Original article **UDC:577.15:[616.379-008.64:616.833**
doi: 10.5633/amm.2017.0212

CORRELATION BETWEEN ERYTHROCYTE SUPEROXIDE DISMUTASE AND CATALASE LEVELS AND PERIPHERAL NERVE CONDUCTION IN DIABETIC NEUROPATHY PATIENTS

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Reduced systemic antioxidant defence is considered to play an important mediating role in the pathogenesis of diabetic neuropathy.

The aim of this study was to determine superoxide dismutase (SOD) and catalase (CAT) levels in the erythrocytes of patients with type 2 diabetes mellitus (DM) and diabetic distal symmetrical polyneuropathy (DDSP), and to analyze the connection between the activity of these antioxidative enzymes and peripheral nerve function.

This study involved 100 patients with type 2 DM and signs of DDSP, as well as the control group of 50 healthy subjects and 40 diabetic patients without DDSP. The evaluation of DDSP was based on physical examination and nerve conduction studies. The degree of peripheral nerve dysfunction was estimated by analyzing and scoring sensory and motor nerve conduction parameters.

Laboratory analyses involved erythrocyte SOD and CAT values. SOD values were significantly lower in the patients in comparison with the control group ($p<0.0001$) and diabetic patients without DDSP. The values of erythrocyte CAT were also reduced in diabetic neuropathy patients compared with the controls and patients without DN, although the reduction was not statistically significant. A number of electroneurographic parameters correlated significantly with SOD and CAT levels in the studied patients. Erythrocyte SOD and CAT values were reduced in patients with type 2 DM and DDSP and they correlated with certain electroneurographic parameters of peripheral nerve conduction, which suggested that oxidative stress was potentially implicated in the development of diabetic neuropathy. *Acta Medica Medianae 2017;56(2) :78-84.*

Key words: *diabetes mellitus, diabetic neuropathy, oxidative stress, superoxide dismutase, catalase.*

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Introduction

The results of recent clinical and experimental in vivo and in vitro studies unequivocally suggest that diabetes mellitus (DM) is a disease associated with intensified oxidative stress which modulates numerous cell transduction pathways (1, 2). This eventually results in tissue damage and onset of numerous diabetic complications, including peripheral neuropathy.

Chronic hyperglycemia causes oxidative stress (OS) in a number of ways, including enzymatic, non-enzymatic and mitochondrial pathways, thus disrupting the prooxidative/antioxi- dative balance in cellular systems. Intracellular antioxidative defence is primarily enabled by antioxidative enzymes, the most significant of which are superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GSH-Px) (3-6). SOD works as the first line of enzymatic protection against superoxide radicals. This enzyme catalyses the dismutation of superoxide anion radicals into hydrogen peroxide and oxygen. Hydrogen per- oxide is further metabolized by CAT and GSH-Px, and due to lower Km values, GSH-Px is active in lower concentrations of hydrogen peroxide, while the activity of CAT increases with increased hydrogen peroxide concentration (6, 7). During reduced antioxidative protection and/or increased production of free radicals OS occurs, playing an important role as the mediator of apoptosis of both neurons and supportive glial cells, which has been confirmed in studies using animal models and tissue cultures (8-14).

Studies in patients with diabetic neuropathy (DN) are mainly based on a study of the impact of antioxidant drugs on the function of peripheral nerves, as well as certain biomarkers of oxidative stress (15-20). The studies are lacking that

would examine the direct correlation between prooxidant/antioxidant parameters and development of diabetic neuropathy, especially when human population is concerned.
Special difficulties appear in direct determination of reactive oxygen types in biological systems, due to their short lives, so oxidative stress measurements are mostly based on indirect and nonspecific measurements of products of reactive oxygen type activities.

Aims

The aim of this study was to determine the activities of antioxidant enzymes (SOD, CAT) in the erythrocytes of patients with type 2 diabetes mellitus (DM), as well as to analyze the possible connection between the activity of these antioxidant parameters and the function of peripheral nerves.

