DOI: https://doi.org/10.2298/SARH180828028P
UDC: 616.379-008.64

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

The synergistic action of antioxidative enzymes – correlations of catalase and superoxide dismutase in the development and during the treatment of type 2 diabetes

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SUMMARY

Introduction/Objective The wider literature review of analysis in levels of catalase (CAT) or superoxide dismutase (SOD) enzymes in type 2 diabetes mellitus (T2DM) patients shows no pronounced consistency. We have assumed that the onset of diabetes does not significantly change individual quantities of these enzymes, but instead it changes the relationship of these enzymes.

Methods The study consisted of four groups (n = 30 for each group): obese individuals with disturbed glucose metabolism (subjects with newly diagnosed T2DM) before and after metformin treatment initiation, obese subjects with normal glucose tolerance (NGT) and a control group of healthy normal weight subjects. Appropriate anthropometric measurements and laboratory tests of biochemical parameters and antioxidative enzymes were carried out in all participants.

Results Our study has confirmed that correlation of enzymes CAT and SOD is significantly changed in patients with newly diagnosed T2DM, and that it can be restored by reestablishment of glucose homeostasis with adequate antidiabetic treatment.

Conclusion The applied therapy restores the dynamic balance of CAT and SOD, mainly through the reintegration of the new equilibrium in the enzyme system after achieving better glycemic control. These conclusions are only valid in the initial stages of T2DM treatment.

Keywords: antioxidative enzymes; obesity; glucose metabolism; metformin

INTRODUCTION

Oxidative stress is one of the important factors contributing to the pathogenesis of the large number of diseases such as obesity, diabetes, atherosclerosis, inflammatory, malignant and certain neurodegenerative diseases [1, 2]. The enzyme superoxide dismutase (SOD) protects the cells from superoxide anion radicals entering into the chemical reaction and turning these radicals into hydrogen peroxide, which is further detoxified to H_2O in the lysosomes through the enzyme catalase (CAT), or in the mitochondria through the enzyme glutathione peroxidase (GPX) [3].

Hyperglycemia, increased intake of free fatty acids and excessive exposure to ultraviolet radiation are leading to increased oxidative stress, but the role of antioxidant enzymes is still not fully clarified [4, 5]. Previous studies came to conflicting results regarding the activities of these antioxidant enzymes in diabetic patients. Levels of SOD in diabetic patients were found to be significantly elevated, significantly reduced [6, 7], or unchanged in comparison to the control group [8]. Similarly, other authors concluded that CAT level is significantly higher, significantly lower, or is the same as in individuals from the control group [9, 10, 11].

For the purpose of clarifying the role of some of antioxidant enzymes, we studied the functional association between glycemia and CAT and SOD function. Although number of previous studies already assessed levels of CAT and SOD in type 2 diabetes (T2DM) patients, correlation of these two enzymes has rarely been the subject of previous researches. The principal aim of this study is to examine functional association of these two enzymes, which may be crucial for the optimal antioxidative protection achievement. Secondary, this study aims to evaluate the possible influence of the metformin therapy on these enzymes in diabetic patients.

Received • Примљено: August 28, 2018
Revised • Ревизија: January 14, 2019
Accepted • Прихваћено: March 5, 2019
Online first: March 29, 2019

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Table 1. Parameters and distributions (mean value and standard deviation) for SOD, CAT, fasting and postprandial 2 h glucose (G0H and G2H) in study groups

	SOD (U/g) (Figure 1)	CAT (U/mL) (Figure 2)	G0H (mmol/l) (Figure 3)	G2H (mmol/l)
Control group	N (303.28; 57.73)	N (-141.24; 47.13)	N (4.54; 0.35)	N (4.952; 0.654)
Obese	N (247,05; 55.25)	N (-147.35; 37.61)	N (5.06; 0.54)	N (5.528, 0.965)
T2DM group before the treatment	X (283.72; 122.35)	N (-140.62; 39.92)	X (9.48; 3.72)	X (12.74; 5.42)
T2DM group after the treatment	U (238.82; 35.91)	U (-128.95; 35.91)	lnN (7.42; 2.45)	lnN (9.307; 3.218)

Types of distribution (N – normal; U – uniform; lnN – lognormal; X – undefined); T2DM – type 2 diabetes mellitus; SOD – superoxide dismutase; CAT – catalase; G0H – fasting glucose; G2H – postprandial 2 h glucose

METHODS

The study was conducted at the Clinic for Endocrinology, Diabetes and Metabolic Disorders, Clinical Center of Vojvodina, Novi Sad, Serbia and it enrolled 90 age- and sex-matched individuals who gave their written consent prior to participation in the study. The study was carried out in accordance with Helsinki declaration and it was approved by the local ethical committee.

Body mass index (BMI) was calculated as weight (kg) divided by height squared (m) (kg/m^2). We excluded individuals with all chronic conditions that affect the oxidative status of the organism.

Subjects were divided in the following groups:

1) Thirty obese individuals with normal glucose tolerance and normal distribution of BMI (37.37 ± 6.11 kg/m^2);

2) Thirty obese individuals with newly diagnosed T2DM and normal distribution of BMI on the baseline (34.41 ± 4.68 kg/m^2) analyzed before and during metformin therapy;

3) Thirty healthy normal weight control individuals with a normal distribution of BMI (23.34 ± 3.12 kg/m^2).

The values of glycemia, CAT and SOD in Group 2 were analyzed before and three months after the initiation of metformin therapy (1,000 mg per day in all subjects).

