THE EFFECT OF EXERCISE ON BRAIN ANTIOXIDANT STATUS OF DIABETIC RATS

Y.G. ÖZKAYA, A. AGAR, P. YARGIÇOGLU, G. HACIOĞLU, S. BILMEN-SARIKÇIOĞLU, I. ÖZEN, Y. ALICİGÜZEL

SUMMARY - Background: To investigate the effect of exercise on brain antioxidant status of diabetic rats.

Methods: Wistar rats were divided into four groups: Control (C), exercise (CE), diabetic (D), and diabetic+exercise (DE). Diabetes was induced by single administration of streptozotocin (60 mg/kg). We used an aerobic exercise program for 8 weeks of CE and DE rats. After the end of the experimental period, Cu, Zn-superoxide dismutase (Cu, Zn-SOD), catalase (CAT), glutathione peroxidase (GSH-Px), xanthine dehydrogenase (XDH) and xanthine oxidase (XO) activities and thiobarbituric acid reactive substances (TBARS) levels of brain were measured.

Results: Diabetes caused significant reduction of brain Cu, Zn-SOD and GSH-Px activities in the D and DE groups. CAT activity was decreased only in the D group. Exercise did not alter CAT activity of brain, whereas markedly increased Cu, Zn-SOD activity in the DE group. In contrast to diabetes-related decrease in the activity of Cu, Zn-SOD, increase in the XO and GSH-Px activities were observed in the DE group compared with the D group. XO activity was significantly reduced in two exercise groups according to the control rats, but the decrease was not accompanied with the activity of XO elevation in all groups. On the other hand, TBARS levels were found to be elevated in all diabetic animals.

Conclusions: Our results show that aerobic exercise did not affect lipid peroxidation of brain, but in diabetic condition improved antioxidant defense.

Key-words: diabetes mellitus, exercise, antioxidant status, lipid peroxidation, rat, GSH-Px.

RESUME - Effet de l'exercice sur le status antioxydant cérébral chez le rat diabétique.

Objectif : Investiguer l'effet de l'exercice sur le status antioxydant cérébral de rats diabétiques.

Méthodes : Quatre groupe de rats Wistar ont été étudiés : Contrôle (C), exercice (CE), diabétique (D), et diabétique-exercice (DE). Le diabète a été induit par une administration unique de streptozotocine (60 mg/kg). Nous avons utilisé un programme d'exercice aérobie pendant 8 semaines chez les rats CE et DE. Après la fin de la période expérimentale, les activités Cu, Zn-superoxide dismutase (Cu, Zn-SOD), catalase (CAT), glutathion peroxidase (GSH-Px), xanthine deshydrogénase (XDH) et xanthine oxidae (XO) ont été mesurées au niveau cérébral ainsi que les niveaux de TBARS (thiobarbituric acid reactive substances) (TBARS).

Résultats : Le diabète est associé à une réduction significative de l'activité cérébrale Cu, Zn-SOD et GSH-Px dans les groupes D et DE. L'activité CAT est diminuée dans le seul groupe D. L'exercice n'altère pas l'activité CAT du cerveau, mais augmente de façon marquée l'activité Cu, Zn-SOD du groupe DE. Par opposition à la diminution de l'activité Cu, Zn-SOD observée au cours du diabète, on note une augmentation des activités XO et GSH-Px dans le groupe DE par rapport au groupe D. L'activité XD est significativement diminuée dans les deux groupes exercice par rapport au groupe contrôle, mais cette diminution n'est pas accompagnée d'une élévation de XO. L'augmentation de l'activité XO et la diminution de l'activité XD chez les rats DE révèle que le diabète et l'exercice ont potentiellement un effet sur la production radicale. D'un autre côté, le niveau de TBARS est significativement augmenté chez tous les rats diabétiques.

Conclusions : Nos résultats montrent que l'exercice aérobie n'affecte pas la peroxydation lipidique dans le cerveau, mais améliore la défense antioxydante en cas de diabète.

Mots-clés : diabète, exercice, status anti oxydant, peroxydation lipidique, rat, GSH-Px.

