Research Article

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Effects of exercise and quercetin on muscle energy charge in metabolic syndrome model of rats

[Ratların metabolik sendrom modelinde kas enerji yükü üzerine kuersetin ve egzersizin etkileri]

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Abstract**Objectives:** This study was performed to investigate whether exercise and quercetin have an effect on muscle energy charge in the metabolic syndrome (MetS) model of rats.**Methods:** Male Sprague-Dawley rats consisting of Control, Fructose, Quercetin, Exercise, Fructose + Exercise, Fructose + Quercetin, Fructose + Quercetin + Exercise groups were randomly divided into seven groups, six rats in each group. Consequently, it was determined that the 20% fructose supplement for 10 weeks with drinking water led to metabolic syndrome in the animals depending on the increase of systolic blood pressure, serum triglyceride, serum insulin and high HOMA-IR scores. MetS criteria were successfully established by oral fructose administration.**Results:** ATP and AMP levels were higher in fructose and exercise groups, and ADP levels were lower. The energy

charge increased in quercetin treated groups. We found that regular aerobic exercise and quercetin application might be beneficial in the fructose-mediated MetS in accordance with previous studies. However it was found that quercetin was more effective than exercise in muscle.

Conclusions: Consequently, it is thought that the regular aerobic exercise alone is a preventive method for the MetS and also it can be used together with quercetin as a beneficial treatment.**Keywords:** energy charge; exercise; fructose; metabolic syndrome; quercetin.**Öz****Amaç:** Bu çalışma; ratların metabolik sendrom (MetS) modelinde, egzersiz ve kuersetin'in kas enerji yükü üzerine etkisi olup olmadığını araştırmak için yapılmıştır.**Gereç ve Yöntem:** 42 erkek Sprague-Dawley ratları rastgele yedi gruba ayrıldı (n = 7): Kontrol, Fruktoz, Kuersetin, Egzersiz, Fruktoz + Egzersiz, Fruktoz + Kuersetin, Fruktoz + Kuersetin + Egzersiz. Sonuç olarak, içme suyu ile 10 hafta süreyle % 20 fruktoz takviyesinin; sistolik kan basıncı, serum trigliserit, serum insülin ve yüksek HOMA-IR skorlarındaki artışa bağlı olarak hayvanlarda metabolik sendroma yol açtığı belirlendi. MetS kriterleri, oral fruktoz uygulamasıyla başarıyla oluşturulmuştur.**Bulgular:** ATP ve AMP düzeyleri fruktoz ve egzersiz gruplarında daha yüksek, ADP düzeyleri daha düşük bulundu. Kuersetin uygulaması gruplarda enerji yükü artırdı. Düzenli aerobik egzersiz ve kuersetin uygulamasının fruktoz aracılı MetS'de, önceki çalışmalarla uyumlu olarak faydalı olabileceğini bulduk. Ancak kuersetin'in kasta egzersizden daha etkili olduğu bulundu.**Sonuç:** Sonuç olarak, düzenli aerobik egzersizin tek başına MetS için önleyici bir yöntem olduğu ve ayrıca***Corresponding author: Professor Dr. Behzat ÇİMEN**, Department of Biochemistry, Faculty of Pharmacy, Erciyes University, 38030, Melikgazi, Kayseri, Turkey, Phone: +903522076666, E-mail: bcimen@erciyes.edu.tr. <https://orcid.org/0000-0001-6904-1474>**Fatmanur Er**, Department of Coaching Education, Department of Action and Training Sciences, Faculty of Sport Sciences, Atatürk University, Erzurum, Turkey. <https://orcid.org/0000-0002-9203-4974>**Canan Yılmaz and Nurten Türközkan**, Department of Medical Biochemistry, Faculty of Medicine, Gazi University, Ankara, Turkey. <https://orcid.org/0000-0002-6799-6522> (C. Yılmaz)**Erdal Zorba**, Department of Physical Education and Sports, Faculty of Sport Sciences, Gazi University, Ankara, Turkey. <https://orcid.org/0000-0001-7861-8204>

yararlı bir tedavi olarak kuersetin ile birlikte kullanılabilirliği düşünülmektedir.

Anahtar Kelimeler: egzersiz; enerji yükü; fruktoz; kuersetin; metabolik sendrom.

Introduction

Metabolic syndrome (MetS) is a disease descriptive of hypertension, dyslipidaemia and insulin resistance and MetS is a serious risk factor such as obesity, cardiovascular disease, type 2 diabetes [1]. It was determined a close relationship between incidence of MetS and increased fructose consumption in clinical and animal studies. The major resource of fructose is corn syrup that is used in sugary drinks and home foods nowadays [2, 3].

