The effect of exercise and antioxidant enzyme levels in syndrome X and coronary slow flow phenomenon: an observational study

Sendrom X ve yavaş koroner akım fenomeninde antioksidan enzim düzeyleri ve egzersizin etkisi: Gözlemsel bir çalışma

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ABSTRACT

Objective: In this study the antioxidant enzyme [catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GPx)] levels at rest in patients with syndrome X and coronary slow flow are measured. Then it has been investigated whether there is any enzymatic difference between the normal controls and syndrome X patients or patients with coronary slow flow and ascertain if exercise has any effects on the antioxidant enzyme levels.

Methods: Fifty-five patients were included in this prospective observational controlled study. Patients were divided into 3 groups: Group 1- normal controls (n=20); Group 2-patients with coronary slow flow (n=20); and Group 3-patients diagnosed with syndrome X (n=15). In all patients, blood samples were collected at rest and after maximal exercise. The antioxidant enzymes (SOD, CAT, Gpx) in the erythrocytes were studied for these three groups of blood sample. Statistical analysis was performed using Student t-test, Mann-Whitney U and Chi-square tests, Kruskal-Wallis variance analysis and ANOVA.

Results: Under basal conditions the lowest SOD and GPx levels were measured in the 2nd Group, whereas significant differences in paired comparisons were observed only between the 2nd and 3rd Groups (p=0.024 vs. p<0.01, respectively) during paired comparisons. The post-exercise SOD levels were decreased significantly in the 3rd Groups when compared with the basal concentrations (p=0.014), however no significant pre- and post-exercise differences were observed in the CAT and GPx concentrations (p>0.05).

Conclusion: The post-exercise SOD level when compared with basal SOD levels were decreased significantly in the syndrome X group, however no differences were observed between the other groups. This can be interpreted as the reduction in the exercise related symptoms and ischemic findings are resulting from the decrease of SOD activity. *(Anadolu Kardiyol Derg 2013; 13: 641-6)*

Key words: Coronary slow flow, syndrome X, antioxidant enzymes

ÖZET

Amaç: Bu çalışmada, sendrom X ve yavaş koroner akım hastalarında istirahatte antioksidan enzim [katalaz (CAT), süperoksid dismutaz (SOD) ve glutatyon peroksidaz (GPx)] düzeyleri ölçülerek normal kontrollerle fark gösterip göstermediği, egzersizin enzim düzeylerine etkisi olup olmadığı araştırılmak istenmiştir.

Yöntemler: Prospektif kontrollü gözlemsel bu çalışmaya 55 kişi alındı. Hastalar, normal kontroller (Grup 1, n= 20), koroner yavaş akımı olan hastalar (Grup 2, n=20) ve Sendrom X tanısı konan hastalar (Grup 3, n=15) olmak üzere 3 gruba ayrıldı. Tüm hastalardan istirahatte ve maksimum efor sonrası kanlar alındı ve eritrosit içindeki antioksidan enzimler (SOD, CAT, GPx) çalışıldı. İstatistiksel analiz Student t-testi, Mann-Whitney U, Ki-kare testi, Kruskal-Wallis varyans analizi ve ANOVA (post-hoc) kullanılarak yapıldı.

Bulgular: Bazal şartlarda ölçülen SOD ve GPx değerleri en düşük olarak Grup 2'de saptanırken, ikili karşılaştırmada yalnızca Grup 2 ve 3 arasında anlamlı fark vardı (p sırasıyla 0,024 ve <0,01). Grup 3'de ise efor sonrasında ölçülen SOD değeri bazal değere göre anlamlı derecede azalırken (p=0,014), CAT ve GPx değerlerinde anlamlı değişiklik olmadı (p>0,05).

Sonuç: Egzersiz testi sonrasında ölçülen SOD değerleri bazalle karşılaştırıldığında sendrom X grubunda anlamlı olarak azalırken diğer gruplarda fark olmamıştır. Bu da Sendrom X hastalarında eforla ilişkili semptom ve iskemi bulgularının egzersizle SOD aktivitesindeki azalmaya bağlı olduğunu düşündürmektedir. *(Anadolu Kardiyol Derg 2013; 13: 641-6)*

Anahtar kelimeler: Yavaş koroner akım, sendrom X, antioksidan enzimler

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Introduction

It is known that atherosclerotic disease changes the coronary flow pattern of atherosclerosis process before showing clinical symptoms and angiographic manifestations (1). It has been thought that, slow coronary flow and syndrome X are part of this process (2-9). The relation between oxidant enzyme level and coronary artery disease has been revealed by previous studies (10-13).