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Diabetes mellitus is a complex disease associated with systemic and neural abnormalities [1, 2]. There is little known about pathogenetic mechanisms responsible for functional and physiological impairments in diabetes mellitus. A variety of hypotheses concerning the etiology of diabetic complications have been postulated [3, 4]. In the last decade, it is well known that free radicals play an aberrant role on the formation of toxic lipid peroxidation products. Moreover, these radicals are reported to have part in various pathologic and nonpathologic conditions such as ischemic heart disease, bronchial asthma, aging, diabetes mellitus and exercise [5, 6]. Because oxygenated free radicals can initiate series of events in tissues that might eventually lead to the development of many complications, because it is well known that all tissues were affected by diabetes mellitus but highest effect was observed in brain.

Brain is one of the organs which consumes the highest amount of oxygen in human body. Although most of the oxygen used in brain converted CO$_2$ and water, some little amount of oxygen forms free radicals like O$_2^·$, H$_2$O$_2$ and OH. The existence of polyunsaturated fatty acids which are targets of those of the free radicals in brain make this organ more sensitive to oxidative damage [7]. Therefore, there are various antioxidant mechanisms in brain neutralizing harmful effects of free radical yet with diabetes the loss of efficiency of antioxidants mechanisms and the alterations in the electron transfer chain in mitochondria increase the free radical formation due to hypermetabolism.

In recent years, numerous studies have been published concerning the beneficial effects of exercise on human health. It is widely accepted that an increase of free radicals play an important role as mediators of tissue damage during exercise. On the other hand, there are indications that acute bouts of strenuous exercise can increase lipid peroxidation and regular physiocal training can elevate antioxidant status and decrease lipid peroxidation [8].

Therefore, it is reasonable to expect that exercise is beneficial effect for the complications of diabetes mellitus. However, the relationship between exercise and antioxidant enzyme activities of brain in diabetes mellitus has not yet been investigated. Regarding this point, the purpose of this study was established the extent to which alterations in brain antioxidant status occurred in exercise, to research the effect of training on antioxidant enzymes of brain in diabetic condition, and to evaluate if exercise can be recommended diabetic alterations of the brain antioxidant status.

# MATERIALS AND METHODS

Animal care and exercise training

The study protocol was approved by the Akdeniz University Animal Care and Use Committee. Forty male Wistar rats (aged 3 months) were used in this study. Standard rat cow and tap water were given ad libitum and the animals were housed in groups of 4-5 rats in stainless steel cages at standart conditions (24 ± 2 °C and 50 ± 5% humidity) with 12: 12 hours light-dark cycles. Animals were randomly divided into four groups: Control (C), diabetic (D), exercise (CE) and diabetic exercise (DE). Following an overnight fast, diabetes was induced by single intraperitoneal injection (60 mg/kg) of streptozocin (Sigma, S-0130) in a citrate buffer. The buffer was citrate phosphate: 2.30 g citrate monohydrate, 2.58 g sodium phosphate dibasic anhydrous in 200 ml deionized water (pH: 4.5) [9]. Other two groups were injected with equivalent volume of citrate buffer. Three days later the glucose concentration in the tail blood of streptozotocin-administered rats was determined with Hypoguard Supreme Petit strips with a glucometer.

One streptozotocin-treated group and one control group were trained by running on a motor-driven treadmill on 5 days per week. Familiarisation of the rats with treadmill began two days before the injection of streptozocin or vehicle. Running time and speed were gradually increased during 8 weeks of the training. The animals began running at 10 m/min, 0% grade, 10 min/day and reached to a level of 28 m/min, 6% grade, 60 min/day by week 8 [10]. Exercise training was performed in the dark cycle of the animals. Because rats are nocturnal animals. The rats were encouraged to run by an electric shocking grid on the rear barrier. Shortly after the run (5 min) blood samples were taken into a capillary tube from the tail vein to measure the lactate levels. Blood lactate measurement was made to determine anaerobic threshold of rats and performed by using commercial kits (Abott aerose, 73052HW00, Abott Labs in USA).

The rats weighed weekly and daily food and water consumption were recorded during the experiments.

**ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Cu, Zn-SOD</th>
<th>Cu, Zn-superoxide dismutase</th>
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<tbody>
<tr>
<td>CAT</td>
<td>Catalase</td>
</tr>
<tr>
<td>GSH-Px</td>
<td>Glutathione peroxidase</td>
</tr>
<tr>
<td>XDH</td>
<td>Xanthine dehydrogenase</td>
</tr>
<tr>
<td>XO</td>
<td>Xanthine oxidase</td>
</tr>
<tr>
<td>TBARS</td>
<td>Thiobarbituric acid reactive substances</td>
</tr>
<tr>
<td>CO$_2$</td>
<td>Carbon dioxide</td>
</tr>
<tr>
<td>O$_2$</td>
<td>Oxygen radical</td>
</tr>
<tr>
<td>H$_2$O$_2$</td>
<td>Hydrogen peroxide</td>
</tr>
<tr>
<td>OH$^·$</td>
<td>Hydroxyl radical</td>
</tr>
<tr>
<td>GSH</td>
<td>Glutathione</td>
</tr>
<tr>
<td>GLUT-4</td>
<td>Glucose transporter 4</td>
</tr>
<tr>
<td>G6-PD</td>
<td>Glucose 6-phosphate dehydrogenase</td>
</tr>
<tr>
<td>Mn-SOD</td>
<td>Mn-superoxide dismutase</td>
</tr>
</tbody>
</table>
The mean daily food and water consumption were estimated from the recorded values.

Sample collection

After 3 days of the last bout of exercise, animals were anesthetized with diethyl ether and their abdomens were opened by a midline incision. Blood samples were taken for determine the glucose level and animals were killed by cardiac puncture. Then the brain was removed. Brain tissue homogenates were used for TBARS analysis, and antioxidant enzyme activities.

Chemical Analysis

**TBARS assay**

TBARS levels were measured by a fluorometric method by Wasowicz et al. [11] using 1,1,3,3-tetramethoxypropane as a standart and the results are given as nmol/mg protein. Tissue samples (50 µl) were introduced a tube containing 1 ml of distilled water. After addition of 1 ml of a solution containing 29 mmol/l 2-thiobarbituric acid (TBA) in acetic acid (8.75 mol/l), samples were placed in a water bath and heated for 1 h at 95-100 °C. After samples had cooled, 25 µl of 5 mol/l HCl were added and the reaction mixture was extracted by agitation for 5 min with 3.5 ml of n-butanol. After centrifugation, the butanol phase separated and the fluorescence of the butanol extract was measured in a spectrofluorometer (Shimadzu RF-5000, Kyoto, Japan) using wavelengths of 525 nm, for excitation, and 547 nm, for emission. The results are given as nmol/g protein.

Enzyme Assays

**Assay of Cu, Zn-SOD Activity**

Cu, Zn-SOD activity was determined on supernatant obtained from tissue homogenate. SOD activity was measured using the method of Sun et al. [12]. The final volume of the reaction systems is 3.0 ml and contains, per liter, 0.1 mmol of xanthine, 0.1 mmol of EDTA, 50 mg of bovine serum albumin, 25 µmol of NBT, 9.9 mmol of xanthine oxidase, and 40 mmol of Na2CO3 (pH 10.2). The production of formazan is estimated from the recorded values. The mean daily food and water consumption were monitored using a Shimadzu 1601 spectrophotometer.

**Assay of Catalase Activity**

CAT activity was assayed by the method of Aebi [13] with hydrogen peroxide as substrate. The final volume of each enzyme assay was 1.5 ml containing 0.5 ml of 30 mM hydrogen peroxide and 1.0 ml supernatant of tissue homogenate. Assay was performed at 25 °C and 240 nm. Enzyme activity was expressed as U/g protein.

**Assay of GSH-Px Activity**

GSH-Px activity was measured by the method of Paglia and Valentine [14]. Each assay consisted of 2.5 mM GSH, 0.5 mM NaN3, 0.3 mM EDTA, 0.1 mM NADPH, 0.5 unit of glutathione reductase, 0.4 mM t-butyl hydroperoxide in 50 mM phosphate buffer, pH 7.2, and an appropriate amount of supernatant in a final volume of 1.0 ml. The optical density changes at 340 nm were spectrophotometrically monitored at 37 °C: One unit of GSH-Px activity represents 1 µmol t-butyl hydroperoxide/min under the defined assay conditions. Data are expressed as U/g protein.