Blood was sampled for the analysis of various parameters. Fasting and two-hour postprandial glycose were determined by enzymatic methods. Determination of parameters of oxidative stress was performed after the following preparation of the blood sample: 0.5 mL of heparinized blood was centrifuged for 10 minutes at 3,000 rotations per minute. After the plasma separation, red blood cells were washed four times with 3 mL of saline followed by stirring and centrifuging for 10 minutes at 3,000 rotations per minute. Washed red blood cells were supplemented with 2 mL of distilled water. The obtained hemolysate was divided into two samples for analysis of CAT and SOD in red blood cells. The analysis of CAT was carried out by monitoring of the fall in absorbance at 240 nm in a solution of hydrogen peroxide with phosphate buffer. The obtained values were expressed as U/mL. The minus sign ahead of the value was (can be) ignored. The analysis of SOD of red blood cells was performed by enzymatic kinetic method using commercial BIOREX kit. The obtained values were expressed as U/g of hemoglobin.

RESULTS

Statistical analysis of parameters and distribution superoxide dismutase, catalase and blood glucose

In Table 1, values are given (mean value and standard deviation) for parameters SOD, CAT, fasting and postprandial 2 h glucose (G0H and G2H) in study groups.

For the established normal distributions of SOD in the control group and in the group of obese individuals, t-test confirms a significant difference in mean values of this enzyme ($t = 3.53$, $p = 0.0014$). Uniform distribution in T2DM group refers to the systematic change of SOD after the treatment.

For the established normal distributions of CAT in the control group, the group of obese individuals and in the T2DM group before the treatment, using t-test founds no significant changes in the mean value of CAT.

Significant change in the structure of distribution of CAT in the T2DM group after the treatment also refers to the systematic change and to absolute differences in CAT with complementary groups. This difference is caused by treatment.

For the established normal distributions of G0H in the control group and in the group of and obese individuals, using t-test confirms a significant difference in mean values of G2H ($t = -3.09$, $p = 0.0044$).

The difference between mean values of G0H ($Z = 4.31$; $p = 0.000016 < 0.05$) and G2H ($Z = 3.31$; $p = 0.000856 < 0.05$) in the T2DM group before and after the treatment is significant (Signum test). Therapy had a significant effect.

Correlations of superoxide dismutase and catalase

In order to determine the nature of the oxidative stress, the starting point was the relationship between SOD as the independent variable, and CAT as the dependent variable. The following equations of linear regression and correlation coefficients were established and given in Figure 4.

It should be noted that analytical parameters of the regression line, i.e. free member, and the coefficient for the independent variable are very close (-160.6 for control group and -163.4 for obese individuals).

However, in the group of patients with newly diagnosed diabetes systematic change in the relation between SOD and CAT is occurring. The value of the free member (-90.07) changes drastically for about 44% (from initial ≈-160) while the coefficient for the independent variable changes the sign (-0.1782). Dependent systematic change

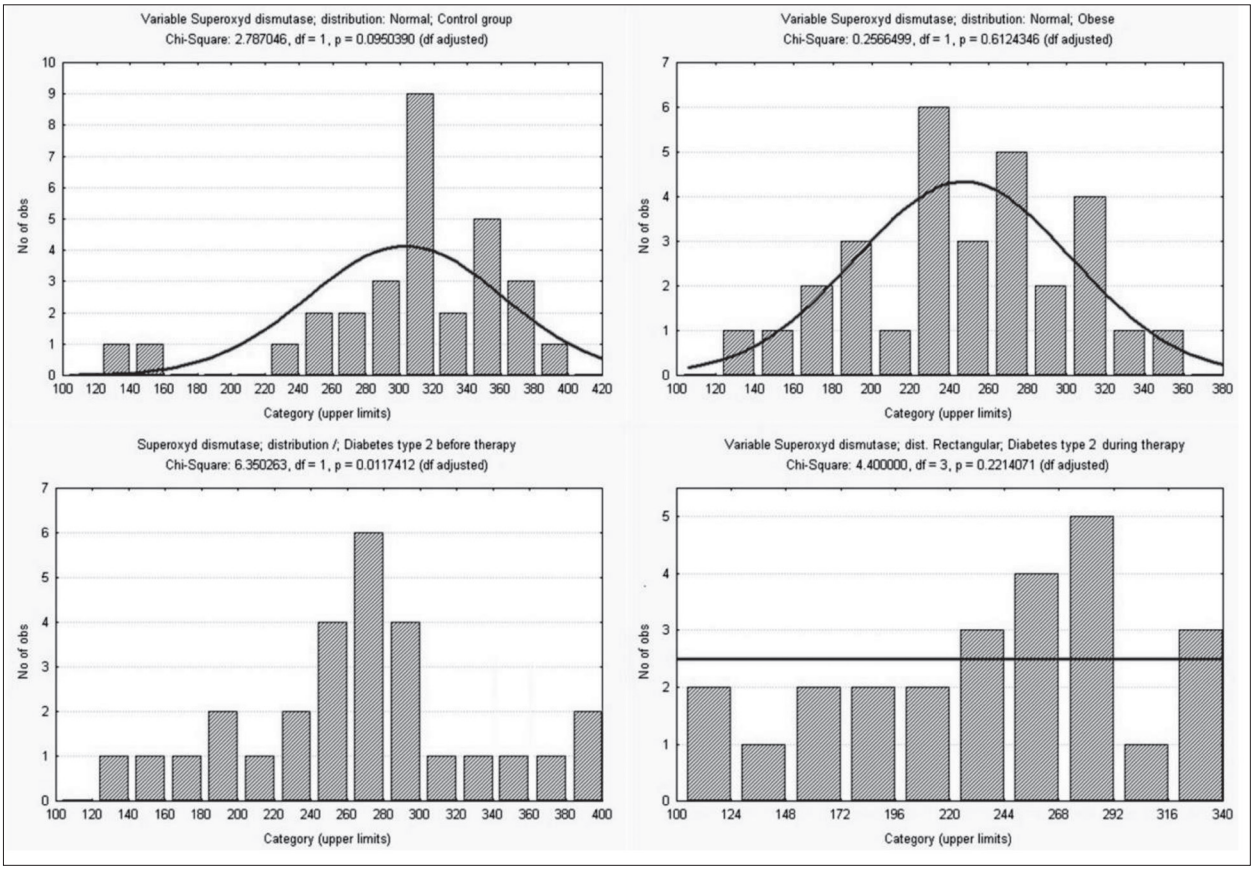

Figure 1. Distribution and verification of superoxide dismutase in control group, group of obese individuals without diabetes, type 2 diabetes patients at the baseline and after the treatment period