Insulin resistance is generally defined as the insensitivity to insulin of peripheral tissues for glucose uptake. Skeletal muscle is responsible for 85 percent of insulin-stimulated glucose uptake in insulin target tissues [4]. Additionally, increased fatty acid in skeletal muscle has been related with higher insulin resistance and lower aerobic capacity [5, 6].

The insulin resistance is defined by alteration in mitochondrial activity in skeletal muscle. In skeletal muscles of patients with insulin resistance show a decrease in both mitochondrial oxidative activity and mitochondrial ATP synthesis [4, 7]. The change in skeletal muscle mass would considerably affect the general energy stocks and metabolism [7]. Moreover, skeletal muscle has been defined by its capability to ease voluntary movement via contraction and is related with exercise. Therefore, all risk factors defining the MetS are related with lower physical activity severity. In addition, exercise and other physical activities increase mitochondrial oxidative levels of muscles [7, 8]. Moreover, several plants that are effective in amelioration of MetS have been used.

Quercetin, a flavanoid found in abundance in onions, tea and apples, is a strong antioxidant [9, 10]. Dietary quercetin has also demonstrated to increase skeletal muscle activity. It was reported that the effect of dietary quercetin dependent on the time and dose. High doses of quercetin have been found to reduce mitochondrial activity in skeletal muscle. It also reported that the protective effects of quercetin in preventing insulin resistance occurred with a low dose of it [11]. It was reported that the effect of high dose quercetin supplementation on eccentric exercise induced muscle injury, but chronic quercetin supplementation can reduce the severity of muscle injury induced by eccentric exercise [12].

The aim of this study was to investigate the effects of exercise and quercetin on skeletal muscle ATP, ADP, AMP

and energy charge levels (energy charge is an index used to measure the energy status of biological cells) in rats with a metabolic syndrome model.

Materials and methods

Animals and experimental design

Adult Sprague-Dawley male rats were obtained from Gazi University Laboratory Animals Raising and Experimental Researches Center. Animals were housed on 12:12 h light:dark cycle and fed with standard rat diet and tap water. The rats were randomly divided into seven groups (n=6):

Control: The rats in this group were fed with standard diet and water.

Fructose: Fructose group animals fed with standard diet and tap water supplemented with 20% fructose for 10 weeks [13, 14].

Exercise: Treadmill running exercise was administered to an exercise groups every day at the same hour and experimental period of 10 weeks in total, being 30 min a day, 5 days a week [15].

Fructose plus Exercise: Rats in this group both fructose was given 10 weeks and Treadmill running exercise was applied [15].

Quercetin: To rats in this group 15 mg/kg/day quercetin in prepared 0.2% DMSO was administered by oral gavage 10 weeks [16].

Fructose plus Quercetin: To rats in this group both fructose and quercetin were administered at the same dose fructose and quercetin group 10 weeks.

Fructose plus Quercetin and Exercise: In this group rats were administered fructose, quercetin and applied exercise 10 weeks.

Weight was controlled at the beginning of the study and at the end of every week. Systolic blood pressures of all animals by tail-cuff method at the beginning of the study, at the end fourth and the end of 10 weeks.

The animals were sacrificed by taking intracardiac blood under ketamine-xylazine anesthesia and their muscle tissues (gastrocnemius, soleus, plantaris, and extensor digitorum) were harvested. Muscle tissues were frozen in liquid nitrogen and stored at -80°C together with the obtained serum samples.

Biochemical measurement

Serum glucose and triglyceride concentrations were measured by using enzymatic method in autoanalyzer. Serum insulin concentrations were measured by using ELISA kit (Milipore, Billerica, MA). Insulin resistance calculated by Homeostasis Model Assessment Index (HOMA-IR: $\text{insulin (mU/l)} \times \text{Glucose (mmol/l)} / 22.5$).

Determination of Lee Index: In order to obtain obesity parameter in experimental animals, Lee Index was calculated. After completing the 10th week of the experiment, the Lee index of each animal was calculated. This index is considered normal for the first three months of life if the index is equal to or less than 0.300, whereas rats with a value higher than 0.300 are classified as obese [17].

ATP, ADP, AMP measurement and the calculation of energy charge:

Muscles (0.15 g) were homogenized in perchloric acid and followed by neutralization with K_2HPO_4 , then centrifugation and filtration. The

supernatant was used for analysis. ATP, ADP, AMP levels were measured by the HPLC. Concentrations of ATP, ADP and AMP were calculated and were expressed as micromole/g tissue. The cellular energy charge (EC) was calculated as $(\text{ATP} + 0.5\text{ADP}) / (\text{ATP} + \text{ADP} + \text{AMP})$ [18].

