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# Clinical evaluation of oxidative stress in patients with diabetes mellitus type II – impact of acute exercise

## Uticaj fizičke aktivnosti na kliničku procenu oksidativnog stresa kod bolesnika sa dijabetesom melitusom tip 2

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**Abstract**

**Background/Aim.** Exercise is a well recognized model of oxidative stress and, also, an important tool in diabetes management. The aim of our study was to evaluate oxidative stress in patients with diabetes mellitus type 2 and to determine influence of acute exercise training on the investigated parameters. **Methods.** To evaluate oxidative stress in the patients, we determinated following parameters: triglycerides (TG), total cholesterol, low density lipoprotein cholesterol (LDL), oxidized LDL cholesterol (Ox LDL), superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), plasminogen activator inhibitor (PAI) which were measured at rest and immediately after the acute bout of cardiopulmonary exercise cycle-ergometer test. **Results.** In basal condition, diabetic patients compared to controls have significant higher values of TG (3.12 ± 1.09 *vs* 1.74 ± 0.9 mmol/L, $p < 0.01$), Ox LDL (84.73 ± 16.90 *vs* 79.00 ± 29.26 mmol/L, $p < 0.05$) and SOD enzyme activity (913.38 ± 120.36 *vs* 877.14 ± 153.18 U/g Hb, $p < 0.05$). During the acute exercise test, there was significant increase of Ox LDL in both the study patients (from 84.73 ± 16.90 to 92.33 ± 23.29 mmol/L, $p < 0.05$) and in the control group (from 79.00 ± 29.26 to 89.30 ± 29.07 mmol/L, $p < 0.05$). SOD activity was significantly increased in both groups during exercise, in diabetic patients from 913.38 ± 120.36 to 921.50 ± 130.03 U/gHb, $p < 0.05$, and in the controls from 877.14 ± 153.18 to 895.00 ± 193.49, U/gHb, $p < 0.05$. GSH-Px activity was significantly increased only in the diabetic patients after the acute exercise (from 45.04 ± 11.19 to 51.81 ± 15.07 U/gHb, $p < 0.01$), but not in the controls (from 44.63 ± 13.73 to 43.97 ± 25.97 U/gHb, $p$ = ns). PAI significantly decreased during the exercise test, only in the healthy subjects (from 2.60 ± 0.35 to 2.22 ± 0.65, $p < 0.05$). Type 2 diabetic patients with complications had only significant increase in GSH-Px activity (from 47.10 ± 7.37 to 54.52 ± 11.97 U/gHb, $p < 0.01$). **Conclusion.** Elevated Ox LDL, SOD and GSH-Px levels are associated with acute exercise in type 2 diabetic patients. We suggest that it could be a compensatory mechanism to preventing free radicals tissue damage. We hypothesize that a physical training program induces an enhance of muscular and liver antioxidant enzymes activity and reduces oxidative stress. Further studies are needed to explore the relationship between exercise and antioxidant system in diabetic patients with and without complications.

**Key words:**
**diabetes mellitus, type 2; oxidative stress; oxidoreductases; exercise.**

**Apstrakt**

**Uvod/Cilj.** Poznato je da fizička aktivnost prouzrokuje oksidativni stres, ali i da predstavlja važan element u tretmanu dijabetesa. Cilj ove studije bio je da se proceni oksidativni stres kod bolesnika sa dijabetes melitusom tip 2 i da se ustanovi uticaj fizičke aktivnosti na ispitivane parametre. **Metode.** Kako bi se izvršila evaluacija oksidativnog stresa kod bolesnika, određivani su sledeći parametri: trigliceridi (TG), ukupni holesterol, lipoproteini male gustine (LDL), oksidisani LDL holesterol (Ox LDL), superoksid dismutaza (SOD), glutation peroksidaza (GSH-Px), inhibitor aktivatora plazminogena (PAI). Parametri su mereni u vreme mirovanja i odmah nakon aerobnog treninga (ergometrijskog testa). **Rezultati.** U bazalnim uslovima bolesnici oboleli od dijabetesa, u odnosu na kontrolnu grupu imali su značajno više vrednosti TG (3,12 ± 1,09 prema 1,74 ± 0,9 mmol/L, $p <$ 0,01), Ox LDL (84,73 ± 16,90 prema 79,00 ± 29,26 mmol/L, $p < 0,05$) i aktivnosti SOD (913,38 ± 120,36 prema 877,14 ± 153,18 U/g Hb, $p < 0,05$). Tokom ergometrijskog testa uočen je statistički značajan porast koncentracije Ox LDL u ispitivanoj grupi bolesnika (sa 84,73 ± 16,90 na