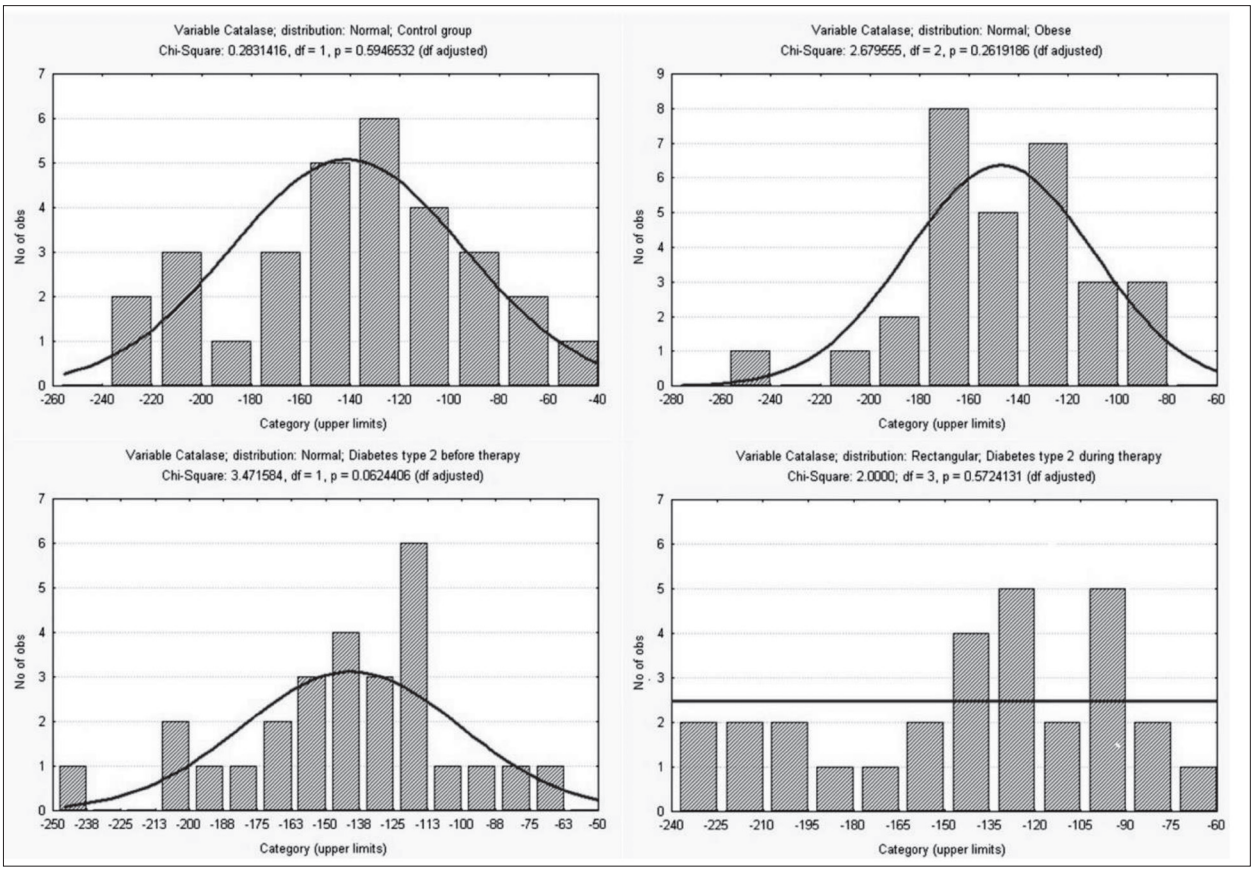

Figure 2. Distribution and verification of catalase in control group, group of obese individuals without diabetes, type 2 diabetes patients at the baseline and after the treatment period