Statistical analysis

All statistical analyses were carried out using “IBM SPSS Statistics 24” statistical package software (SPSS Inc., Chicago, IL). The Kolmogorov–Smirnov test was used to determine whether the distributions of continuous variables were normal. Study groups with a normal distribution were compared with one-way analysis of variance (ANOVA) and those without a normal distribution were compared with the Kruskal–Wallis analysis. Non-parametric Tukey tests were used for multiple comparisons. The descriptive statistics of numerical variables with a normal distribution were expressed as Mean $\pm$ Standard Deviation. The statistics of numerical variables without a normal distribution were expressed as medians (25th–75th percentile).

$p < 0.05$ was considered statistically significant.

Results

The body weights and systolic blood pressure are given in Table 1. As seen in Table 1, a statistically significant difference was found when the body weights and systolic blood pressure values of the fructose group animals were compared with the values of the control group.

According to our results, the lee index values of fructose group, which was applied with 20% fructose in drinking water for 10 weeks, showed a statistically significant increase compared to the control group ($p < 0.05$). Biochemical parameters, Lee index and HOMA-IR values are given in Table 2. In addition, as seen in Table 2, a statistically significant difference was found when the triglyceride,

glucose, insulin and HOMA-IR levels of the fructose group animals were compared with the control group levels.

Muscle tissue ATP, ADP levels and EC are shown in Table 3 and Figure 1.

When the ATP levels of all groups were compared with the control group, a statistically significant decrease was found in Fructose group ($p < 0.05$), and there was a statistically significant increase in Exercise and Fructose + Quercetin + Exercise group ($p < 0.05$). The lowest ATP levels were found in the Fructose group ($p < 0.05$). When the ATP levels of the groups were compared with the quercetin group, a statistically significant decrease in the Fructose group ($p < 0.05$), Exercise and Fructose + Quercetin + Exercise group were found to be statistically significant ($p < 0.05$). When the ATP levels of all groups were compared with the Exercise group, a statistically significant difference was found. The highest ATP levels were observed in the Exercise and Fructose + Quercetin + Exercise group (Table 3).

When ADP levels of the groups were compared with the control group, ADP levels increased significantly in Fructose, Exercise, Fructose + Exercise and Fructose + Exercise + Quercetin groups. It was noted that the statistically significant increase in ADP levels were in Fructose and Exercise treated groups. It was found that ADP levels did not increase in Quercetin groups (Table 3).

When the AMP levels of the groups were compared with the control group, there was a statistically significant increase in Fructose, Exercise, Fructose + Exercise groups. It was noted that the statistically significant increase in AMP levels were in Fructose and Exercise groups. AMP levels were found to be similar to the Control group in the Quercetin treated groups.

Table 1: Body weights and systolic blood pressures of groups.

Group	Body weight, g		Systolic blood pressure, mmHg		
	Beginning	End	Beginning	4th week	10th week
Control	203.16 $\pm$ 10.12	256.83 $\pm$ 8.28	126.25 $\pm$ 5.75	118.62 $\pm$ 10.09	123.41 $\pm$ 8.73
Fructose	227.40 $\pm$ 13.16 ^a	292.60 $\pm$ 24.89 ^a	124.51 $\pm$ 10.42	145.15 $\pm$ 6.91 ^a	183.57 $\pm$ 3.93 ^a

^a $p < 0.05$, compared with the Control group.

Table 2: Biochemical parameters of groups.

Group	Triglyceride (mg/dl)	Glucose (mmol/L)	Insulin (mU/L)	HOMA-IR	Lee index, mm
Control	31.66 $\pm$ 8.45	8.49 $\pm$ 0.75	5.93 $\pm$ 1.05	2.25 $\pm$ 0.38	0.29 $\pm$ 0.009
Fructose	54.14 $\pm$ 14.03 ^a	13.22 $\pm$ 1.08 ^a	9.24 $\pm$ 0.35 ^a	5.28 $\pm$ 0.46 ^a	0.32 $\pm$ 0.007 ^a

^a $p < 0.05$, compared with the Control group.

Table 3: ATP, ADP levels and energy charge in muscle tissue.