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92,33 ± 23,29 mmol/L, $p < 0,05$) i u kontrolnoj grupi (sa 79,00 ± 29,26 na 89,30 ± 29,07 mmol/L, $p < 0,05$). Uočeno je statistički značajno povećanje SOD aktivnosti u obe grupe tokom vežbe: kod obolelih od dijabetesa sa 913,38 ± 120,36 na 921,50 ± 130,03 U/gHb, $p < 0,05$, i u kontrolnoj grupi sa 877,14 ± 153,18 na 895,00 ± 193,49 U/gHb, $p < 0,05$. Do statistički značajnog povećanja GSH-Px aktivnosti došlo je kod obolelih od dijabetesa nakon fizičke aktivnosti (sa 45,04 ± 11,19 na 51,81 ± 15,07 U/gHb, $p < 0,01$), ali ne i u kontrolnoj grupi (sa 44,63 ± 13,73 na 43,97 ± 25,97 U/gHb, $p$ = ns). Koncentracija PAI statistički je značajno opala tokom ergometrijskog testa samo u kontrolnoj grupi (sa 2,60 ± 0,35 na 2,22 ± 0,65, $p < 0,05$). Oboleli od dijabetesa tip 2 sa postojećim komplikacijama imali su samo značajan porast aktivnosti GSH-Px (sa 47,10 ± 7,37 na 54,52 ± 11,97 U/gHb, $p < 0,01$). **Zaključak.** Povišene vrednosti Ox LDL, SOD i GSH-Px udružene su sa povećanjem fizičke aktivnosti kod bolesnika sa tipom 2 dijabetesa melitusa. Ovakav rezultat mogao bi biti kompenzatorni odgovor organizma u prevenciji oštećenja tkiva od slobodnih radikala. Pretpostavlja se da određeni program fizičke aktivnosti podstiče i pojačava dejstvo antioksidativnih enzima jetre i mišića i smanjuje nivo oksidativnog stresa. Potrebno je uraditi još studija u cilju ispitivanja odnosa između fizičke aktivnosti i antioksidativnog sistema kod obolelih od dijabetesa melitusa sa komplikacijama i bez njih.

**Ključne reči:**
**dijabetes melitus, tip-2; stres, oksidativni; oksidoreduktaze; vežbanje.**

## Introduction

Oxidative stress has been involved in the pathogenic process of a variety of diseases including diabetes mellitus (DM). The products of an oxidative stress could play an important role in diabetic complications which involve micro and macroangiopathic processes through lipid peroxidation (low density lipoprotein oxidation) and the production of advanced glycosylation end-products (AGEs), which are responsible for producing fragmentation, cross-linking and damage of basic structures, carbohydrates, lipids, proteins and DNA [1, 2].

Hyperglycemia leads to metabolic disorders and various complications. An enhanced oxidative stress has been observed in diabetics as indicated by increased free radicals production, lipid peroxidation and diminished antioxidant stress [3, 4]. Oxidative stress, as well as non-enzymic glycosylation, is now considered as a major factor contributing to the extent of chronic diabetes complication. Diabetes produces disturbances of lipid profiles, especially an increased susceptibility to lipid peroxidation, which is responsible for increased incidence of atherosclerosis, a major complication of diabetes mellitus [5, 6]. Experimental and clinical evidence has demonstrated impairment of endothelium function caused by oxidative products in diabetic patients.

Growing evidences indicate that oxidative stress is increased in diabetes due to overproduction of reactive oxygen species (ROS) and decreased efficiency of antioxidant defences [7]. Antioxidant system, which includes enzymic and non-enzymatic components, consists of antioxidant molecules such as glutathione peroxidase (GSH-Px), superoxide dismutase (SOD), and catalase (CAT).