**Assay of XDH and XO activity**

XDH and XO activities were measured by the method of Beckman [15] with pterin as a substrate. Enzyme activities were determined on supernatant obtained from tissue homogenate. Tissue samples centrifugated and rapidly chromatographed containing Sephadex G-25. Supernatants from brain tissue homogenates were diluted in pH: 7.4 buffer (2 ml final volume), warmed to 37 °C in the cuvette and baseline drift measured in a spectrophotometer (Shimadzu RF-5000, Kyoto, Japan) using wavelengths of 525 nm, for excitation, and 547 nm, for emission. The rate of pterin oxidation was determined after adding 20 µl of 1 mM pterin and a linear rate had been measured. Afterwards, 20 µl of 1 mM methylene blue was added as an electron acceptor to measure to combined activities of xanthine dehydrogenase plus oxidase. The reaction was then inhibited by the addition of 20 µl of 1 mM allopurinol and a known final concentration of isoxanthopterin ranging from 0.1-1 µM was added. The immediate fluorescence increase after addition of isoxanthopterin corrected for fluorescence quenching and provided an internal standart for calculating enzyme activity. Data are expressed as U/g protein.

In all enzymatic determinants the proteins were evaluated according to Lowry et al. [16]. All spectrophotometric assays were monitored using a Shimadzu 1601 spectrophotometer.

Statistical analysis

Data are expressed as means ± S.E., and the statistical significance of the data was assessed by analysis of variance followed by Tukey’s post hoc test. A level of p < 0.05 was accepted statistically significant.
RESULTS

Body weight and food intake

The mean body weight and daily food and water intakes of rats of the four groups are shown in Table I. Exercise trained animals did not exhibit a marked change in either food and water consumption, or body weight as compared to the control group. Daily food and water consumption of the diabetic and DE groups were significantly increased with respect to the beginning values and non-diabetic groups.

Blood glucose and lactate levels

The mean glucose values are given in Figure 1A. Blood glucose level was multifold higher in the diabetic groups than in the control group, indicating that hyperglycemia was sustained in these groups. The glucose level was significantly reduced in diabetic-exercise rats compared to the diabetic group. There was no significant difference in the plasma glucose concentration between control and control-exercise groups.

To determine whether this exercise program was an aerobic training, we examine blood lactate levels (Fig. 1B). There was no significant difference between C and CE groups. On the other hand, lactate values were significantly increased in the diabetic groups compared with the control group, but lactate level was decreased in the DE group compared with the D group.

DISCUSSION

These animals showed significant loss of body weight and hyperphagia and polydipsia. These results are accordance with results previously reported after treatment of streptozotocin diabetic rats [7, 17].

The speed and the duration of exercise were increased in a graded manner. Blood samples are obtained from the subjects in 5 minutes following the

Table I. Initial and final body weight and daily consumption of food and water of the four groups of rats. Values are means ± SE.

<table>
<thead>
<tr>
<th>Group</th>
<th>Body weight (g)</th>
<th>Daily consumption</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial</td>
<td>Final</td>
</tr>
<tr>
<td>Control (n = 10)</td>
<td>245.0 ± 5.16</td>
<td>341.5 ± 9.13</td>
</tr>
<tr>
<td>Exercise training (n = 10)</td>
<td>240.30 ± 7.6</td>
<td>316.1 ± 6.55</td>
</tr>
<tr>
<td>Diabetic (n = 10)</td>
<td>250.00 ± 4.71</td>
<td>241.0 ± 5.8</td>
</tr>
<tr>
<td>Diabetic-exercise (n = 10)</td>
<td>243.60 ± 5.00</td>
<td>242.2 ± 9.65</td>
</tr>
</tbody>
</table>

* Groups vs control group; ** D vs CE; *** DE vs CE; **** DE vs D; # Final vs initial.
exercises and used for lactic acid determination. Plasma lactic acid level is an indicator of anaerobic threshold which is 4 mM/l for human [18] and 4.2 mM/l for rats [19]. Plasma lactate level measured in the CE group shows that this threshold is not reached. On the other hand, plasma lactic acid levels were higher in the diabetic groups than in the non-diabetic groups which is in accordance with previous studies [20, 21]. The exercise program had no effect on high lactate concentrations seen in the diabetic groups. In our study, plasma glucose level of the CE group was slightly higher than the C group supports this finding. However, this difference was insignificant. The exercise in rats accepted as a behavioral and psychological

