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An Investigation of the Effect of Curcumin on Fructose-Induced Metabolic Syndrome Rat Models

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ABSTRACT

Aim: This study aimed to evaluate the potential effect of curcumin on glucose homeostasis, insulin resistance, inflammation, and oxidative stress in a fructose-induced metabolic syndrome rat model.

Material and Methods: 24 male adult Wistar albino rats were randomly separated in to 4 groups: control (Group 1), 20% fructose (Group 2), 20% fructose and 100 mg/kg curcumin (Group 3), and 20% fructose, and 200 mg/kg curcumin (Group 4). Serum glucose, insulin, and plasma lipoprotein levels were determined by an auto-analyzer. Other parameters were determined by the Elisa Assay Method. Mann-Whitney U test was performed using the Bonferroni Correction to determine the significance of the difference between the two group ($p \leq 0.008$). Spearman Correlation Analysis was performed among parameters.

Results: Metabolic Syndrome (MetS) was successfully created by observing increased serum glucose, high blood pressure, insulin resistance, and dyslipidemia in Group 2 compared to Group 1 ($p \leq 0.008$). The significance of serum total antioxidant capacity (TAC) levels among the groups could not be determined. While serum total oxidant status (TOS) and oxidative stress index (OSI) levels of Group 2 increased significantly compared to Group 1, and the levels of these parameters were significantly decreased in Group 3 and Group 4 compared to Group 2 ($p \leq 0.008$). The serum tumor necrosis factor-α (TNF-α) level of Group 2 increased significantly compared to Group 1 ($p \leq 0.008$). It was determined that the serum TNF-α level of Group 3 and Group 4 decreased significantly compared to Group 2 ($p \leq 0.008$). There was a positive correlation between serum OSI and TNF-α levels and serum HOMA-IR and TNF-α levels ($p \leq 0.01$).

Conclusion: Our findings indicated that curcumin has a healing effect against MetS in the rat experimental animal model.

Keywords: *Metabolic syndrome, Insulin resistance, Oxidative stress, Inflammation*

Kurkuminin Fruktoza İndüklenmiş Metabolik Sendromlu Sıçan Modelleri Üzerindeki Etkisinin İncelenmesi

ÖZ

Amaç: Çalışmamızda, fruktoza bağlı metabolik sendrom sıçan modelinde kurkuminin glukoz homeostazı, insülin direnci, inflamasyon ve oksidatif stres üzerindeki olası etkilerinin değerlendirmesini amaçladık.

Gereç ve Yöntemler: 24 adet erkek erişkin Wistar albino rat rastgele 4 gruba ayrıldı: kontrol (Grup 1), %20 fruktoz (Grup 2), %20 fruktoz ve 100 mg/kg kurkumin (Grup 3) ve %20 fruktoz, ve 200 mg/kg kurkumin (Grup 4). Serum glukoz, insülin ve plazma lipoprotein seviyeleri otoanalizör tarafından belirlenmiştir. Diğer parametreler ise Elisa Assay Metodu ile incelenmiştir. İki grup arasındaki farkın anlamlılığını belirlemek için Mann-Whitney U testi kullanılarak Bonferroni Düzeltmesi yapılmıştır ($p \leq 0{,}008$). Parametreler arasında ise Spearman Korelasyon Analizi yapılmıştır.

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Bulgular: Grup 2'de Grup 1'e göre artan serum glukozu, yüksek tansiyon, insülin direnci ve dislipidemi gözlenerek Metabolik Sendrom (MetS) başarıyla oluşturulmuştur (p≤0,008). Gruplar arasında serum total antioksidan kapasite (TAC) düzeylerinde farkın anlamlılığı bulunamamıştır. Grup 2'nin serum total oksidan durum (TOS) ve oksidatif stres indeksi (OSI) seviyeleri Grup 1'e göre anlamlı olarak artarken, Grup 3 ve Grup 4'te Grup 2'ye göre bu parametrelerin düzeyleri anlamlı olarak azalmıştır (p≤0,008). Grup 2'nin serum tümör nekrozis faktör-α (TNF-α) düzeyi Grup 1'e göre anlamlı düzeyde artmıştır (p≤0,008). Grup 3 ve Grup 4'ün serum TNF-α düzeyinin Grup 2'ye göre anlamlı düzeyde düştüğü belirlenmiştir (p≤ 0,008). Serum OSI ve TNF-α düzeyleri ile serum HOMA-IR ve TNF-α düzeyleri arasında pozitif korelasyon saptanmıştır (p≤0,01).