We can provide evidence for oxidative stress by measuring markers of this stress or antioxidant molecules. Many studies have been done with contradictory results about changing levels of antioxidative substances. Unchanged, elevated or decreased levels for SOD and GSH-Px, have been reported in diabetic patients compared to healthy subjects [8–12].

Exercise, paradoxically, is a well recognized model of oxidative stress and also an important therapeutic tool in diabetes management [13]. There is a little evidence about the role of physical exercise as a promoter of oxidative stress and antioxidant status in diabetics. Physical exercise is associated with a significant increase of oxygen uptake both in the whole body level and at skeletal muscle. A small fraction of oxygen (2–5%) is converted into intermediate oxidative products and biochemical changes and tissue damage are produced. Reduced activity of antioxidant system could be a cause of increased oxidative state during exercise. Since physical activity protects against the development of cardiovascular disease (CVD) and modifies risk factors, a regular exercise program seems to be desirable. There is a biochemical paradox: considerable amounts of oxygen are necessary to obtain a good performance and a satisfactory cardiopulmonary status, while an excess of oxygen with altered metabolism could be harmful [13, 14].

In relation to antioxidant enzymes, an increase of SOD and GSH–Px activity has been observed in skeletal muscle, heart and liver during a single bout of acute exercise [15]. It is important that physical training induces an increase of muscular and liver antioxidant enzymes activity, facilitating the removal of reactive oxygen species and the reduction of oxidative stress levels.

The aim of our study was to estimate the oxidative stress and antioxidant status in patients with type 2 diabetes mellitus compared to the control group at rest and during acute physical exercise. We also investigated if there was any difference of changes in antioxidant parameters during exercise test between patients with and without diabetic complications.

## Methods

The study population was consisted of consecutive outpatients from the Endocrinology and Cardiology Departments of the University Clinical Centre "Dr Dragiša Mišović" Belgrade. We evaluated 50 patients with type 2 diabetes mellitus: 20 males, aged 50.47 ± 17.1 and 30 females aged 56.09 ± 15.6 years, and 20 age matched controls. Exclusion criteria were secondary arterial hypertension, coronary artery disease, rhythm disturbances, cerebrovascular disease chronic obstructive lung disorder or severe renal failure. All

patients included were treated with oral antidiabetics. Selection criteria for poor glycemic control was a level of glycosylated hemoglobin (HbA1c) highter than 6.5%.

The patients with DM were divided into groups using several criteria such as the presence of diabetic microangiopathic complications, level of metabolic control and body mass index (BMI).

For providing an objective assessment of exercise capacity and impairment we applied cardiopulmonary exercise cycle ergometer test (Jaeger Oxycon Delta ER – 900). All the study subjects underwent the symptom-limited incremental test protocol with 25 W increment per each 3 minutes. Test was designed to be progressive and incremental in order to elicit the important parameters: $VO_2$ max (mL/min) – maximal $O_2$ uptake; FAI index (%) – maximal $O_2$ uptake compared to predictive value; $VO_2$/kg (mL/kg/min) – uptake related to body weight; VE (L/min) – ventilation per minute; RER – respiratory exchange ratio, anaerobic threshold; T – time to anaerobic threshold (min). Heart rate and rhythm were continuously monitored using a 12 lead electrocardiogram. Blood pressure was measured before each load change. Gas analyses and flow probes were calibrated before each test. Gas exchange data was collected in a breath by breath manner and averaged into 30 – second time periods. All parameters were calculated as highest 30 – second time period recorded before volitional fatigue was reached.

This investigation was approved by the Ethical Committee of the University Clinical Centre "Dr Dragiša Mišović".

Biochemical analyses included lipid parameters: triglycerides (TG), total cholesterol, high density lipoprotein (HDL) and low density lipoprotein (LDL) cholesterol, oxidized LDL cholesterol (OxLDL); glucose, glycosilated hemoglobin (HbA1c), plasminogen activator inhibitor type-1 (PAI-1), and antioxidant enzymes: SOD and GSH-Px.

Triglycerides were measured with an enzymatic colorimetric method-Elitech.

LDL-cholesterol was calculated according to the Friedwald formula.

Oxidized LDL-cholesterol was measured by Elisa method (Mercodia).

