the parameters DP max, HRR, HR reserve, the TA drop, the exercise test duration and the maximum workload in W, had statistically significantly lower values (Table 4).

Our results suggest that endothelial dysfunction in patients with type 2 DM is significantly associated with the maximum power achieved during exercise testing. The significance of maximal exercise power as a prognostic factor forrardiovascular mortality was demonstrated in several large population studies, such as the Framingham Study (29), Aerobics Center Longitudinal Study (30), and the Harvard Alumni Study (31).

The exercise test duration observed in our patients represents a significant negative indicator. In the study by Blair et al., involving about 10,000 men, a 7.9% reduction in mortality was observed for each additional minute of exercise test duration (30).

Changes in the heart rate during exercise and recovery are determined by the balance between the sympathetic and vagal activity. Over the past two decades, increasing evidence, both experimental and clinical, has confirmed the close association between autonomic nervous system abnormalities and both sudden and non-sudden cardiac death in MI (32).

It is well established that whenever the markers of tonic or reflex vagal activity are reduced, the cardiovascular mortality risk is increased. This has been demonstrated for baroreflex sensitivity (32), heart rate variability, heart rate turbulence (following premature ventricular contractions) and heart rate recovery after stress tests. The mortality risk associated with reduced HR recovery is

independent of the extent of the angiographic modifications to the coronary blood vessels, suggesting that alternative mechanisms are involved (33).

In the large study conducted by Jouven et al., a statistically significant association was found between increased heart rate during exercise and overall mortality rate. Moreover, heart rate values during recovery (after 1, 2, 3 and 4 minutes of rest) were associated with total mortality, particularly sudden cardiac death, but not with non-sudden death due to myocardial infarction (34).

The influence of glycemic control on exercise test parameters, particularly heart rate response in patients with type 2 DM, is still not well defined. Most studies, however, report a lower HR response during submaximal exercise testing in patients with type 2 DM compared to the healthy control subjects (35).

Patients with type 2 DM have reduced baroreflex sensitivity, which may contribute to an abnormal chronotropic response. Therefore, a slower HR increase in type 2 DM may result from reduced baroreceptor sensitivity linked to the presence of hyperglycemia or hyperinsulinemia (36).

In our patients with type 2 DM, significantly higher blood pressure values were recorded before the test, as well as higher systolic pressures during and after exercise. These findings align with literature data showing that reduced maximal power during exercise testing is associated with cardiac autonomic dysfunction in diabetic patients.

Subclinical autonomic dysfunction occurs very early after the diagnosis of type 2 DM (36). One clinical manifestation of cardiac autonomic neuropathy is decreased exercise tolerance, likely due to reduced HR response and elevated blood pressure during exertion (21). Therefore, it is most likely that autonomic nervous pathway alterations contributed to the reduced HR response and a higher blood pressure increase during submaximal exercise testing in the group of patients with type 2 DM.

Conclusion

The patients with coronary artery disease and type 2 diabetes mellitus exhibit reduced physical capacity compared to the expected values, even with satisfactory glycemic control. The analysis demonstrated that the fasting morning glucose is a significant factor that negatively affects the exercise stress test results. These findings emphasize the importance of optimizing metabolic control, particularly the fasting glucose levels, to improve physical performance and reduce the overall cardiovascular risk in this population of patients.

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Table 1. **Characteristics of the study groups.**

	Total		Female		Male	
	n	(%)	n	(%)	n	(%)
I	40	44.5	23	25.5	17	19.0
II	30	33.5	14	15.5	16	18.0
III	20	22.0	12	14.0	8	8.0
Total	90	100.0	49	55.0	41	45.0
Average age (years)	58.8±6.49		58.8±5.48		58.7±7.7	

NS for all parameters

Table 2. **Lipid risk factors for atherothrombotic diseases**

	With DM	Without DM	Total
triglycerides	2.88±1.0**	1.6±0.7	2.62±1.05
total cholesterol	6.2±1.3	5.8±1.2	6.09±1.36
LDL-cholesterol	3.8±1.1	3.7±0.8	3.81±1.16
HDL-cholesterol	1.2±0.33	1.3±0.22	1.22±0.33

**p<0.01

Table 3. **Indicators of myocardial systolic function in patients with DM type 2**

	sa DM	bez DM	ukupno
Sd	12.07±2***	10.20±1.86	11.26±2.13
EDD	49.78±6.63*	45.42±11.24	47.28±9.65
PWd	11.77±1.4***	10.26±1.19	11.13±1.49
Ss	15.26±2.33**	13.68±1.75	14.62±2.22
ESD	33.63±6.49	32.95±5.76	33.24±6.15
PWs	15.1±1.48**	14.29±1.58	14.76±1.55
EF	56±9***	62.56±7.05	58.71±8.78
FS	29.55±6.27***	33.72±5.35	31.41±6.21

*p<0.05; **p<0.01; ***p<0.001

Table 4. **Stress test parameters in CAD patients in relation to the existence of DM.**

	With DM	Without DM	Total
SF pre	71.31±8.92	70.48±5.39	71.01±7.52
sisTA pre	146.47***	131.4±5.3	140.08±14.45
dijTA pre	89.11±8.65***	83±5.77	86.41±8.08
SF max	129.41±21.17	140.28±13.48**	134.2±18.85
sisTA max	174.26±13.87*	168.84±13.29	171.51±13.77
dijTA max	105.58±7.25	109.56±11.5*	107.31±9.34
SF/1min	114.79±19.8	121.8±13.99*	117.96±17.71
sisTA/1min	160.38±11.64***	145.2±8.22	154.01±12.65
dijTA/1min	94.55±6.98	94±8.16	94.25±7.35
DP pre	10.37±1.21	9.26±0.86	9.91±1.19
DP max	21.61±4.45*	23.68±3.74	23.09±4.13
DP/1min	18.41±3.49	17.76±2.71	18.18±3.17
HRR	14.61±6.22***	18.48±5.83	16.23±6.26
HR reserve	0.65±0.22***	0.77±0.13	0.7±.19
TA drop	13.88±5.31***	22.64±6.71	17.46±7.33
test duration	6.61±2.97***	8.3±2.12	7.32±2.73
max W	61.76±24***	89±20.51	73.33±25.9

* p<0.05; ** p<0.01; *** p<0.001.

Table 5. **Correlation between the glycoregulation parameters and the stress test parameters in CAD and type 2 DM.**

	HbA1c	glycemia
SF pre	-0.025	0.041
sisTA pre	0.193	0.223
dijTA pre	0.225	0.286
SF max	0.048	0.058
sisTA max	0.249	0.228
dijTA max	0.148	0.288
SF/1min	0.062	0.096
sisTA/1min	0.292	0.234
dijTA/1min	0.159	0.236
DP pre	0.155	0.28
DP max	0.147	0.137
DP/1min	0.179	0.176
HRR	-0.037	-0.11
HR reserve	0.176	0.048
TA drop	0	0.082
test duration	0.271	0.344*
max W	0.17	0.254

* $p<0.05$; ** $p<0.01$.