Sonuç: Bulgularımız, sıçan deneysel hayvan modelinde kurkuminin MetS'e karşı iyileştirici bir etkiye sahip olduğunu göstermiştir.

Anahtar Sözcükler: *Metabolik sendrom, İnsülin direnci, Oksidatif stres, İnflamasyon*

INTRODUCTION

Metabolic syndrome (MetS) consists of a combination of abdominal fat, hyperglycemia, hypertriglyceridemia, low high density lipoprotein cholesterol (HDL-C), and several metabolic risk factors. Complications such as hypertension, hyperglycemia, hypertriglyceridemia,insulin resistance, and obesity that occur in MetS can cause cardiovascular diseases and type 2 diabetes mellitus (T2DM). Insulin resistance has a crucial role in the pathogenesis of MetS, and the evidence associated insulin resistance with increased fat accumulation, obesity, and fructose consumption (1). Excessive fructose consumption has been reported to lead to an increased incidence of insulin resistance and diabetes (2). If reactive oxygen species (ROS)(such as $O_2^{\cdot-}$, H_2O_2, and $OH^{\cdot}$) exceeds the antioxidant capacity, they cause oxidative stress and disrupt the structures of biomolecules such as DNA (deoxyribonucleic acid), protein, and lipid (3). High fructose intake causes oxidative stress, resulting in increased secretion of proinflammatory cytokines and ultimately MetS (4).

Curcumin [1,7-bis (4-hydroxy-3-methoxyphenyl) -1,6-heptadiene-3,5-dione] is a bright orange-yellow natural polyphenol found in rhizomes of the Curcuma species (5). Curcumin shows activity at the cellular level and provides multiple benefits by targeting more than one signal molecule (6). Curcumin is effective in the treatment of inflammation (7), MetS (8), pain (9), and degenerative eye diseases (10, 11). It has been observed that curcumin can modulate the activity of transcription factors, growth factors, and anti-inflammatory cytokines apart from the activity of various protein kinases and other enzymes (12-14). Studies show that curcumin decreases plasma low density lipoprotein cholesterol (LDL-C) and triglyserid (TG), and increases HDL-C (15). Important findings have also been obtained in improving insulin sensitivity (16), obesity (17, 18), and prevention of hypertension (19).

Investigating the therapeutic effects of curcumin in MetS models created by fructose metabolism will make a significant contribution to the literature and to public health. Therefore, in our study, we planned to investigate the parameters determining total antioxidant capacity (TAC), total oxidant level (TOS), oxidative stress index (OSI), and tumor necrosis factor-α (TNF-α), with 100 mg/kg curcumin and 200 mg/kg curcumin administration in MetS rats model by inducing fructose for 8 weeks.

MATERIALS and METHOD

Experimental Animals and Formation of Groups

In the study, 24 male Wistar albino rats (206±10) were used. All rats constituting the experimental groups were obtained from the Laboratory Animal Husbandry and Experimental Research Center and were fed freely with normal tap water and standard rat food. Throughout the experiment, the animals were kept in an environment at 22±2°C, complying with a 12 daytime-12 hour night period.

Four groups were formedwith equal numbers (n=6), and the rats were placed in each cage. Group 1 (Control Group): Corn oil was given by gavage in a volume suitable for their body weight and normal tap water in order to drink. Group 2 (20% Fructose): Corn oil was given by oral gavage in a volume suitable for their body weight and a 20% D-fructose prepared with tap water was given to drink. Group 3 (Curcumin 100 mg/kg): 100 mg/kg Curcumin dissolved in corn oil was given by oral gavage, and 20% D-fructose prepared with tap water was given to drink. Group 4 (Curcumin 200mg/kg): 200 mg kg Curcumin dissolved in corn oil was given by oral gavage, and 20% D-fructose prepared with tap water was given to drink.The experiment continued for 8 weeks, and the rats were sacrificed under ketamine-xylazine anesthesia at the end of the 8th week. The blood samples of the rats were taken andplaced into serum tubes. The sera were separated by using centrifugation and were stored at -80°C.

Systolic Blood Pressure, Body Weight, and Lee Index

The body weights of the rats in all groups were measured in the study. Systolic blood pressure (SBP) was determined using the Tail-Cuff Method (Tail-Cuff, BIOPAC Systems).

Following the last week of the experiment, the animals' Lee Index (LI) was calculated according to the formula (LI= $\sqrt[3]{}$ (Bodyweight (g))/(Nose-to-anus distance (mm))×10). Rats with a reference value less than or equal to 0.3 were considered normal, while those with a value greater than 0.3 were classified as obese (20).