HbA1c was measured by immunoturbidometric method using commercially available kit (Roche). Hitachi 902 analyser system was used. Glucose were determined using GOD-PAP method.

Plasminogen activator inhibitor type 1 was measured by spectrophotometric method using commercially kit (Behring).

The activity of SOD was measured from serum by testing the inhibition degree of tetrazolium salt oxidation reaction at 500 nm sample with a commercially available kit (Randox Laboratories, kit Ransod superoxide dismutase). The coefficient of variability between assays was 4.2%.

The erythrocyte activity of GSH-Px was determined by a commercial kit (Ransel glutathione peroxidase, Randox Laboratories) in erythrocytes at 340 nm by measuring the decrease of NADPH absorbency. The coefficient of variability between assays was 4%.

All data were expressed as mean ± standard deviations (SD).

Statistical analysis was done by a statistical program called Statistical Package for the Social Sciences Program (SPSS). Comparisons of all measurements were made with paired Student's *t*-test and Mann-Whitney *U*-test. Simple and multiple linear regression analysis determined all correlations.

The *p* values were considered significant at $p < 0.05$.

## Results

All demographics and biochemical parameters are shown in Table 1. The mean duration of diabetes was 7.18 years, body mass index (BMI) was 27.7 ± 7.3 kg/m$^2$ in the diabetic group and 27.10 ± 8.1 in the controls. Twenty patients were with poor metabolic control (HbA1c: 8.14 ± 1.4%) and 20 were well regulated (HbA1c: 3.54 ± 0.8%). All diabetic patients were divided into two groups according to the occurrence of diabetic complications (29 without complications and 21 with complications).

HbA1c ($p < 0.01$) was significantly higher at rest in the diabetic patients compared to the controls.

Table 2 shows that $VO_2$ peak was significantly greater in the healthy group ($p < 0.01$) and VE was significantly higher in the diabetic group ($p < 0.05$).

**Table 1**

**Clinical and biochemical parameters in all subjects at rest**

| Parameters | Diabetic patient (n = 50) | Controls (n=20) |
|---|---|---|
| Female/Male | 30/20 | 10/10 |
| Body mass index (kg/m$^2$) | 27.27 ± 7.3 | 27.16 ± 8.1 |
| Duration of diabetes (years) | 7.18 ± 1.1 | |
| Glycosilated hemoglobin – HbA1c (%) | 8.03 ± 2.95* | 5.34 ± 0.59 |

*$p < 0.01$

**Table 2**

**Values of cardiopulmonary parameters in the patients with Diabetes mellitus and the controls**

| Variable | Diabetic patients | Controls |
|---|---|---|
| RER max (arbitary units) | 1.21 ± 0.25 | 1.14 ± 0.20 |
| VO2 peak (mL/min) | 21.09 ± 4.40 | 26.35 ± 10.53† |
| VE (L/min) | 57.37 ± 17.15 | 52.00 ± 9.89* |
| T-time (min) | 11.23 ± 2.27 | 11.05 ± 1.48 |

*$p < 0.05$; †$p < 0.01$; RER max – maximal respiratory exchange ratio; VO2 peak – peak oxygen uptake; VE – ventilation per minute; T – time to anaerobic threshold in minutes

Table 3 shows that the patients with poor metabolic control had significantly increased levels of Ox LDL, SOD and GSH-Px after exercise. After exercise in both groups (control and diabetics) significantly higher levels of Ox LDL and SOD ($p < 0.05$) were found. GSH-Px was significantly higher only in patients with DM type 2 after exercise ($p < 0.01$). PAI-1 significantly decreased during the exercise test only in healthy subjects ($p < 0.05$), but there was no change in the patients with DM.

Our results showed that after the acute exercise, Ox LDL and SOD activity were significantly increased only in type 2 diabetic patients without complications ($p < 0.01$) (Table 4). In patients with diabetic complications we found a decreased value of Ox LDL and SOD activity after the exercise test, but the difference was not statistically significant. GSH-Px activity was higher after acute exercise in the both groups of diabetic patients (with and without complications) ($p < 0.01$).