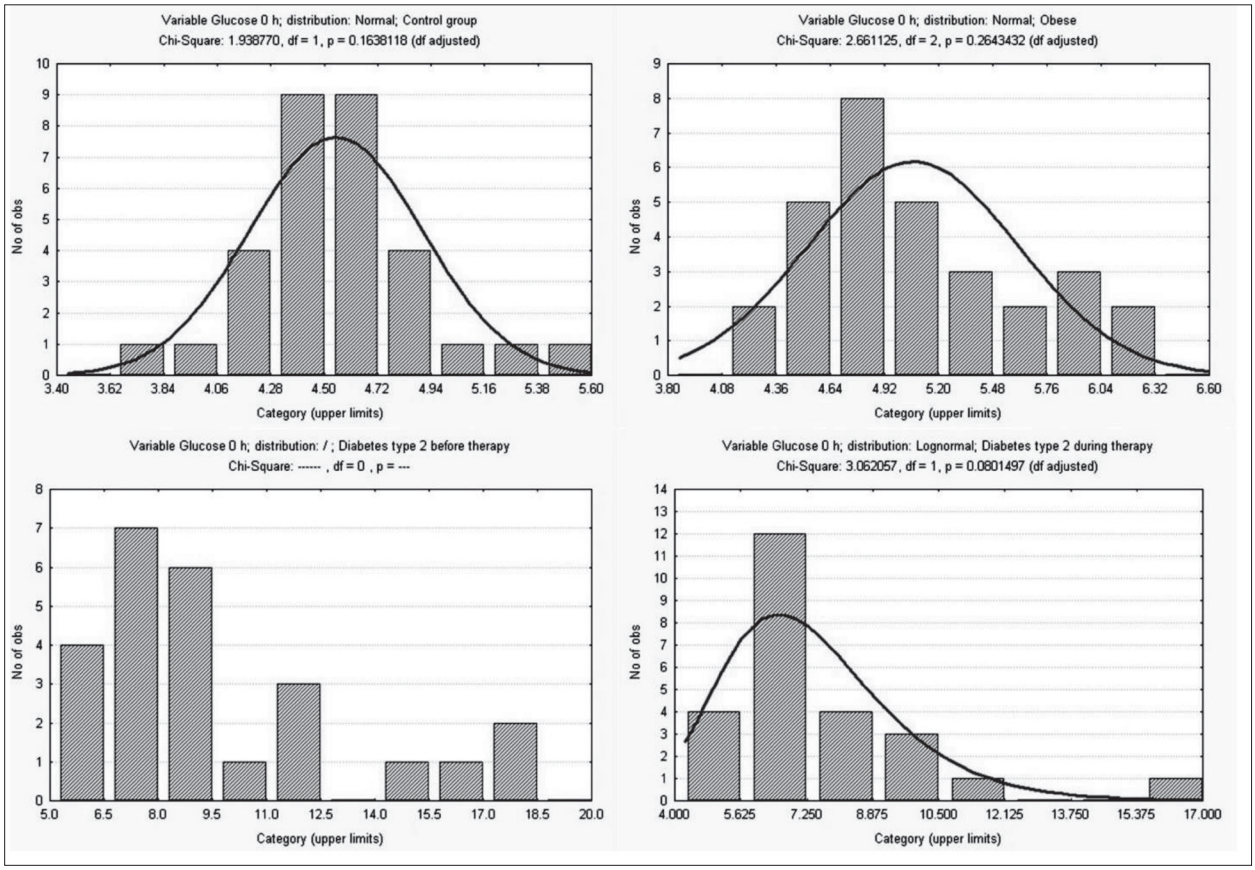

Figure 3. Distribution and verification of fasting glucose in control group, group of obese individuals without diabetes, type 2 diabetes patients at the baseline and after the treatment period