Serum Analysis

The serum lipid profile (triglyceride, total cholesterol, HDL-C, LDL-C and VLDL-C) and glucose parameters were measured enzymatically using an auto-analyzer (Beckmann AU480). The serum insulin levels were measured using a USCN ELISA kit (Catalog No: CEA448Ra).The insulin resistance was specifiedby the "homeostatic model assessment (HOMA-IR)". The HOMA-IR value was calculated using the fasting glucose (mg/dl) x fasting insulin (μU/ml)/405 formula, and those with a value of 2.5 and above were considered to have insulin resistance (21).

Measurement of serum TOS, TAC, and OSI levels

The serum TOS levels were determined using the RelAssay Diagnostics Kit (Catalog No: RL0024). The serum and TAC levels were measured using the Rel Assay Diagnostics Kit (Catalog No: RL0017). TAC and TOS units were converted into μmol, and the OSI value was calculated by taking the percentage of TOS/ TAC ratio.

Data Analysis

The IBM SPSS (Statistical Package for Social Sciences) version 25 was used in order to specify significant differences among the groups. Mean, median, standard error, and interquartile range values were used for the presentation of the obtained data. The Kruskal Wallis Test was chosen to specify the significance level of the difference between groups under nonparametric test conditions. Mann-Whitney U test and Bonferroni Correction wereused to specify the significant differences. For this purpose, 6 comparisons were made for the 4 groups, the p-value ($p \leq 0.05$) was divided into 6 according to the Bonferroni Correction (0.05/6=0.0083). For the significance level between the two groups, the p-values equal and below 0.008 were considered significant. In order to examine the correlation between parameters, Spearman Correlation Analysis was conducted between groups. In the correlation analysis, values below the p-value of equal and below 0.05 were considered as significant, and values equal and below 0.01 were considered as strongly significant.

RESULTS

As Table 1 illustrates, SBP levels of Group 2, Group 3, and Group 4 increased significantly in comparison to Group 1 (respectively; p=0.002, p=0.002, p=0.002). The SBP levels

Table 1: The median (interquartile range) levels of parameters and comparision among the groups

Groups*	Group 1 (n=6)	Group 2 (n=6)	Group 3 (n=6)	Group 4 (n=6)
SBP (mmHg)	114.17 (113-118)	173.1 (166-176) [a]	154.7 (149-160)[b,d]	153.5 (152-159)[c,e]
LI	0.28 (0.27-0.29)	0.31 (0.30-0.32) [a]	0.29 (0.28-0.3)	0.27 (0.28-0.29) [e]
TG (mg/dl)	57.95 (42.2-62.8)	142.8 (104-190) [a]	175.9 (123-206)[b]	121.6 (103-128)
TC (mg/dl)	48.5 (44.6-51.5)	72.25 (62.65-84) [a]	79.9 (64.7-84.2) [b]	68.8 (57.1-77.4) [c]
LDL-C (mg/dl)	13.6 (11.88-15.38)	16.7 (16.1-17.8) [a]	14.85 (12.78-17.4)	17.05 (15.4-19.78)
HDL-C (mg/dl)	23.2 (21.7-25.3)	27.5 (24.9- 28.9)	24.6 (24-36.1)	26.9 (24.2-35.2)
VLDL-C (mg/dl)	11.6 (8.43-12.6)	28.55 (20.8-38.1)[a]	35.2 (24.6-41.3) [b]	24.3 (20.5-25.6)
Glucose (mg/dl)	142.3 (139-148)	212.3 (263-184)[a]	249.3 (223-270)[b]	159.3 (142-215)
Insulin (μU/ml)	6.6 (6.02-6.82)	8.13 (7.9-8.94)[a]	5.49 (5.01-5.77)[d]	4.5 (3.37-5.17) [c,e]
HOMA-IR	2.3 (2.14-2.36)	4.23 (3.82-5.28)[a]	3.31 (3.04-3.54)[b,d]	1.89 (1.27-2.0)[c,e,f]
TAS (μmol/L)	0.95 (0,9-1,3)	1 (0.9-1.1)	0.98 (0.96-1.03)	1.01 (0.96-1.05)
TOS (μmol/L)	7.83 (6.9-8.9)	14.69 (10.2-18)[a]	6.06 (5.5-8.4)[d]	8.07 (6.8-9.1)[e]
OSI	0.77 (0.6-1)	1.41 (1.2-1.6)[a]	0.63 (0.5-0.9)[d]	0.78 (0.7-0.9)[e]
TNF-α (ng/L)	43.6 (31.1-49.2)	61.4 (53.4-74.2)[a]	36.8 (29-43.4)[d]	32.44 (28.3-34.4)[e]