Therefore, we thought that there was a relation between antioxidant enzymes and syndrome X and slow coronary flow. Furthermore, we thought that exercise would facilitate this relation.

The aim of this study was to measure the specific enzymes superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) levels, as well as to investigate the relation between oxidation process and exercise in patients with slow coronary flow and syndrome X.

Methods

Study design

This study was a prospective observational controlled study.

Study populations

Overall, 55 patients were included in this study between 2008 and 2009 years at the university hospital. There were 20 normal control patients (Group 1), 20 patients with slow coronary flow (Group 2), and 15 patients with syndrome X (Group 3). These patients` records were obtained by review of archive and then they were called upon to a control visit. Patients in the syndrome X group had either a positive scintigraphy scan or a positive exercise test result. Patients showed no signs of infection. Subjects with coronary artery disease, previous myocardial infarction, left ventricular dysfunction, or left ventricular hypertrophy on echocardiography were excluded. In addition, patients with uncontrolled hypertension, renal dysfunction, connective tissue diseases or thyroid function disorders were not included. Patients with coronary vasospasm, coronary ectasia, or any hemodynamic changes that could affect 'Thrombolysis In Myocardial Infarction' (TIMI) frame count (TFC) during angiography were also excluded. The study has been carried out according to the principles of the Declaration of Helsinki and its protocol was approved by Ondokuz Mayıs University Hospital Ethical Committee.

The informed consent was obtained in all patients.

Study protocol

Exercise test was performed using Schiller (Switzerland) trademark instrument according to the Bruce protocol. In these patients blood samples from the median cubital venules, approximately 2 mL from each participant, were collected into EDTA containing tubes for 2 mL antioxidant analysis, at rest and after exercise test using Bruce protocol was completed. In this study the erythrocyte Gpx, SOD and CAT levels are studied. In order to determine the erythrocyte GPx, SOD and CAT levels, test kits that are obtained from Cayman Chemical Company (Michigan, USA) are used.

Study variables

In all cases, baseline variables [age, gender, presence of diabetes, hypertension, smoking, body mass index and levels of C-reactive protein, glucose, plasma total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and plasma triglycerides (Thermo clinical lab system with Konelab 60 I kits, Helsinki, Finland)] were recorded. The level of TFC was recorded as predictor a variable and GPx, SOD and CAT levels were recorded as the outcome variables.

Detection of slow coronary flow and TIMI frame count

Coronary flow velocities are detected by TFC method first described by Gibson et al. (14). The velocity of coronary artery flow velocity in each case are determined for each major artery. The vision taken during right anterior oblique projection and caudal angulation is used for left anterior descending coronary artery (LAD) and circumflex coronary artery (CX), the vision taken during left anterior oblique projection and cranial angulation is used for right coronary artery (RCA). In order to determine the corrected TFC for LAD, estimated TFC was divided by 1.7 (14). The mean TFC was estimated for each case. Consequently, corrected LAD -TFC and RCA and CX -TFC were added up and divided by three. Coronary angiographies were carried out using Siemens Axiom Artis (Munich, Germany) digital angiography equipment. This machine was recording images at 15 frame/s. Therefore, values compared to 30 frame/s during counting. Two cardiologists detected TFC of all three arteries and estimated mean TFC. These evaluations were made individually and in case of any discrepancy reassessment was done by a third cardiologist. The slow and normal coronary flow pattern limits accepted in literature were 36.2±2.6 frame for LAD, 36.2±2.6 frame for CX, and 20.4±3 frame for RCA (15, 16). In this study the TFC exceeding these limits are accepted as SCF.

Statistical analysis

Data are analyzed using SPSS version 16 software (SPSS Inc, Chicago, Illinois, USA). To determine whether data fits to normal distribution, Shapiro-Wilk test was executed. Continuous variables are presented as mean±standard deviation, and qualitative variables are presented by percentage. Between group comparisons were executed by using ANOVA followed by post-hoc Tukey HSD test for normally distributed data. Kruskal-Wallis variance analysis followed by Bonferroni corrected Mann-Whitney U test was executed for data that was not normally distributed. Student t-test and Mann-Whitney U test were used to compare continuous variables between two groups. During intra-group comparisons paired-t test was used for normally

distributed data and for the others Wilcoxon sample test was used.

A value of p<0.017 was considered statistically significant for Mann-Whitney U test and for the remaining tests, p<0.05 was considered as a significant.

Results

Overall 55 patients, 22 male, mean age 51.5±8.9 years, who have normal epicardial coronary arteries according to coronary angiography are included. Demographics and laboratory findings are shown in Table 1.