Methods

The research took place in the form of a prospective study, which included 100 patients suffering from type 2 DM and diabetic distal symmetric polyneuropathy (DDSP). Patients suffering from another acute or chronic illness, patients previously subjected to cytotoxic therapy or radiotherapy, and patients who had been treated with antioxidative substances were excluded from the experimental group. The control group consisted of 50 healthy individuals who reported no ailments and diseases and whose clinical observation and laboratory tests showed no abnormalities. DDSP was diagnosed after clinical and electrophysiological testing.

Electrophysiological testing assessed the conductivity of sensory and motor fibers of upper and lower extremity peripheral nerves. Due to symmetric nature of the disease, the protocol included unilateral (right) testing of sural, peroneal, tibial, ulnar and median nerves. We analyzed the latency, amplitude, and conduction velocity of the tested nerves. The minimal criterion for electrophysiological validation of diabetic neuropathy (DN) was the abnormality of any electroneuro graphic (ENG) conduction parameter in at least two nerves, one of which had to be the sural nerve (21).

The values of tested electroneurographic parameters were expressed as the score from 1 to 4, where 1 corresponded to a normal result, while 4 meant that the motor or sensory evoked potential was absent. The ENG testing was carried out on the ENG device (Schwartzer, Mios 2+). During the testing, the surface electrodes were used: the stimulation electrode for the electrical stimulation of the peripheral nerve and the registration electrode for the registration of motor evoked potential (MEP).

Laboratory analysis determined the level of morning glycemia and glycosylated hemoglobin (HbA1c) by the standard laboratory tests from the venous blood of patients and halthy persons. Erythrocyte SOD activity was determined by a commercial test Ransod provided by Randox (Randox Laboratories, Crumlin, UK), based on the McCord and Fridovich method (22). Erythrocyte CAT activity was determined by the method of Beutler (23)

Statistical method: To process results we used widely accepted statistical techniques: means and standard deviation, statistical significance calculation tests, correlation tests. We utilized stan-dard statistics software tools (Origin Pro and MATLAB Statistics Toolbox). The results are presented as means ± SD.

Results

The study enrolled 100 type 2 DM patients who showed signs of distal symmetrical polyneuropathy, and whose average age was 58.62 ±11.62 years. The average duration of the disease was 11.32±7.05 years. The control group included 50 healthy individuals, whose average age was 51.64±12.25 years (Table 1). There was a significant increase in glycemia and HbA1c values in the patients compared with the controls (*p<0. 0001) (Table 1).

There was a statistically significant decrease of SOD in the erythrocytes of diabetic neuropathy patients compared with the control group and patients without DN. The values of erythrocyte CAT were lower in patients compared to the control ones, but this difference did not reach statistical significance (Table 2).

All electrophysiological parameters related to the conduction of motor and sensory fibers of the tested upper and lower extremity nerves showed that there was a statistically significant difference between diabetic neuropathy patients and controls (Table 3).

A number of scored ENG parameters correlated significantly with erythrocyte SOD and CAT levels in the studied patients (Table 4).

Table 1. Demographic and biochemical characteristics of diabetic neuropathy patients and the control group

	Number	Sex(M/F)	Age (years) mean ±SD	Duration of DM (years)	Glycemia (mmol/L) mean ±SD	HbA1C (%) mean ±SD
Control	50	22 / 28	51.64±12.25	0	4.81 ±0.63	5.73 ± 0.56
Patients without DSP	40	24 / 16	57.73±11.08	11.23±7.94	8.99±3.11*	9.26 ± 3.33*
Patients with DSP	100	55 / 45	58.62±11.62	11.32±7.05	9.50 ±4.13*	9.09 ±2.13*

Table 2. Erythrocyte SOD and CAT in diabetic neuropathy patients and in the control group

	SOD (U/gr Hb) mean ±SD	CAT (U/gr Hb) mean ±SD
Control	1238.36 ± 136.86	7.34 ± 1.62
Patients without DSP	1144.26 ± 103.92**	7.22 ± 2.01
Patients with DSP	1101.00 ± 64.36**,*	6.68 ± 1.26

** p<0.001 vs. control, * p<0.05 vs. patients without DN

Table 3. ENG parameters in diabetic neuropathy patients and in the control group.