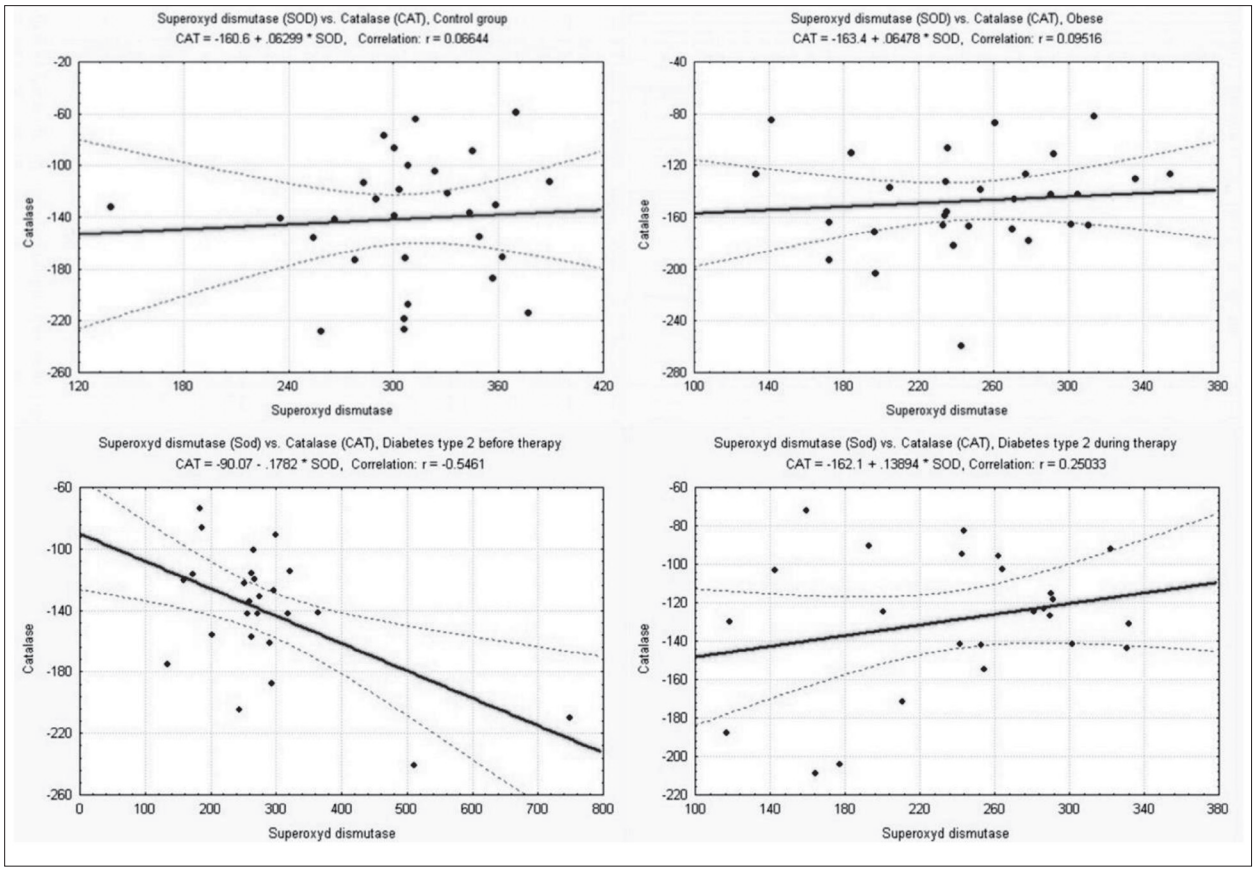

Figure 4. Equations, correlation coefficients, graphical display of lines of linear regressions of superoxide dismutase and catalase in control group, group of obese individuals without diabetes, type 2 diabetes patients at the baseline and after the treatment period

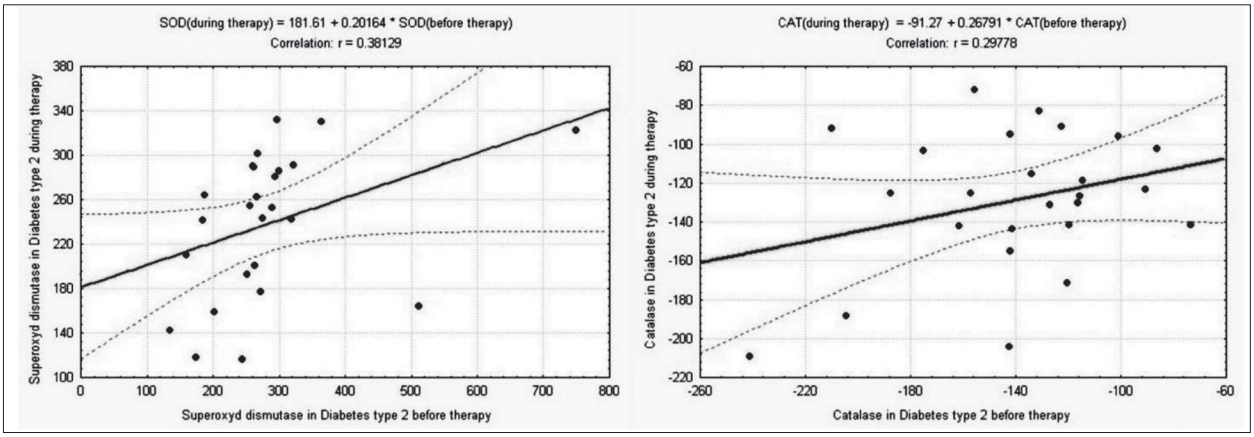

Figure 5. Effects of metformin therapy on mutual relationships between superoxide dismutase and catalase values