All parameters have been shown with median and minimum-maximum values. a: The condition which the p≤0.008 in the comparison between Group 1 and Group 2, b: The condition which the p≤0.008 in the comparison between Group 1 and Group 3, c: The condition which the p≤0.008 in the comparison between Group 1 and Group 4, d: The condition which the p≤0.008 in the comparison between Group 2 and Group 3, e: The condition which the p≤0.008 in the comparison between Group 2 and Group 4, f: The condition which the p≤0.008 in the comparison between Group 3 and Group 4.

of Group 3 and Group 4 reduced significantly in comparison to Group 2 (respectively; p=0.008, p=0.004). The LI level increased significantly in Group 2 compared to Group 1(p=0.004). A partial decrease was measured in Group 3 compared to Group 2, but this decrease was not statistically significant (p=0.063). However, the LI value of Group 4 decreased significantly compared to Group 2 (p=0.002). Serum glucose levels increased significantly in Group 2 and Group 3 compared to Group 1 (respectively; p=0.004, p=0.004). There was a partial decreasein the glucose levels in Group 4 when compared to Group 2, but this decrease was not statistically significant (p=0.109).The insulin level of Group 2 increased significantly compared to Group 1, and the insulin level of Group 4 decreased significantly (respectively; p=0.004, p=0.005). The insulin level decreased significantly in Group 3 and Group 4 compared to Group 2 (respectively; p=0.004, p=0.004).

HOMA-IR values of Group 2 and Group 3 were higher than Group 1 (respectively; p=0.004, p=0.004), while HOMA-IR values of Group 4 decreased significantly compared to Group 1 (p=0.004). Additionally, HOMA-IR values of Group 3 and Group 4 decreased significantly in comparison to Group 2 (respectively; p=0.006, p=0.004). When HDL-C levels were evaluated among the groups, there were no significant differences (p=0,219). However, the TC level of Group 2, Group 3 and Group 4 increased significantly in comparison to Group 1 (respectively; p=0.002, p=0.002, p=0.002). VLDL-C level of Group 2 and Group 3 increased significantly in comparison to Group 1 (respectively; p=0.002, p=0.002). LDL-C level of Group 2 increased significantly in comparison to Group 1 (p=0.006). TG levels of Group 2 and Group 3 increased significantly when compared to Group 1 (respectively; p=0.004, p=0.004). A partial decrease was observed in the TG level in Group 4 in comparison to Group 2 and Group 3, but there were no statistically significant differences (respectively; p=0.631, p=0.078).

There were no significant differences among the groups in terms of the serum TAC levels (p=0.867). On the other hand, a statistically significant difference was measured in serum TOS and OSI levels among the groups (respectively; p=0.003, p=0.004). TOS level increased significantly in Group 2 compared to Group 1 (p=0.004). Serum TOS levels decreased significantly in Group 3 and Group 4 compared to Group 2 (respectively; p=0.003, p=0.004). OSI value increased significantly in Group 2 compared to Group 1 (p=0.006), while OSI value of Group 3 and Group 4 decreased significantly in comparison to Group 2 (respectively; p=0.004, p=0.004). Serum TNF-α levels of Group 2 increased significantly in comparison to Group 1 (p=0,002), while TNF-α levels of Group 3 and Group 4 decreased significantly in comparison to Group 2 (respectively; p=0.002, p=0.002) (Table 1).

There were a strong positive correlation and a strong significant between OSI and TNF-α levels (r=0.624, p=0.001) and between HOMA-IR and TNF-α levels (r=0.597, p=0.002). A positive correlations and a strong significant were found between OSI and TNF-α levels (r=0.483, p=0.017) (Table 2).

DISCUSSION

Metabolic syndrome (MetS) was first described by Reaven in 1988 and was characterized by insulin resistance, hyperinsulinemia, hyperglycemia, hypertension, and dyslipidemia, and then the focus was put on visceral obesity (22). However, increased inflammation provided a new perspective for MetS (23). Experimental animal models demonstrated that those fed with fructose develop MetS compared to those fed with glucose (24). Recent studies have demonstrated that administration of 20% D-fructose for 8 weeks in rat models

Table 2: Correlation among parameters

Parameters		OSI	TNF-α	HOMA-IR
OSI	**r**	1	0.624	0.483
	p	-	0.001 **	0.017**
	n	24	24	24
TNF-α	**r**	0.624	1	0.597
	p	0.001 **	-	0.002**
	n	24	24	24
HOMA-IR	**r**	0.483	0.597	1
	p	0.017**	0.002**	-
	n	24	24	24

* 2-tailed p-value below 0.05 correlation,** 2-tailed p-value below 0.01correlation

causes MetS with hypertension, hyperinsulinemia, insulin resistance and high TAG (25–27).