ENG parameters		Controls mean±SD	Patients mean±SD	t	p
CMAP peroneal nerve	Latency (ms)	3.54±0.56	4.66±1.13	-6.64	<0. 0001
	Amplitude (mV)	5.77±2.47	3.46±2.13	5.88	<0. 0001
	NCV (m/s)	51.65±5.79	41.24±6.77	9.20	<0. 0001
CMAP tibial nerve	Latency (ms)	3.56±0.51	4.94±1.32	-7.13	<0. 0001
	Amplitude (mV)	11.19±4.73	4.62±2.98	10.28	<0. 0001
	NCV (m/s)	43.37±3.07	35.72±7.30	7.083	<0. 0001
CMAP median nerve	Latency (ms)	3.45±0.55	4.88±2.24	-4.47	<0. 0001
	Amplitude (mV)	7.00±2.51	4.90±2.35	5.23	<0. 0001
	NCV (m/s)	56.57±7.01	49.52±6.22	6.27	<0. 0001
CMAP ulnar nerve	Latency (ms)	2.90±0.63	3.17±0.78	-2.12	0. 0359
	Amplitude (mV)	7.87±3.35	4.93±7.27	6.36	0. 0025
	NCV (m/s)	57.54±8.57	48.59±8.00	6.30	<0. 001
SEP sural nerve	Latency (ms)	2.93±0.50	4.14±0.90	-8.60	<0. 0001
	Amplitude (mV)	15.61±6.16	8.79±5.77	6.31	<0. 0001
	NCV (m/s)	36.37±4.48	29.49±6.35	6.63	<0. 0001
SEP median nerve	Latency (ms)	3.96±0.49	4.70±0.82	-5.83	<0. 0001
	Amplitude (mV)	43.07±9.33	15.75±9.70	16.47	<0. 0001
	NCV (m/s)	47.36±5.63	38.77±7.85	6.86	<0. 0001
SEP ulnar nerve	Latency (ms)	3.28±0.68	4.12±0.82	-6.23	<0. 0001
	Amplitude (mV)	36.46±11.63	17.28±12.22	9.16	<0. 0001
	NCV (m/s)	46.32±6.10	38.20±7.37	6.69	<0. 0001

CMAP – compound muscle action potential,
SEP - sensory evoked potentials,
NCV-nerve conduction velocity

Table 4. Correlation between ENG parameters and parameters of OS (SOD and CAT) in diabetic neuropathy patients. The bold values indicate a statistically significant correlation.

Nerve	ENG parameters	SOD		CAT	
		r	p	r	p
MEP Peroneal nerve	Latency	-0.1096	0.2777	-0.1597	0.1126
	Amplitude	-0.2526	**0.0112**	-0.2859	**0.0039**
	MEP NCV	-0.2633	**0.0081**	0.0199	0.8442
MEP Tibial nerve	Latency	-0.1866	0, 0630	0.0406	0.6883
	Amplitude	-0.1575	0.1175	-0.0568	0.5747
	NCV	-0.2524	**0.0113**	0.0254	0.8016
MEP Median nerve	Latency	-0.2326	**0.0199**	-0.0959	0.3425
	Amplitude	-0.0663	0.5123	0.0188	0.8529
	NCV	-0.2171	**0.0301**	0.0462	0.6483
MEP Ulnar nerve	Latency	-0.0442	0.6627	-0.0043	0.9659
	Amplitude	-0.1531	0.1282	0.0174	0.8639
	NCV	-0.1387	0.1687	-0.0629	0.5339
SEP Median nerve	Latency	-0.2183	**0.0291**	-0.0501	0.6205
	Amplitude	-0.0881	0.3836	-0.0057	0.9549
	NCV	-0.2079	**0.0379**	-0.0569	0.5741
SEP Ulnar nerve	Latency	-0.1679	0.0949	-0.1659	0.0991
	Amplitude	-0.0213	0.8336	-0.0997	0.3239
	NCV	-0.1202	0.2336	-0.0627	0.5357
SEP Sural nerve	Latency	-0.1129	0.2636	-0.3837	**0.0001**
	Amplitude	-0.2896	**0.0035**	-0.1449	0.1505
	NCV	-0.1122	0.2662	-0.3840	**0.0001**