**Fig 1.** Plasma glucose and lactic acid levels of studied groups.
of glycated Cu, Zn-SOD in the diabetic patients was significantly higher than in controls and the glycated form of Cu, Zn-SOD was less active. As shown previously [29], glutathione (GSH) concentration was decreased in diabetes mellitus due to significant decrease in the activity of red cell glucose 6-phosphate dehydrogenase (G6-PD). Because G6-PD participates indirectly by catalyzing the generation of reduced NADPH, a necessary cofactor for the glutathione system. These effects of diabetes mellitus on red cell glutathione system was also noted in our previous study [30] and in other reports [31].

In the present study, changes of brain Cu, Zn-SOD activity of the control exercise group was not observed. Although Cu, Zn-SOD activity tended to be lower in the control exercise group, it didn’t reach the statistical significance. Brain Cu, Zn-SOD activity was found to be decreased in the diabetic exercise group compared with the diabetic group. Many contradictory results have been obtained in the alterations of brain Cu, Zn-SOD activity. It has been reported to be increased, decreased or unchanged [31, 32]. This different findings may be depend on several factors, such as oxygen consumption, antioxidant enzyme synthesis, activities, mitochondrial biogenesis and the occurrence of antioxidant-induced degeneration, animal strains, exercise protocol or the assay techniques used for the determination of SOD activity. Additionally one explanation for our result could be that Mn-SOD may be elevated to remove the superoxide radicals produced in the mitochondria thus reducing mitochondrial oxidative stress.

Our data were consistent with those from other studies reporting increased GSH-Px activity in exercise groups [33, 34]. The increase was more pronounced in the diabetic exercise group than the control exercise group. Significant increases in brain GSH-Px activities of CÈ and DE groups could be resulted from the increment of tissue GSH concentration. Glutathione peroxidase catalyses the reduction of

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**TABLE II. Cu, Zn-SOD, CAT, GSH-Px, XO and XDH activities and TBARS levels of studied groups.**

<table>
<thead>
<tr>
<th>Groups</th>
<th>Cu, Zn-SOD (U/g protein)</th>
<th>CAT (k/g protein)</th>
<th>GSH-Px (U/g protein)</th>
<th>XO (U/g protein)</th>
<th>XDH (U/g protein)</th>
<th>TBARS (nM/g protein)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (C)</td>
<td>15.92 ± 0.64</td>
<td>36.20 ± 3.48</td>
<td>14.87 ± 0.48</td>
<td>29.52 ± 2.64</td>
<td>21.75 ± 2.15</td>
<td>1.98 ± 0.09</td>
</tr>
<tr>
<td>Exercise (CE)</td>
<td>13.05 ± 0.39</td>
<td>42.03 ± 3.29</td>
<td>16.02 ± 0.45</td>
<td>34.09 ± 2.34</td>
<td>10.43 ± 1.36</td>
<td>2.20 ± 0.38</td>
</tr>
<tr>
<td>Diabetic (D)</td>
<td>10.32 ± 0.29</td>
<td>27.79 ± 2.25</td>
<td>4.84 ± 0.34</td>
<td>27.38 ± 1.56</td>
<td>21.43 ± 2.55</td>
<td>3.191 ± 0.39</td>
</tr>
<tr>
<td>Diabetic + Exercise (DE)</td>
<td>8.74 ± 1.23</td>
<td>33.65 ± 5.22</td>
<td>7.25 ± 0.49</td>
<td>50.56 ± 5.07</td>
<td>10.77 ± 1.54</td>
<td>3.29 ± 0.29</td>
</tr>
</tbody>
</table>

* Groups vs control group; ** D vs CE; *** DE vs CE; **** DE vs D.

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stress factor and after the exercise blood catecholamine levels were found to be increased [22].