In the third group, the number of patients with hypertension rates were greater than the other groups (p<0.05). In addition, body mass index, glucose and CRP levels are varied among the groups (p=0.015).

Table 1. Demographics and laboratory findings of the groups

Variables	Group 1 (n=20)	Group 2 (n=20)	Group 3 (n=15)	*F	* p
Female, n (%)	15 (75)	14 (70)	4 (26.7)	5.5	0.008
Mean age, years	50.3±9.3	50.6±9.5	54.4±7.5	1	0.360
Hypertension, n (%)	0(0)	4 (20)	9 (60)	10.1	0.001
Diabetes mellitus, n (%)	0(0)	4 (20)	1 (6.7)	2.5	0.083
Dyslipidemia, n (%)	5 (25)	11 (55)	6 (40)	1.9	0.153
Smoking, n (%)	4 (20)	8 (40)	1 (6.7)	2.8	0.064
Body mass index, kg/m^2	22.2±1.8	28.1±6	31.1±5.9	15.2	0.001
Glucose, mg/dL	79.9±10.8	103.2±31.2	100±32	4.5	0.015
CRP, mg/dL	3.2±0.31	3.66±0.78	3.98±0.95	4.5	0.013
LDL cholesterol, mg/dL	125±32	118±34.1	131±32.8	0.6	0.521
Triglycerides, mg/dL	124.4±47.2	146.8±71.9	131.7±50	0.7	0.469
HDL cholesterol, mg/dL	41.9±8.1	47.1±17.1	45.7±15	0.7	0.487

Data are expressed as mean±SD and median (minimum-maximum) values
*ANOVA followed by posthoc Tukey HSD test,
CRP-C - reactive protein, HDL-C - high- density lipoprotein cholesterol, LDL-C - low-density lipoprotein cholesterol

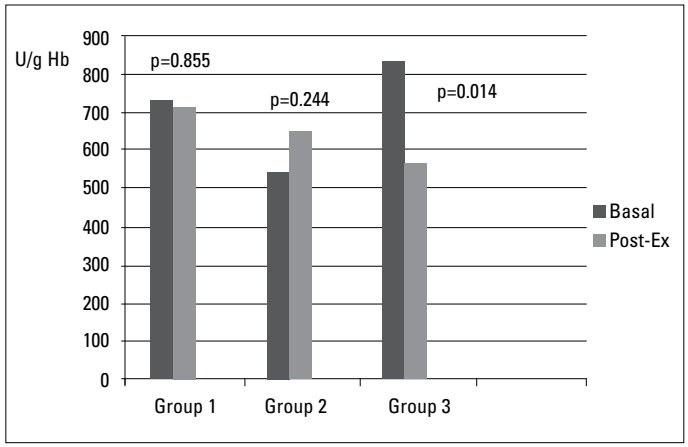

Figure 1. Comparison of basal and post-exercise SOD levels in studied groups
SOD - superoxide dismutase

Basal levels of oxidative enzymes

Superoxide dismutase, catalase and glutathione peroxidase levels measured under basal conditions are varied among the groups (p<0.05). The lowest SOD and GPx levels are measured in Group 2 whereas during in paired comparisons the only significant difference was detected between group 2 and 3 (For SOD p= 0.024, GPx p<0.01). The lowest catalase levels were measured in group 3 and there was a significant difference between groups 1 and 3 (Table 2).

Effect of exercise on oxidative enzyme levels

Post exercise levels are given in Table 3.

SOD ve GPx levels did not change significantly after exercise in group 1 (p>0.05, Fig. 1 and 2). However, significant decrease was detected in the catalase levels in comparison with the basal levels in group 1 (p=0.033, Fig. 3).

In group 2, the CAT level during exercise decreased when compared with basal level, but this change was insignificant (p=0.063, Fig. 3). SOD and GPx levels in group 2 did not change significantly after exercise (p>0.05, Fig. 1 and 2).

The post-exercise SOD levels were found significantly reduced in the 3rd group when compared with pre-exercise levels (p=0.014). Fig. 1), while GPx and CAT levels remained unchanged (Fig. 2 and 3).