MEP- Motor Evoked Potential,
SEP- Sensory Evoked Potentials,
NCV – Nerve Conduction Velocity

Discussion

The results of experimental studies, conducted both in vivo and in vitro, suggest that the peripheral nervous system is sensitive to oxidative damage (8-10). Neurons take over glucose from the blood by the concentration dependent transport, so that hyperglycemia is always associated with increased glucose values in the neurons, which results in oxidative stress (2, 3). On the other hand, antioxidative defense in peripheral nerves is thought to be limited due to primary lower values of glutathione and glutathione-dependent enzymes (GSH-Px and GSH-r) (24, 8), which further increases the sensitivity of nerves to oxidative damage. SOD could provide efficient antioxidative protection, since, contrary to glutathione-depen-dent enzymes, it is relatively more active in the peripheral nerves. However, in spite of such a theoretical assumption, the studies carried out on experimental models have not shown any signi-ficant changes of the endoneural antioxidative status in experimentally induced DN, except for an increased CAT level, which could not be corrected by insulin therapy (25). On the other hand, positive effects of antioxidants on the antioxidative capacity of blood and on disturbed function of peripheral nerves in the very same experimental models, lead one to conclude that systemic OS can have a more significant role compared to endoneural OS in the development of neuropathic changes.

The determination of OS biomarkers is an important step in the understanding of DN pathogenesis. Recent research suggests that there are tissue and time-dependent changes in the activity of various antioxidative enzymes. The results of our study show that there is a statistically significant reduction of erythrocyte SOD levels in patients with type 2 DM and DDSP in comparison with healthy controls, which corresponds to the literature data (26, 27). The main reason for the reduced SOD activity is the glycolization of Cu, Zn-SOD, which has been documented in both in vitro and in vivo experiments (26,28). However, there are also studies which show no changes in the erythrocyte SOD activity (28, 30), or which, on the contrary, suggest an increased activity of this enzyme (29).

In most cases, CAT activity in erythrocytes was not changed in either experimental animals or type 1 and type 2 DM patients (30-32). However, some studies have noted changes in CAT activity, in particular its reduction (33, 34). In this study, erythrocyte CAT values were reduced in patients as compared with the controls, but this reduction did not reach statistically significant levels, which correlates with the literature data presented above. Catalase values were reduced in patients with DSP, compared with patients with out DSP, although these deviations were not statistically significant. Reduced CAT activity could be explained by the accumulation of H_2O_2 in cells, as a result of glucose autooxidation. Since the principal enzymatic role of CAT is to control H_2O_2 concentration, H_2O_2 accumulation in the cells is believed to lead to the depletion of this enzyme, which primarily affects erythrocytes where CAT is most active. Studies have shown that in other tissues H_2O_2 accumulation may stimulate CAT synthesis, thus increasing its activity. However, erythrocytes lack the genetic apparatus for such a synthesis, which is the reason why an increased H_2O_2 concentration results in the depletion and inactivation of catalase (34).

Similar to the literature data, our results suggest that the blood of type 2 DM patients has decreased antioxidative protection. However, in spite of strong evidence in the literature that OS is increased in DM, there is still no conclusive connection between the OS levels and development of late diabetic complications. Accordingly, in this study, we looked into the interrelation between the tested antioxidative enzyme levels and functional damage to the peripheral nerves. Our previous study did not show any correlation between the plasma total antioxidant capacity (TAC) and degree of damage of peripheral nerves in type 2 DM and DDSP patients (35). Having in mind that TAC was not a mere sum of various antioxidant activities, but a dynamic system of interdependent individual serum antioxidant parameters (36), we designed this study with the purpose to observe and analyze the influence of individual TAC constituents on the development of peripheral nerve dysfunction in type 2 DM patients.