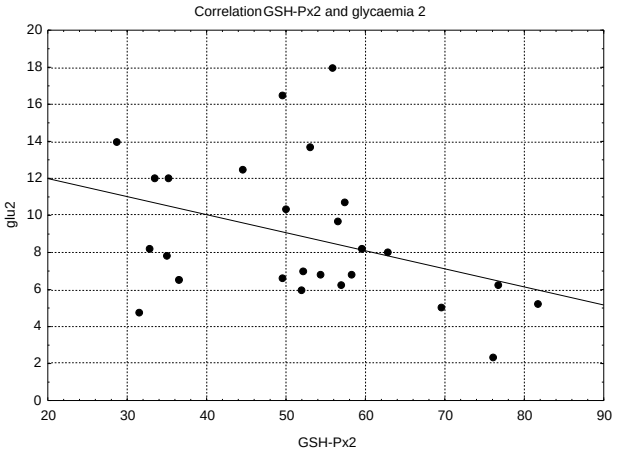


**Fig. 1 – Correlation analysis of GSH-Px and glycemia values in diabetic patients**

**Table 3**

**Values of biochemical and antioxidant parameters before and after the exercise in patients with Diabetes mellitus with poor control and controls subjects**

| Parameters | Controls | | Diabetic patients with poor control | |
|---|---|---|---|---|
| | rest | exercise | rest | exercise |
| Glycaemia (mmol/L) | 5.26 ± 0.86 | 5.35 ± 0.96 | 9.79 ± 4.25 | 7.71 ± 3.83† |
| TG (mmol/L) | 1.74 ± 0.9 | 1.98 ± 1.0 | 3.12 ± 1.09 | 3.13 ± 1.74 |
| LDL (mmol/L) | 3.61 ± 1.56 | 3.55 ± 1.55 | 3.58 ± 0.72 | 3.84 ± 0.97 |
| Total cholesterol (mmol/L) | 5.57 ± 1.67 | 5.9 ± 1.88 | 5.63 ± 0.98 | 5.95 ± 1.12 |
| Ox LDL (mmol/L) | 79.00 ± 29.26 | 89.3 ± 29.07* | 84.73 ± 16.9 | 92.33 ± 23.29* |
| SOD (U/g Hb) | 877.14 ± 153.18 | 895.0 ± 193.49* | 913.38 ± 120.36 | 921.50 ± 130.03* |
| GSH-Px (U/gHb) | 44.63 ± 13.73 | 43.97 ± 25.97 | 45.04 ± 11.19 | 51.81 ± 15.07† |
| PAI-1 (mg/mL) | 2.60 ± 0.35 | 2.22 ± 0.65* | 2.97 ± 1.08 | 2.99 ± 1.02 |

*p < 0.05; †p < 0.01 vs values before the acute exercise
TG – triglycerides, LDL – low density lipoprotein cholesterol, OxLDL – oxidized LDL, SOD – superoxide dismutase, GSH-Px – glutathione peroxidase, PAI – plasminogen activator inhibitor.

**Table 4**

**Values of biochemical and antioxidant parameters before and after the exercise in diabetic patients with and without complications**

| Parameters | Diabetic patients without complications (n = 29) | | Diabetic patients with complications (n = 21) | |
|---|---|---|---|---|
| | rest | exercise | rest | exercise |
| TG (mmol/L) | 3.78 ± 1.74 | 3.85 ± 1.96 | 1.80 ± 0.58 | 1.82 ± 0.88 |
| LDL (mmol/L) | 3.34 ± 0.77 | 3.44 ± 0.92 | 3.74 ± 0.66 | 4.03 ± 0.98 |
| Ox LDL (mmol/L) | 87.86 ± 16.23 | 107.4 ± 7.82† | 80.72 ± 22.05 | 78.5 ± 29.32 |
| SOD (U/g Hb) | 895.0 ± 162.85 | 929.3 ± 147.02† | 917.0 ± 66.8 | 915.5 ± 105.47 |
| GSH-Px (U/gHb) | 43.60 ± 13.24 | 49.54 ± 17.84† | 47.10 ± 7.37 | 54.52 ± 11.97† |
| PAI-1 (mg/mL) | 2.78 ± 1.25 | 3.00 ± 0.95* | 3.10 ± 1.21 | 2.96 ± 0.96 |

*$p < 0.05$; †$p < 0.01$
TG – triglycerides, LDL – low density lipoprotein cholesterol, OxLDL – oxidized LDL, SOD – superoxide dismutase, GSH-Px – glutathione peroxidase, PAI – plasminogen activator inhibitor.