Table 2. Comparison of the basal Ery-CAT, Ery-GPx and Ery-SOD levels between the groups

Variables	Group 1 (n=20)	Group 2 (n=20)	Group 3 (n=15)	*F	*p
Ery-SOD, U/g Hb	732±292	541±309	829±331	2.7	0.024
Ery-CAT, U/g Hb	37161±19169	32323 ±15993	23428±12734	2.6	0.047
Ery-GPx, U/g Hb	34.8±16.1	23.3±11.5	39.1±17.7	3.8	0.008

Data are expressed as mean±SD and median (minimum-maximum) values
*ANOVA followed by post-hoc Tukey HSD test
CAT - catalase, Ery - erythrocyte, GPx - glutathione peroxidase, SOD - superoxide dismutase

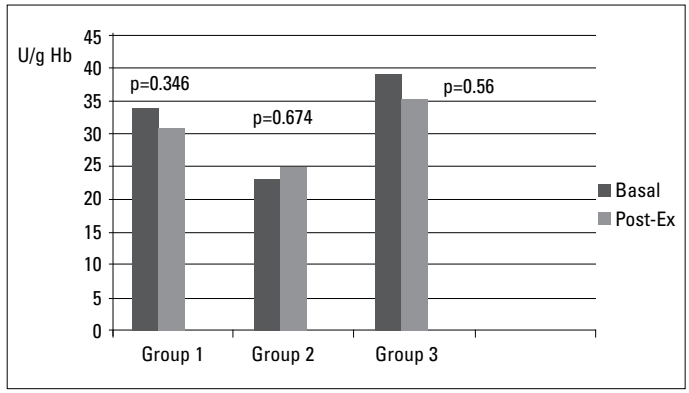

Figure 2. Comparison of basal and post-exercise GPx levels in studied groups
GPx - glutathione peroxidase

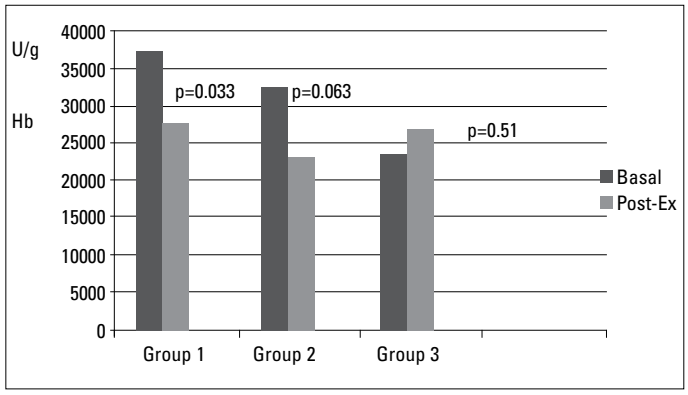

Figure 3. Comparison of basal and post exercise CAT levels in studied groups
CAT - catalase

For both of the patients` groups the basal SOD, CAT and GPx levels are compared between smokers and nonsmokers and patients with and without HT and DM, but a significant difference was not observed (p>0.05).

Relationship between TFC and oxidative enzyme levels

As expected, in the slow coronary flow group mean cTFC of all three coronary arteries were higher than syndrome X group (Table 4). Furthermore, no relation between the enzyme levels and TFC was detected when patients were classified as syndrome X and slow coronary flow.

Discussion

We compared the antioxidant enzyme (CAT, SOD, GPx) levels measured under basal conditions between healthy controls, coronary slow flow and syndrome X patients. Accordingly, basal SOD and GPx levels in coronary slow flow patients were lower than healthy controls. We can say this enzymes used in this group so less has been detected. With respect to our results, during the evaluation of usage of basal enzyme levels (with the exception of CAT) it is argued that patient group with highest oxidative stress can be classified as coronary slow flow group. In all studies demonstrating the role of oxidative stress in these two patient groups, groups are assessed separately (15-18). This is the first study to evaluate syndrome X and coronary slow flow comparing the results with normal controls. Our study has revealed that oxidative stress is higher in coronary slow flow group. This finding together with previous studies comparing two diseases with respect to prognosis (19), supports the notion that coronary slow flow as a syndrome X sub-group has a worse prognosis than syndrome X.

Our aim in adding exercise test to this study was creating an oxidant effect. Then we compared these antioxidant enzymes in control patients, with syndrome X patients suffering from exercise-related chest pain and coronary slow flow patients with atypical complaints. Exercise related increases in different antioxidant enzymes and their levels are displayed in several studies. We assumed that adenosine three phosphate consumption increasing with exercise may be a good source of oxidant products (20) and we evaluated blood erythrocyte antioxidant enzyme levels after an exercise test according to the Bruce protocol. Systematic exercise has a positive effect on antioxidant enzyme levels but there is no evidence whether submaximal or maximal exercise is a destructive exercise or not, no data has been found on the degree of its effect on antioxidants enzymes.