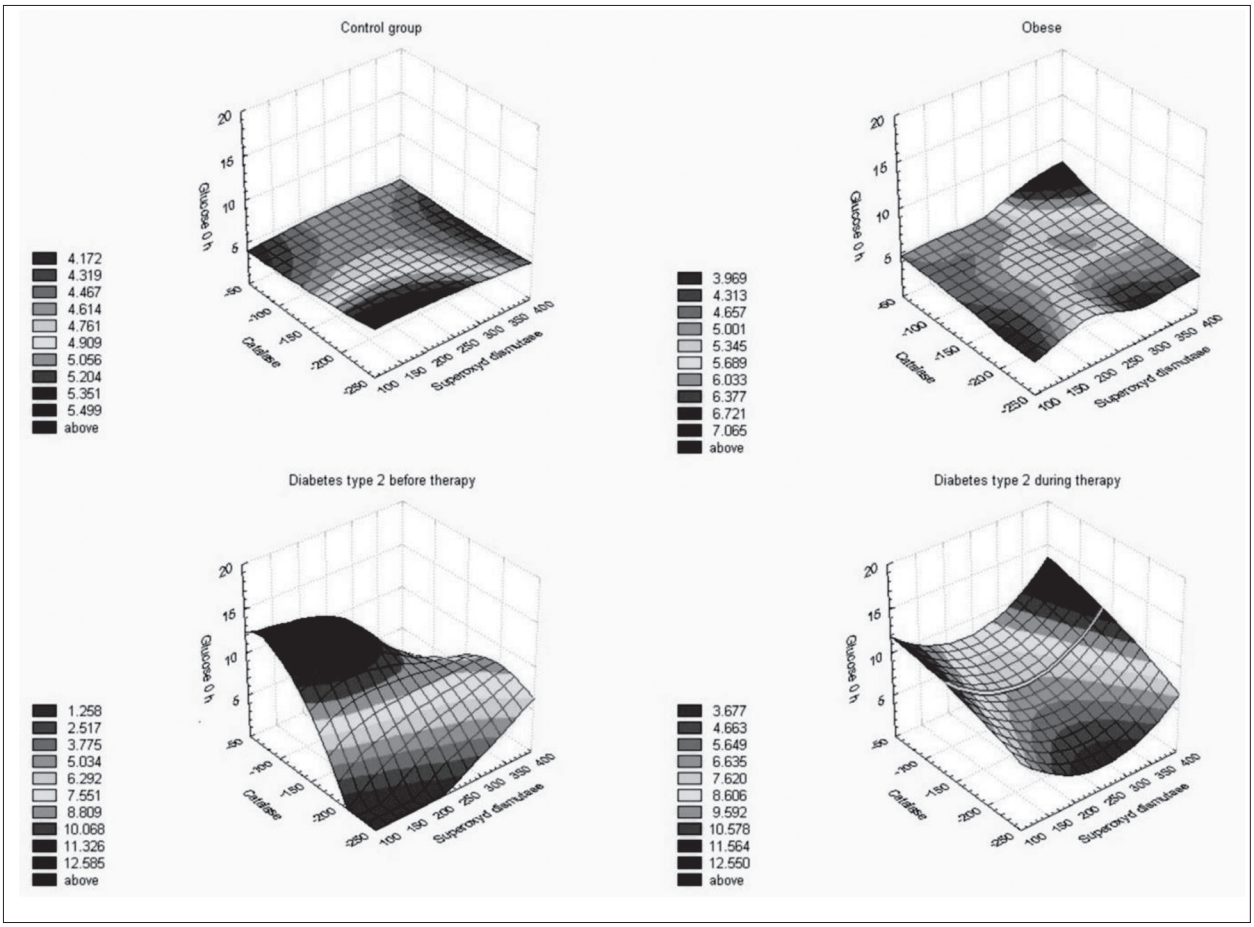

Figure 6. Two-dimensional G0H as dependent variable in the function of independent variables superoxide dismutase and catalase in control group, group of obese individuals without diabetes, type 2 diabetes patients at the baseline and after the treatment period

describes and validates the negative correlation coefficient (r = -0.5461).

The applied therapy in patients with diabetes returns the correlation parameters of SOD and CAT close to established among the control group and the group of obese individuals. The value of the free member of the regression line (-162.1) is close to the value in the control group and in the group of obese individuals (≈-160), so therapy eliminated difference of 44%, which was the result of the diabetes onset. The coefficient of the independent variable is positive again (+0.1389). The value of correlation coefficient of the enzyme after the treatment (r = +0.2503) points out that "moderate" systematic association in diabetes is reduced to "low" after the treatment.

The biggest difference in changes in values of correlation coefficients occurs in the group of T2DM patients before and after the treatment. Pearson's test declares this change as significant p = 0.0011, i.e. therapy significantly changes linear relationships of SOD and CAT. A more detailed insight into the effect of therapy linear regressions of SOD and CAT in T2DM group before and after the treatment is given in Figure 5. Directly proportional

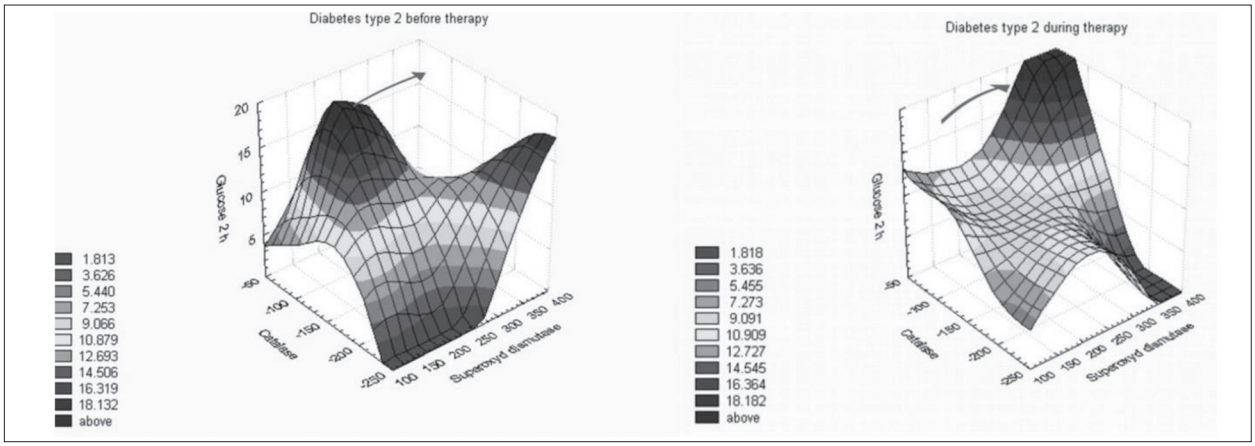

Figure 7. Two-dimensional postprandial 2-hour glucose as dependent variable in the function of independent variables superoxide dismutase and catalase in type 2 diabetes patients at the baseline and after the treatment period

relationships are more pronounced in SOD (r = +0.3812) than in CAT (r = +0.2977).

Low values of coefficients of the variable before the treatment (0.20164 for SOD and 0.26791 for CAT) (Figure 5) are excluding the possibility of the individual intense change in the value of enzymes caused by therapy.

Determining the interval of synergistic influence of superoxide dismutase and catalase on blood glucose levels

Specific and significant change in the correlations between SOD and CAT prior to the treatment, intrigues further analysis of paths through which enzymes influence the basic parameter of diabetes – blood glucose. The analysis continues with exploring of synergic influence of SOD and CAT primarily on the G0H. From statistical data the approximate two-dimensional function of independent variables (SOD and CAT) and dependent variable (G0H) is formed, which is shown in Figure 6. The onset of diabetes in obese individuals, in addition to drastic changes of coefficients in linear regression line equation of the relationship between SOD and CAT, the change of two-dimensional G0H function is expressed. The appearance of the glucose maximum on coordinates of independent variables SOD ≈ 150 and CAT ≈ -110 marked by values of dependent variable G0H > 10.

After treatment period, mild parabola determined by SOD with the minimum line at about SOD ≈ 250 which is in linear decrease in the function of CAT emerges. It is evident that the treatment is "calming" the maximum and that the inflection limit for CAT ≈ -135 (underlined in Figure 6).

When forming two complementary groups of T2DM patients before and after the treatment with regard to cut-off point of CAT ≈ -135, the group with 0 > CAT > -135 have mean G0H of 10.969, while the group with -135 > CAT >-∞ have mean G0H of 7.883. These values differ significantly based on analysis of variance (ANOVA) p = 0.03537 < 0.05 (df = 23, F = 4.9977).