Correlation analysis shown in Figure 1 revealed a significant negative correlation between GSH-Px and glycemia ($r = -0.6336$, $p < 0.01$) in diabetic patients. There was also significant correlation between GSH-Px and TG ($r = -0.5899$, $p < 0.05$), GSH-Px and PAI-1 ($r = -0.5337$, $p < 0.05$) and Ox LDL and PAI-1 after exercise ($r = 0.524$, $p < 0.05$).

**Discussion**

The oxidation of LDL cholesterol is considered a key event in the initiation of arteriosclerosis. In our study Ox LDL was significantly increased in diabetes mellitus type 2 in basal conditions compared to the control group. Diabetics

with complications had significantly lower level of Ox LDL compared to DM patients without complications at rest. We found changes in LDL cholesterol after the exercise test in the both group (diabetics and controls). But, significantly higher level of Ox LDL was seen only in the diabetics without complications after the exercise test. Positive correlation between Ox LDL and PAI-1 after the exercise was found. Our results are consistent with those of other studies on oxidative stress [13, 14]. It has been proposed that oxidative stress may be associated with the pathogenesis of the complications of diabetes mellitus type 2, particularly vascular disease [15].

Hyperglycemia is a main stimulus to overproduce oxidative species or free radicals in the plasma of diabetic patients through the polyol pathway and protein glycosylation.

There are reports on both increased and decreased SOD and GSH-Px activity in diabetic patients at rest [10, 16], while a few studies could not find any significant changes between diabetics and healthy subjects [17, 18].

In our study we observed an increase in SOD activity in DM type 2 patients compared to the controls, particularly those diabetics with complications. This finding is in accordance with that of Palanduz et al [19]. In relation to acute exercise, an increase of SOD was observed in type 2 diabetic patients, but only in the group without complications.

There was no significant change in GSH-Px activity in basal condition, in both groups (diabetics and controls). However, we found a decrease in GSH-Px activity in diabetic patients with poor metabolic control compared to those well regulated, which is in accordance with some studies [19]. GSH-Px was increased only in the group of diabetic patients with complications. An increase of GSH-Px activity was found in all diabetic patients (with and without complications) during a single bout of acute exercise which is in accordance with the literature data [13]. We found no changes in the GSH-Px activity after the exercise test in the control group.

The possible explanation for this finding is that the rise in some enzyme activities in the patients with diabetes mellitus type 2, particularly with complications, could be a compensatory response of the body to prevent tissue damage.

Our results suggest that there seems to be an imbalance between plasma oxidant and antioxidant systems in patients with type 2 diabetes mellitus. We have found elevated concentrations of PAI-1 in the plasma only in patients with diabetic complications, in basal condition. An acute exercise significantly decreased the level of PAI-1 only in the healthy subjects, but not in the diabetic patients. We hypothesized that an increased PAI-1 may contribute to acceleration of atherosclerosis in this condition characterised by insulin resistance [10].

The evidence of a high oxidative profile during exercise in diabetes type 2 has not been directly related to an increase risk of CVD [20]. An increase of antioxidant enzyme activity, related to the intensity of exercise after different levels of training has also been described [21]. We summarized that acute exercise induces a sudden increase of oxidative stress levels, an effect well counterbalanced in both type 2 diabetic patients and the healthy subjects. After a physical training program an improvement on the counterbalance of the oxidative stress could be expected [22, 23].

## Conclusion

Elevated Ox LDL, SOD and GSH-Px levels are associated with acute exercise in type 2 diabetic patients.We suggest that it could be a compensatory mechanism against free radicals tissue damage. We hypothesize that a physical training program induces an enhance of muscular and liver antioxidant enzymes activity and reduces oxidative stress.

Further human studies are needed to explore the role of lipid peroxidation and altered antioxidant defence mechanisms in patients with DM, effect of exercise, and the occurrence of complications in these patients.

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