Despite the decrease in SOD, GPx and CAT levels from basal levels, only the decrease in CAT levels was significant. Reason of insignificance of other enzymes would be the small patient numbers or would be the success of antioxidant defense mechanisms resulting from SOD and GPx during destructive exercise. In coronary slow flow patients, the CAD, SOT and GPx levels when compared to basal levels were not significantly changed after exercise. We supposed that this result for this group of patients is originated from the small amount of enzyme reserves under basal conditions. We determined a significant decrease in SOD levels in syndrome X group compared to basal level conditions. This result is suggesting that exercise related symptoms and ischemic findings of syndrome X patients are related to the decrease of SOD activity with exercise (consumption of the reserves because of oxidative stress).

In previous studies, the results regarding SOD and CAT levels varied and did not appear to be significant (21, 22). In a study on swimmers even if activity of GPx increased during the first minute of exercise, this increase did not continue (23). In previous studies, significant results were obtained concerning GPx, but the participating groups were usually chosen among sportsmen, healthy people or CAD patients but not from an intermediate group

Table 3. Post-exercise CAT, GPx and SOD levels

Variables	Group 1 (n=20)	Group 2 (n=20)	Group 3 (n=15)
Ery-SOD, U/g Hb	713±321	651±394	566±356
Ery-CAT, U/g Hb	27565±16142	23070±17950	26892±170635
Ery-GPx, U/g Hb	31±12.8	25.1±11.3	35.7±13.6

Data are expressed as mean±SD and median (minimum-maximum) values
CAT - catalase, Ery - erythrocyte, GPx - glutathione peroxidase, SOD - superoxide dismutase

Table 4. Comparison of corrected TFC among syndrome X and coronary slow flow patients

Variables	Group 2 (n=20)	Group 3 (n=15)	*p
TFC, LAD	26.3±7.5	13.7±1.7	<0.001
TFC, Cx	24.3±6.5	18.0±2.7	<0.001
TFC, RCA	28.4±5.7	17.5±3.3	<0.001

*Student t-test
Cx - circumflex coronary artery, LAD - left anterior descending coronary artery, RCA - right coronary artery, TFC - TIMI frame count

like coronary slow flow or syndrome X patients (23, 24). In concordance with our study, the association between CAD and the increase or decrease of basal GPx levels is examined (10-11, 25).

In a previous study evaluating syndrome X and SOD activity it is shown that the increased SOD activity would reduce complaints and increase the quality of life in patients with syndrome X (22, 26). SOD is on the first step of the antioxidant system and decreasing SOD levels are reflecting less superoxide anion production. Therefore, this can be considered as a pain mechanism in syndrome X patients.

When group 3 demographical data, it has been seen that they are compatible with metabolic syndrome. The hypertensive, diabetic and dyslipidemic patients and the drugs taken can affect the antioxidant system. However describing whether the level change of SOD is related with hypertension, diabetes, dyslipidemia or syndrome X is difficult with the current data. When the pre-hypertensive and hypertensive women are compared with the normal values, a significant decrease in CAT, GPX and SOD is seen in both of the groups (27). It is concluded that some complex mechanisms take role in the antioxidant system. This is because even if there is a big demographic similarity except gender with syndrome X, antioxidant system shows partial similarity. In addition, none of the earlier studies has studied the relation the enzyme level change on women.

Cardiovascular diseases usually appear and proceed with multifactorial interactions. Therefore, the etiological investigations and explanations should be done in consideration with all these factors.

Study limitations

Small sample size is one of the limitations of our study. However, as a future work, a study with larger sample size is planned to be executed.

Conclusion

In our study, we found that coronary slow flow and syndrome X patients have different basal SOD, CAT and GPx levels. These findings indicate that these enzymes play a role in the pathophysiology of these diseases. For the basal enzyme levels (except CAT) the patient group with the highest oxidant stress is coronary slow flow group and inconsistent with the previous studies. This inconsistency can indicate that the prognosis of slow coronary flow patients is worse. The post-exercise SOD when compared with the basal level was decreased significantly in syndrome X group yet no differences were seen in other groups. This suggests that the exercise related symptoms and ischemic findings are associated with the exercise induced decrease in SOD activity (consumption of the reserves associated with oxidative stress).

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

Authorship contributions: Concept - Ö.K., S.D.; Design - Ö.K., S.D.; Supervision - Ö.K., Ö.Y.; Resource - Ö.K., Ö.Y.; Material - Y.Y.M., G.D.; Data collection&/or Processing - A.K., Y.Y.M., G.D.; Analysis &/or interpretation - Ö.K., Z.A.; Literature search - A.K., M.M.; Writing - Ö.K., S.D.; Critical review - Ö.Y., Z.A., M.M.; Other - Ö.K., S.D.

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