In experimental animal models of curcumin, the LD50 dose was reported to be 2000 mg/kg (28); 100 mg/kg and 200 mg/kg curcumin administration were shown to have an enhancing effect on the lipid profile, exhibiting an anti-inflammatory response, and protecting against oxidative stress (29–31). In rats fed with a high dose of fructose, administration of 200 mg/kg curcumin significantly decreased TG, total cholesterol, LDL cholesterol, and VLDL cholesterol and increased HDL cholesterol (32). In our study, hypertension, obesity, insulin resistance, high cholesterol, VLDL-C, LDL-C, and TG were shown in the MetS group (Group 2), and the MetS was successfully formed. In the 100 mg/kg curcumin administration, the insulin level decreased, insulin resistance was shown as the plasma blood glucose was high, but no improvement was observed in the lipid profile. Despite this, no obesity status was observed according to the LI. In paralel with, it was observed that systolic blood pressure and oxidative stress parameters decreased. The healing effects of 200 mg/kg curcumin were more pronounced. In the administration of 200 mg/kg curcumin, blood glucose decreased insignificantly, and TC, LI, insulin level and insulin resistance decreased significantly.

Curcumin exerts a neuroprotective effect by suppressing oxidative stress and preventing brain damage through the Akt/Nrf2 pathway (33) and ROS associated with endoplasmic reticulum stress through regulation of AMPK activity (34). Maithili Karpaga Selvi et al. observed that plasma and liver MDA, TOS, and OSI levels decreased, whereas TAC levels increased in rats fed with high fructose after 10 weeks of curcumin treatment (29). In our findings, on the other hand, it was measured that while serum TOS and OSI values increased significantly in the MetS group, these values decreased in the administration of 100 mg/kg curcumin and 200 mg/kg curcumin ($p \leq 0.008$).

Increased inflammation in adipose tissue is a normal process in obesity. In obesity, fat tissue cytokines and proteins of the alternative complement system are secreted excessively. Among these inflammatory agents, TNF-α, IL-6, MCP-1, resistin, and adipsin are associated with insulin resistance (35). They increase the expression of TNF-α from adipose tissue in obese and diabetic rat models, inducing insulin resistance with serine phosphorylation of IRS-1 (36). Our findings showed that TNF-α levels increased significantly in the MetS group ($p \leq 0.008$). On the other hand, it was determined that serum TNF-α levels decreased significantly with 100 mg/kg curcumin and 200 mg/kg curcumin ($p \leq 0.008$). There was a positive correlation between TOS and TNF-α and between insulin level and HOMA-IR value and TNF-α ($p \leq 0.01$).

In conclusion, according to the results of our study, administration of fructose had negative effects on body weight, systolic blood pressure, the LI, glucose, insulin, lipoproteins, total antioxidant-oxidant status, oxidative stress index, and TNF-α. However, the administration of 100 mg/kg curcumin and 200 mg/kg curcumin had a healing effect. It was revealed that insulin resistance is associated with TNF-α, a pro-inflammatory cytokine and that curcumin therapy contributes to the development of insulin sensitivity by reducing serum TNF-α levels.

MetS is a disease with increasingly serious complications in Turkey and around the world. The results of our study have revealed that curcumin has a healing effect against MetS in the rat experimental animal model. We believe that curcumin will have positive effects in protecting public health against this disease, and will guide future pharmacological research.

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Authorship Contributions

Suzan Muratoğlu Severcan conducted design of project, ethical and project processes, modelling experimental animals, laboratory experiments and constitution of full text. **Gulce Koca** conducted modelling experimental animals and laboratory experiments. **Çınar Severcan** conducted statistical analysis, translation and constitution of full text. **Canan Yilmaz** conducted modelling experimental animals and laboratory experiments. **Özge Tuğçe Paşaoğlu** conducted ethical and project processes. **Hatice Paşaoğlu** conducted managing and maintain all the processing of project.

Conflicts of Interest

There is no conflict of interest among the authors.

Financial Disclosure

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Ethical Approval

This project has a certificate approved by the Experiments Animal Local Ethics Committee with code number G.U.ET-18.082

Peer-Review Process

Extremely peer-reviewed and accepted.

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