The equation of the linear regression of SOD and CAT (CAT = -90.07 - 0.1782 × SOD) can be expressed in an inverse form in which CAT is independent variable and SOD is dependent variable. If we enter characteristic value of CAT = -135 in this linear regression equation, the assumed characteristic value SOD is obtained:

$$SOD = 48.33 - 1.674 \times CAT \rightarrow SOD = 48.33 - 1.674 \times -135 = 274.32 \approx 270$$

Adopted value SOD=270 is characteristic because it represents the approximate direction of propagation of minimum parabolic drawing, the axis of the two-dimensional function of G0H dependence in T2DM patients Diabetes type 2 (Figure 6, after the treatment).

However, although among low values SOD does not give a significant difference in G0H value by itself, a synergistic effect of factor (0 < SOD < 270) with factor (0 > CAT > -135) reveals a group of patients which has an exceptionally high G0H before the treatment with the mean value of G0H = 12.656 in contrast to the value of complementary group G0H = 7.7063. The analysis of variance for the declared intervals of value of the intervals of both enzymes (MANOVA test) points out the significant difference between groups with the significance threshold of p = 0.000424 < 0.01 < 0.05.

In search for a possible dynamic of influence of SOD and CAT factors on blood glucose levels, analysis of two-dimensional dependence of G2H in a function of independent variables (SOD and CAT) is continued. Graphics of approximate function for T2DM patients before and after the treatment are given in Figure 7. After the treatment, changes are occurring for a variable G2H - from the parabolic form (Figure 6) to the translation of maximum before the treatment into zones of high values of SOD, which are highlighted by arrows in Figure 7. However, these changes are not significant (MANOVA p = 0.0797 < 0.05!).

DISCUSSION

The activities of SOD, CAT and GPX constitute a first line antioxidant defense system, which plays a key role in the defense mechanisms in biological systems [12].

Controversial reports on changes in serum antioxidative enzyme activity of T2DM patients have been published [13]. Our study demonstrated very specific changes in value and distribution of CAT and SOD. CAT has proven to be the more stable enzyme, which did not change the systematic distribution with the onset of diabetes. The mean value of CAT after the onset of diabetes remained at the level similar to one in the control group and in the group of obese individuals without diabetes. Unlike CAT, SOD expressed the clear systematic change with the onset of diabetes. These changes in values of SOD most probably occur due to the faster and more unstable reaction of SOD molecules during the onset of diabetes.

In addition to biochemical changes in glucose levels, the incidence of diabetes caused disorder of dynamics of the relationship between SOD and CAT, through significant changes in their mutual correlations. The system of distribution of CAT and SOD is significantly changed after the metformin therapy. With the onset of diabetes CAT remained normally distributed but SOD lost the allocation system. It is assumed that the breakdown of SOD distribution system is regulatory, due to incomplete exhaustion of CAT and regulatory feedback mechanism of reduced production of hydrogen peroxide by SOD, in order to maintain the normal functioning of CAT. A study by Goth et al. [14], which found that individuals with CAT insufficiency have significantly lower levels of SOD, supports this assumption.

After the treatment period, distribution of both enzymes transforms into uniform. The equilibrium form of uniform distribution without expressed statistical module points out the role of treatment in supporting the balance of these enzymes. In doing so, it does not matter whether the values of enzymes are back to the control group level, or to the level of the group of obese individuals without diabetes, but it is important that the relationship of SOD and CAT returns to the relationship that existed before the onset of diabetes. Correlation of enzymes in the control group, in the group of obese individuals without diabetes, and in the group of T2DM patients after the treatment period was significantly same, and this correlation is significantly different in the group of T2DM patients at the baseline. According to the response to the metformin therapy, it appears that the functional relationship of enzymes is more important than their individual values. This indicates that exhaustion of SOD and CAT with mandatory disorder in their correlations can predict the development of T2DM. Heuristic search for values of critical exhaustion of the enzyme generated the value of CAT = -135 U/mL. T2DM patients at the baseline with CAT less negative than this cut-off point had significantly higher fasting plasma glucose than patients with CAT which was more negative than this cut-off value. Setting the cut-off value of SOD at 270 U/g of hemoglobin revealed that within the same group of patients, ones with lower levels of this enzyme do not have significantly higher values of fasting plasma glucose in comparison to patients with greater levels of SOD. This reflects the most stable level of antioxidant capacity and significance of CAT. However, synergistic effect of CAT and SOD is significant, so at the baseline, T2DM patients with lower level of SOD and lower activity of CAT have significantly higher levels of fasting plasma glucose in comparison with patients with higher SOD value and higher CAT activity. Observed synergistic relationship of enzymes is, at least to some extent, described by Lortz and Tiedge [15], who found that optimal protection of pancreatic β-cells from oxidative damage is provided by combined increased expression of both SOD and CAT. The exhaustion of compensatory mechanisms of CAT and/or its glycosylation in the group of patients with newly diagnosed T2DM likely leads to excessive accumulation of hydrogen peroxide and subsequent suppression of the SOD activity through the feedback mechanism. The suppression of SOD activity may lead to further damage of antioxidative enzymes by accumulated superoxide anions (insufficient elimination of these anions by SOD). However, established critical levels of enzymes and their synergy is losing significance after the additional oxidative load (postprandial state). Significantly superimposed levels of glucose are most probably caused by the insufficiency increase of antioxidant enzymes after a meal. In addition to the recovery correlation between enzymes and significant decrease in glucose levels, the metformin therapy has eliminated the existence of the critical interval of enzymes.

