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Effects of quercetin on adipokine profile in fructose-induced metabolic syndrome

Fruktoz ile indüklenen metabolik sendromda quercetinin adipokin profili üzerine etkileri

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Abstract

Purpose: Metabolic syndrome (MetS) is a health condition characterized by obesity, insulin resistance, dyslipidemia and type 2 diabetes (T2DM). This study aimed to assess the effects of quercetin, a natural flavonoid on MetS induced by fructose in Sprague Dawley rats.

Materials and methods: The rats, aged 8-10 weeks, were divided into 4 groups: control (C) group, metabolic syndrome (MetS) group, control+quercetin (C+Q) group, and metabolic syndrome+quercetin (MetS+Q) group. The MetS groups received a 20% fructose solution in drinking water for a duration of 10 weeks. For the last 4 weeks of the study, rats in the Q groups were administered 50 mg/kg/body weight quercetin. After 10 weeks, serum samples were tested using ELISA for Triglycerides (TG), High-Density Lipoprotein (HDL), fasting insulin, resistin, (Interleukin 6) IL6, Tumor Necrosis Factor-alpha (TNF-α), leptin, C-Reactive Protein (CRP) and, adiponectin (ADP). The body weights, Lee index and HOMA-IR scores were also measured.

Results: Fructose-fed rats showed significant increases in body weight, Lee index, HOMA-IR scores and, fasting insulin with significant decrease in HDL compared to controls. In MetS group, ADP levels were significantly lower compared to control group. In MetS+Q group, there was a tendency for reduced levels of resistin, IL-6, and leptin compared to the untreated MetS group.

Conclusion: These findings suggest that quercetin may be beneficial in managing MetS, though further research is needed to explore its mechanisms and effectiveness.

Keywords: Adipokine, fructose, metabolic syndrome, quercetin.

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Öz

Amaç: Metabolik sendrom (MetS) obezite, insülin direnci, dislipidemi ve tip 2 diyabet (T2DM) ile karakterize bir sağlık durumudur. Bu çalışmada, Sprague Dawley sıçanlarında fruktoz ile indüklenen MetS üzerinde doğal bir flavonoid olan quercetinin etkilerinin değerlendirilmesi amaçlandı.

Gereç ve yöntem: 8-10 haftalık sıçanlar 4 gruba ayrıldı: kontrol (C) grubu, metabolik sendrom (MetS) grubu, kontrol+quercetin (C+Q) grubu ve metabolik sendrom+quercetin (MetS+Q) grubu. MetS gruplarına 10 hafta boyunca içme suyunda %20 fruktoz çözeltisi verildi. Çalışmanın son 4 haftasında Q verilen gruplardaki sıçanlara 50 mg/kg/vücut ağırlığı quercetin uygulandı. 10 hafta sonra, serum örnekleri Trigliserid (TG), Yüksek Yoğunluklu Lipoprotein (HDL), açlık insülini, resistin, (Interleukin 6) IL6, Tümör Nekroz Faktörü-alfa (TNF-α), leptin, C-Reaktif Protein (CRP) ve adiponektin (ADP) için ELISA kullanılarak test edildi. Vücut ağırlıkları, Lee indeksi ve HOMA-IR skorları da ölçüldü.

Bulgular: Fruktozla beslenen sıçanların vücut ağırlığında, Lee indeksinde, HOMA-IR skorlarında ve açlık insülininde kontrol grubuna kıyasla anlamlı artışlar, HDL'de ise anlamlı düşüşler görüldü. MetS grubunda ADP seviyeleri kontrol grubuna kıyasla anlamlı derecede düşüktü. MetS+Q grubunda, tedavi edilmeyen MetS grubuna kıyasla resistin, IL-6 ve leptin seviyelerinde azalma eğilimi vardı.

Sonuç: Bu bulgular, quercetinin MetS yönetiminde faydalı olabileceğini, ancak mekanizmalarını ve etkinliğini keşfetmek için daha fazla araştırmaya ihtiyaç olduğunu göstermektedir.

Anahtar kelimeler: Adipokin, fruktoz, metabolik sendrom, quercetin.