Group	ATP $\mu\text{mol/g}$ tissue	ADP $\mu\text{mol/g}$ tissue	AMP $\mu\text{mol/g}$ tissue	Energy charge
Control				
Mean $\pm$ SD	$2.124 \pm 2.15^{b,d}$	$0.146 \pm 0.13^{b,d,f}$	0	$0.962 \pm 0.96^{b,d}$
Median	0.093	0.063	0	0.014
(25–75%)	2.030–2.205	0.100–0.200	0	0.950–0.975
Fructose				
Mean $\pm$ SD	$1.022 \pm 1.05^{a,c,d,e,f}$	$3.322 \pm 3.37^{a,c,f}$	2.136 ± 2.15^a	$0.412 \pm 0.41^{a,c,d,e}$
Median	0.049	0.081	0.069	0.008
(25–75%)	0.975–1.055	3.235–3.385	2.088–2.177	0.405–0.420
Quercetin				
Mean $\pm$ SD	$2.110 \pm 2.12^{b,d}$	$0.146 \pm 0.14^{b,d,f}$	0 ^b	$0.964 \pm 0.96^{b,d}$
Median	0.055	0.052	0	0.011
(25–75%)	2.055–2.160	0.100–0.195	0	0.955–0.975
Exercise				
Mean $\pm$ SD	$2.744 \pm 2.72^{a,b,c,d,e,f}$	$3.698 \pm 3.63^{a,c,f}$	$7.943 \pm 7.99^{a,b,c}$	$0.318 \pm 0.33^{a,b,c,e}$
Median	0.223	0.260	1.323	0.036
(25–75%)	2.545–2.955	3.485–3.945	6.480–9.392	0.280–0.350
Fructose + Quercetin				
Mean $\pm$ SD	$2.012 \pm 2.20^{b,d}$	$0.068 \pm 0.06^{b,d,f}$	0 ^{b,d}	$0.980 \pm 0.98^{b,d}$
Median	0.433	0.050	0	0.010
(25–75%)	1.690–2.240	0.020–0.012	0	0.970–0.990
Fructose + Exercise				
Mean $\pm$ SD	$1.732 \pm 1.70^{b,d}$	$4.710 \pm 4.95^{a,b,c,d}$	$12.620 \pm 12.34^{a,b,c,e}$	$0.222 \pm 0.22^{a,b,c,d,e}$
Median	0.144	0.714	4.292	0.049
(25–75%)	1.600–1.880	4.110–5.190	9.615–16.25	0.180–0.265
Fructose + Quercetin + Exercise				
Mean $\pm$ SD	$3.252 \pm 3.26^{a,b,c,d,e,f}$	$1.226 \pm 1.25^{a,b,c,d,f}$	0 ^{b,d,f}	$0.860 \pm 0.86^{a,b,c,e}$
Median	0.072	0.085	0	0.007
(25–75%)	3.180–3.320	1.150–1.290	0	0.855–0.865

^a $p < 0.05$, compared with the Control group. ^b $p < 0.05$, compared with the Fructose group. ^c $p < 0.05$, compared with the Quercetin group. ^d $p < 0.05$, compared with the Exercise group. ^e $p < 0.05$, compared with the Fructose plus Quercetin group. ^f $p < 0.05$, compared with the Fructose plus Exercise group.

Figure 1: ATP, ADP, AMP levels and energy charge in muscle tissue.

When the energy charge of the Control group and the other groups were compared, the energy charge decreased in Fructose, Exercise, Fructose + Exercise groups (Table 3). In

addition, as seen in Table 3, it has been observed that quercetin treatment was increased the decreased energy charge.

Discussion

In our study, fructose-induced hyperinsulinemia, hypertriglyceridemia, hypertension, and insulin resistance as a MetS critters were observed in fructose given groups compared to the control group.

Performed study has reported that fructose fed rat model develops insulin resistance syndrome [13]. It was reported, insulin resistance, raised arterial pressure, increased triglyceride level and central obesity are important criteria for MetS. Diagnosis of metabolic syndrome is made when two or more of the above mentioned components are exit in the presence of impaired glucose regulation [19].

Skeletal muscle consist of 50–60% of body cell mass and demonstrate that largest organ affected by systemic

disease [7]. The insulin resistance is characterized by alterations in the mitochondrial activity in skeletal muscle. Skeletal muscle mitochondrial ATP synthesis has decreased in insulin resistant patients. Moreover, MetS-stimulated insulin resistance could be because of deficient fat acid oxidation which is caused by mitochondrial dysfunction of muscles [4].