In the DE group, exercise training also caused a significant decrease in plasma glucose level compared to the diabetic group. This result can be explained by exercise causing an increase in uptake of glucose of muscle which induces increase of GLUT 4 expression and translocation from intracellular pool [10, 23]. In increase in glucose uptake seems to be related to the increased number of GLUT-4 glucose transporters, although the type of training, strain, age and sex of the animals seem to affect significantly the expression of GLUT-4 [10, 23]. On the other hand, Etgen et al. [23] found that exercise training, but not acute bouts of exercise of normal rats results in an elevated maximal hindlimb glucose uptake. They suggested that this increase was only partially explained by an increase in total muscle GLUT-4 protein content [24] also observed that contraction stimulates glucose transport by mobilizing an insulin-insensitive GLUT-4 pool appears to be directly related to calcium release and does not use key insulin signaling intermediates such as phosphatidylinositol-3-kinase (PI-3-K) [24]. In addition, decrement of glucose level in the DE group of rats could be a consequence of stimulated epinephrin and cAMP and perhaps the inhibited tyrosine kinase activity.

There has recently been considerable interest in the idea that free radical-induced tissue damage may play a role in the development of complications in diabetes mellitus [2, 25]. Thus in this context, the results of our study indicating significant elevation of lipid peroxidation and the reduction in brain Cu, Zn-SOD activity in the diabetic rats, also support earlier studies [7, 26]. Regarding previous studies [25, 27], the decrease of SOD activity may be explained at least in part as a result of inhibition of the enzyme activity by glycation. Kawamura et al. [28] found that the percentage of glycated Cu, Zn-SOD in the diabetic patients was significantly higher than in controls and the glycated form of Cu, Zn-SOD was less active. As shown previously [29], glutathione (GSH) concentration was decreased in diabetes mellitus due to significant decrease in the activity of red cell glucose 6-phosphate dehydrogenase (G6-PD). Because G6-PD participates indirectly by catalyzing the generation of reduced NADPH, a necessary cofactor for the glutathione system. These effects of diabetes mellitus on red cell glutathione system was also noted in our previous study [30] and in other reports [31].
both H₂O₂ and organic hydroperoxide, but it has an absolute requirement for GSH as a cosubstrate. It has been shown that GSH is greater in the liver and kidney than the brain and muscle [33]. Exercise training increased GSH level in the cerebral cortex and brainstem of rats [34]. This increase in GSH may be due to an increased activity of γ-glutamyl transpeptidase, regeneration of GSH from GSSG by glutathione reductase and the synthesis of the GSH by γ-glutamyl cysteine synthase and glutathione synthase.

Many contradictory results have been obtained in alterations of brain CAT activity. CAT activity has been reported to be decreased, increased or unchanged [26, 31, 32]. Unaltered brain CAT activity in the exercise groups were in agreement with previous papers mentioned above. Interpretation of this finding may be that the activity of GSH-Px was increased in brain of exercise groups in defence against the excessive accumulation of H₂O₂ and organic hydroperoxides.

OX/XDH system is one of the mechanism producing free radicals in diabetes. While under normal conditions, the enzyme is found in the form of XDH in the environment, but turns to in XO form under the ischemic and hypoxic conditions and triggers an important free radical producing mechanism. It is known that endoneural hypoxia occurs in diabetes [35]. In this case, an increase in the activity of XO can be expected. According to our results, the brain XO activity is not increased. The unchanged activity of XDH supports this finding. In exercise group, we have observed that the activity of XDH were decreased, but the activity of XO were not increased. No study concerning the activity of XO/XDH is found currently. But our findings have shown that the changes occurred in that of the system following exercise has no relation with the production of free radical. However, in DE group the increase in the XO activity and the decrease in XDH activity have shown that diabetes and exercise have potentializing effect in free radical production via XO/XDH system. The mechanism of this potentializing has not been known yet. But a suggestion about the possible effect of the metabolic changes implied by XO/XDH enzyme activities in CE and DE groups.

The results of this study can be summarized as below: i) Chronic mild-intensity exercise had improved the hyperglycemia occurred in diabetes. ii) Exercise did not affect the antioxidant system under normal conditions, whereas increased the activities of CAT and GSH-Px in diabetes. Final thought, the different response of control and diabetic rats to exercise needs further examination. Although the improvement may be partially due to a decrease of glucose, lactate levels and glucose metabolism, this mechanism probably was not fully explained in changes of antioxidant enzyme. Further studies should be focus on the changes of antioxidant enzymes to determine in diabetes and exercise.

Acknowledgement – This study was supported by a grant from Akdeniz University Research Foundation (98.02.0103.04).

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