In our study, recovery of correlations between enzymes after the metformin treatment may be a result of short duration of diabetes, so this hypothesis should be tested in the larger population of T2DM patients and with a longer period of the follow-up.

Bakala et al. [16] were examining mitochondrial extracts from the liver of experimental animals and fond that CAT is the most vulnerable to glycosylation of all antioxidant enzymes. High levels of hydrogen peroxide are present in cells with sufficient quantity of GPX, but with reduced reserve of CAT [17]. These results are in accordance with ours, which report association between higher levels of glucose and lower levels of CAT activity, and even more pronounced association of higher glucose levels with combined presentation of lower levels of SOD and lower activity of CAT. Since CAT appears also as an anticancer target, the elucidation of mechanisms regulating its expression is an important issue [18].

Goth et al. [19] considered that elevated concentrations of hydrogen peroxide, due to reduced activity of CAT, can contribute to the oxidative damage of pancreatic β-cells, thus reducing the secretion of insulin and leading to the onset of diabetes and the increase in carotid intima media thickness [20]. New research by Goth et al. [21] reports low levels of CAT in T2DM patients but not in patients with type 1 diabetes. Mutual cooperation of antioxidative enzymes is also vital for normal functioning of the organism [22]. Alfa-lipoic acid (ALA) an essential co-enzyme for energy production in mitochondria, demonstrates substantial antioxidant properties and an effect on whole-body physiology like inhibition of glycation reactions and prevention of beta-cell destruction [23]. It has been used in several oxidative-stress models such as diabetes, ischemia-reperfusion injury, cataract, and neurodegenerative disorders.

The current findings suggest that α-lipoic acid is beneficial and thus should be considered for routine administration in patients with diabetes and peripheral neuropathy [24]. A study by Yang et al. [25] demonstrated that metformin might be effective for reducing blood glucose and promoting glucose uptake and utilization and that ALA might be effective for improving insulin sensitivity and activating insulin-signaling pathways. They demonstrated that ALA enhances hepatic insulin sensitivity and prevents the development of Non-alcoholic fatty liver disease, furthermore, ALA ameliorates glucose metabolism by modulating the insulin-signaling pathway.

CONCLUSION

Although significant differences in absolute values of CAT between groups were not observed, significant changes in linear correlation of CAT and SOD, in particular in the group of T2DM patients treated with the metformin therapy, are clearly visible. In cases of low CAT activity caused by physiological reserves exhaustion, followed by the hydrogen peroxide accumulation, which beside its toxic oxidative action, also inhibits the SOD activity through the feedback mechanism. Significantly higher fasting plasma glucose levels are found among group with low CAT activity and low SOD level comparing to the complementary group. Taking into account that CAT is the most vulnerable to glycosylation among all antioxidant enzymes, and that it has the highest metabolic turnover rate among all known enzymes due its physiological role in removing molecules of hydrogen peroxide (as the most stable oxidative compound), it seems that its activity is the key point of maintaining the oxidative-reduction balance in terms of glycemic control [26]. The question remains of the cause and the effect. If the disorder of enzymes relationship precedes diabetes development, then these conclusions could be used in the individual prevention of diabetes. However, in most cases we do not have the data on the diabetes onset and duration prior to its diagnosis. Longitudinal follow-up of values of these antioxidant enzymes in obese patients prone to diabetes could lead to an answer. Long-term monitoring of dynamics of these enzymes during diabetes duration may provide a more detailed insight into their function, which may not be identical as in the newly diagnosed T2DM patients. It remains an open question whether long-term treatment with metformin maintains correlation antioxidant enzymes relationships in the same way as is observed after the three-month treatment period. This may be an important issue because the primary therapeutic response is relationship synchronization between antioxidant enzymes, and not the impact on their individual absolute values, which are influenced by many other factors.

Conflict of interest: None declared.

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Узајамно деловање антиоксидативних ензима – корелациони односи каталазе и супероксидне дисмутазе током развоја и лечења дијабетеса типа 2

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САЖЕТАК

Увод/Циљ Литературни преглед појединачних анализа вредности ензима каталазе или супероксидне дисмутазе код оболелих од дијабетеса типа 2 (ДТ2) нема изражену конзистентност. Уз уважавање резултата свих претходних студија, пошли смо од претпоставке да се при појави дијабетеса не мењају значајно појединачни квантитети наведених ензима, али да се значајно нарушава однос наведених ензима изражен кроз поремећај њихове динамичке равнотеже.

Методе Студија се састојала од четири групе (n = 30 за сваку групу): гојазне особе са поремећеним метаболизмом глукозе (субјекти са новодијагностикованим ДТ2) пре и у току метформинске терапије, гојазне особе са нормалном толеранцијом глукозе и контролне групе здравих нормалне телесне масе. Одговарајућа антропометријска мерења и лабораторијска испитивања биохемијских параметара и антиоксидативних ензима су спроведена код свих учесника.

Резултати Налаз наше студије доказује знатне промене вредности линеарних корелација ензима каталазе и супероксидне дисмутазе код болесника са новооткривеним ДТ2. Примењена терапија метформином враћа динамичку равнотежу ензима каталазе и супероксидне дисмутазе на ниво гојазних болесника пре појаве дијабетеса.

Закључак Примењена терапија метформином враћа динамички баланс ензима каталазе и супероксидне дисмутазе на ниво ензима гојазних болесника са нормалном гликорегулацијом, кроз реинтеграцију новог равнотежног система вредности ензима и расподела вредности ензима. Ови закључци важе само за почетне фазе лечења ДТ2.

Кључне речи: антиоксидативни ензими; гојазност; метаболизам глукозе; метформин