ATP is the direct energy source of skeletal muscle cells in rats, long time feeding, high fructose–low fat diet causes the development of insulin resistance and increase in mitochondrial energetic performance in muscles [20]. Our results are agreement with these evidences. As seen our results, ATP level decreased after fructose administration but ADP and AMP level increased. ATP participates in metabolic process and decomposes into ADP and AMP and inorganic phosphate. In this case, energy released and major portion of this energy is used by muscles to perform mechanical work, and synthesize protein and metabolic intermediates [21]. We found also the decreased energy charge significantly to the control group in fructose fed rats. We calculated the energy charge of muscle cells using ATP, ADP, AMP levels. It is well known that the energy level of a cell depends on the balance between phosphates (ATP, ADP, AMP) [22].

In this study, treadmill running exercise was applied on exercise group every day at the experimental period 10 weeks alone and with fructose. In alone exercise group, ATP and its metabolites ADP and AMP levels increased and energy charge decreased compared to fructose and control group. The Investigators reported that skeletal muscle cells has been defined by its capability to facilitate voluntary movement via contraction and related with physical activity. Thus, the risk factors defining the MetS are related with physical activity [7, 8].

The source of energy that used to strength the action of contraction in working muscles is ATP. However ATP is not stored to large amount of in cells [23]. It was reported that ATP and its metabolite ADP subsequently binds endothelial receptors, resulting in vasodilatation [24]. We reported that physical activity (treadmill running exercise) have shown to improve skeletal muscle ATP synthesis and on the other hand to increase the using the ATP for energy of muscle contraction. In this case ADP and AMP level is high, but energy charge is low.

In fructose + exercise group, ATP level is low, but ADP and AMP levels are higher to only exercise group, energy charge also is low in this group. The reason of high ADP and AMP levels in fructose + exercise may be as follows: ANT (adenosine nucleotide translocator) is a protein complex of two subunits, located in the inner mitochondrial membrane and facilitates the exchange of

mitochondrial ATP and cytosolic ADP. It has been suggested that increased concentration of fatty acid in fructose induced metabolic syndrome in cell interfere with mitochondrial function through inhibition of ATP/ADP translocase activity [25] in case, ATP level is low but ADP and AMP levels may be high. On the other hand, the relationship between the exercise induced skeletal muscle dysfunction and AMP accumulation is important factor. In skeletal muscles, excessive energy demands during contractions lead to a net production ADP, because ATP hydrolysis exceeds ADP re-phosphorylation. Elevations in ADP increases AMP level. The accumulation of AMP lead to a reduction in energy state in muscle cell. With AMP deaminase enzyme and nucleotide cycle, the removal of AMP to inosine monophosphate (IMP) in times of excessively high energy demands (ATP) have been demonstrated that as essential to protect the energy content of the muscle cell. During AMP–IMP conversion, a large amount ATP produce for contraction of muscle [26–28].

In our study, we observed the increased AMP level in fructose, exercise and fructose plus exercise group. In fructose plus exercise group AMP level was higher to exercise group. We could not any source about fructose effect on AMP level and fructose may be inhibit the AMP removal by enzymatically.

Another aim of our study was to investigate the effect of quercetin alone and on fructose in addition to together exercise-fructose in energy alteration of muscles. When alone, quercetin has not any effect on muscle ATP, ADP, AMP and energy charge compared to control group. Quercetin alone was administrated to form quercetin-control group and to see its effect alone. We think that quercetin administrated alone will not have a negative effect on the energy charge due to its antioxidant properties. We observed that quercetin improved skeletal muscle energy balance in fructose-induced MetS model of rat muscle. Our results are consistent with other evidences. It is shown that dietary quercetin to increase skeletal muscle function [10].

It was reported that the effect of quercetin dependent on the time and dose. It was found the protective effects of quercetin in preventing high fructose mediated insulin resistance formed only with a low dose of quercetin [10, 11, 29].

Davis et al. [30] showed that seven days of quercetin feedings (12.5 and 25 mg/kg/day) in mice increased skeletal muscle markers of mitochondrial biogenesis in a dose-dependent. In this study when quercetin was applied with fructose and together fructose with exercise, we observed it regulated energy balance. Our results are in agreement with others [31]. They compared the metabolic effects of a

combination of exercise and poly phenols supplementation in obese insulin resistance rats with high fat diet. During 8 weeks their results show that polyphenols supplementation combined with exercise has a synergistic effect by increasing muscle lipid peroxidation and sparing glycogen utilization which thus enhances endurance capacity of muscles.

In conclusion, it was found that the chronic regular aerobic exercise and quercetin application might be effective in fructose mediated MetS model of rats. However, although it was observed that quercetin was more effective than exercise on muscle ATP, ATP, AMP and energy charge in fructose-induced MetS, it is thought that regular aerobic exercise alone may be preventive method for MetS or it can be used together with quercetin as a beneficial treatment.

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