All electroneurographic parameters of peripheral nerve conduction showed a deviation in patients compared with controls, and these deviations were statistically significant. In the studied patients, we found a significant negative linear correlation between the erythrocyte SOD levels and a number of scored ENG parameters indicators of DSP (the lower the SOD values, the higher the ENG score, i.e. the more pronounced the functional damage). The correlation that was found between SOD and ENG indicators of the degree of neuronal damage indicated that there was an important role of toxic effects of superoxide anion radicals in the development of neuronal damage. In vivo, superoxide anion radicals are removed mostly enzymatically, by SOD. When superoxide anion radicals are excessively produced, they react with nitric oxide and form a peroxynitrite, which has numerous cytotoxic effects. A tenfold increase in superoxide anion radicals and nitric oxide has been found to increase peroxynitrite production one hundred times (7). An excessive production of superoxide anion radicals, nitric oxide and peroxy nitrite may thus be a significant pathogenetic factor for neuronal damage.

As for catalase, even though the reduced activity of this enzyme did not reach statistical significance in this study, the analysis of correlation between CAT blood levels and electrophysiological conduction parameters of the peroneal, sural, median (MEP-amplitude of peroneal nerve, the latency and NCV of the sural nerve) revealed a statistically significant value. Such results suggest that CAT has a pathogenetic importance, i.e. that hydrogen peroxide has toxic effects on the degree of neuronal damage.

Conclusions

DM is closely associated with an imbalance in pro/antioxidant status of cells and changes in the redox potential. Oxidative stress, as a common denominator, is the biochemical mechanism by which disturbed glucose metabolism and deregulation of cell signaling leads to the development of diabetic complications. The results of our study stressed a reduced systemic antioxidative defense in the patients with type 2 DM and diabetic distal symmetrical polyneuropathy and indicated that systemic oxidative stress could potentially have a role in the development of diabetic neuropathy. A better understanding of the role of oxidative stress and antioxidative mechanisms requires further investigations with standardized methodology, molecular biological techniques and better defined experimental models and subjects, aiming to prevent, delay or slow the progression of the disease.

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Originalni članak **UDC:577.15:[616.379-008.64:616.833**
doi: 10.5633/amm.2017.0212

KORELACIJA NIVOA ERITROCITNE SUPEROKSID DIZMUTAZE I KATALAZE I PROVODLJIVOSTI PERIFERNIH NERAVA KOD BOLESNIKA SA DIJABETESNOM POLINEUROPATIJOM

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Smatra se da redukovana antioksidativna zaštita igra važnu medijatorsku ulogu u patogenezi dijabetesne neuropatije.

Cilj ove studije bio je da se utvrde nivoi superoksid dizmutaze (SOD) i katalaze u eritrocitima bolesnika sa dijabetesom melitusom (DM) tip 2 i distalnom simetričnom polineuropatijom (DDSP) kao i da se utvrdi moguća povezanost između aktivnosti ovih antioksidativnih enzima i funkcije perifernih nerava.

Studija je obuhvatila 100 bolesnika sa DM tip 2 i DDSP. Kontrolnu grupu sačinjavalo je 50 zdravih individua kao i 40 bolesnika sa DM tip 2, ali bez DDSP. Evaluacija DDSP zasnovana je na kliničkom pregledu i elektroneurografskom testiranju.

Laboratorijske analize su uključivale određivanje nivoa SOD i katalaze u eritrocitima ispitanika. Vrednosti SOD su bile statistički značajno niže u eritrocitima bolesnika sa DDSP u poređenju sa zdravim individuama i dijabetičarima bez DDSP. Vrednosti eritrocitne katalaze su takođe bile niže kod bolesnika sa DDSP u poređenju sa kontrolnom grupom i bolesnicima sa DM ali bez DDSP, ali ta razlika nije dostizala statističku signifikantnost. Utvrđeno je postojanje statistički značajne korelacijie određenih elektroneurografskih parametara provodljivosti perifernih nerava i nivoa SOD i katalaze u eritrocitima bolesnika sa DDSP. Vrednosti SOD i katalaze bile su snižene kod ispitanih bolesnika sa DM tip2 i DDSP, što ukazuje na redukovanu antioksidativnu zaštitu. Korelacija elektroneurografskih parametara provodljivosti perifernih nerava i nivoa SOD i katalaze sugeriše potencijalni značaj oksidativnog stresa u razvoju DDSP. *Acta Medica Medianae 2017;56(2):78-84.*

Ključne reči: *dijabetes mellitus, dijabetesna neuropatija, oksidativni stres, superoksid dizmutaza, katalaza*