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Introduction

Metabolic syndrome (MetS) is an illness that is characterized by the following clinical manifestations: hypertension, insulin resistance, dyslipidemia, abdominal obesity, and hyperglycemia [1]. The development of MetS is greatly affected by factors caused by increased adipose tissue and visceral obesity [2]. Hyperplasia and hypertrophy are the processes that contribute to adipose tissue growth [3]. Insulin resistance develops as a result of the production of many cytokines by hypertrophied adipocytes. Adipose tissue releases a wide range of biomolecules, many of which have been identified and the metabolic impacts and role they play in the development of disease have been thoroughly studied. Adipose tissue releases chemicals known as adipocytokines, which cross the bloodstream and help control how fat and carbohydrate metabolism are regulated [4]. For example, various bioactive molecules secreted by adipocytes, such as visfatin, resistin, adiponectin (ADP), leptin and tumor necrosis factor alpha (TNF-α), are involved in the regulation of many physiological processes, including inflammation, insulin sensitivity and energy metabolism [5, 6]. ADP is an adipokine negatively correlated with visceral adipose tissue mass and exerts anti-inflammatory effects by suppressing pro-inflammatory factors such as TNF-α, interleukin 6 (IL6) and C reactive protein (CRP). Conversely, pro-inflammatory factors are also known to suppress ADP production [7]. Disruption of adipose tissue-derived adipokine secretion in favor of pro-inflammatory cytokines may be one of the causes of systemic inflammation and ultimately the development of metabolic diseases. Limited results are obtained with treatments such as lifestyle modification (diet and exercise), pharmacotherapy, bariatric and metabolic surgical interventions for the control of MetS [8]. Plant metabolites, known as flavonoids and phytochemicals, possess antioxidant, anti-inflammatory, and anti-diabetic properties that are recognized for their protective benefits on MetS-related illnesses [9]. Quercetin is a significant member of the flavonoid family. Quercetin has been found to have several pharmacological effects in both animal and human research. These effects include reducing blood pressure [10], protecting the cardiovascular system [11], promoting weight loss, and improving hyperglycemia [12]. As far as we know, no research has been conducted to examine the impact of quercetin on the release of cytokines from adipose tissue and its potential beneficial effects on different pathophysiological processes. We hypothesized that quercetin affects the inflammatory process in metabolic syndrome. The objective of this study was to examine the impact of quercetin on the levels of pro-inflammatory cytokines, including IL-6, TNF-α, resistin, and CRP, as well as anti-inflammatory cytokines such as leptin and ADP, in a MetS model caused by high fructose.

Materials and methods

The Pamukkale University Animal Experiments Ethics Committee for authorized all experimental protocols utilized in this study (PAUHDEK-2023/32-19.10.2023, 2023/06). The animals were kept in stainless-steel cages under controlled conditions, with a temperature of 24±2°C and 50±5% humidity. They were exposed to a 12-hour cycle of light and darkness.

Experimental design

In this investigation, 28 Sprague-Dawley male rats (8-10 weeks old, 130-200 grams) were utilized. The rats were randomly assigned to one of two groups: control (C) (n=14) and metabolic syndrome (MetS) (n=14). MetS group had a D-fructose-enriched drink (D-fructose 20% (20 g/ml) for 6 weeks (Biomatik, CAS:57-48-7, MW: 180.16), while the other group C had tap water. In this study, the experimental period is 10 weeks in total. At the end of 6 weeks, the MetS and C rats were assigned to two experimental groups. C groups: control (C) (n=7) and control+quercetin (C+Q) (n=7), MetS groups: metabolic syndrome (MetS) and metabolic syndrome +quercetin (MetS+Q) groups. In the last 4 weeks of the study; the C group had tap water, the C+Q group: had tap water+50 mg/kg/day quercetin was administered by oral gavage, the MetS group: had a fructose-enriched drink

(D-fructose 20%), MetS+Q: fructose-enriched drink (D-fructose 20%) +50 mg/kg/day Q (Lot: SLCC9071, 10G SIGMA) was administered by oral gavage. Details of the experimental timeline are shown in Figure 1. It was observed that the effect size obtained in the reference study was quite strong (F=11.06). As a result of the power analysis performed considering that a lower effect size (F=0.9) could be obtained; it was calculated that 90% power could be obtained at 95% confidence level when at least 24 rats (at least 6 rats for each group) were included in the study. Considering the possibility of subject loss, it was considered to include 1 more rat in each group.

Preparation of fructose

In this investigation, a 20% solution of D-Fructose (Biomatik 99%, CAS:57-48-7, MW: 180.16) was used to create a rat model of MetS. Fructose-enriched beverages were freshly prepared on alternate days. In order to create a mixture consisting of 20% fructose, 20 grams of fructose were mixed with 100 milliliters of tap water [13]. The rats were provided with no limit to the HF drinks.

Application of quercetin

A solution of quercetin (Lot: SLCC9071, 10G SIGMA) powder (1 ml ethanol + 4 ml 0.9% saline) was given orally via gastric gavage to rats at a dose of 50 mg/kg/day [14].

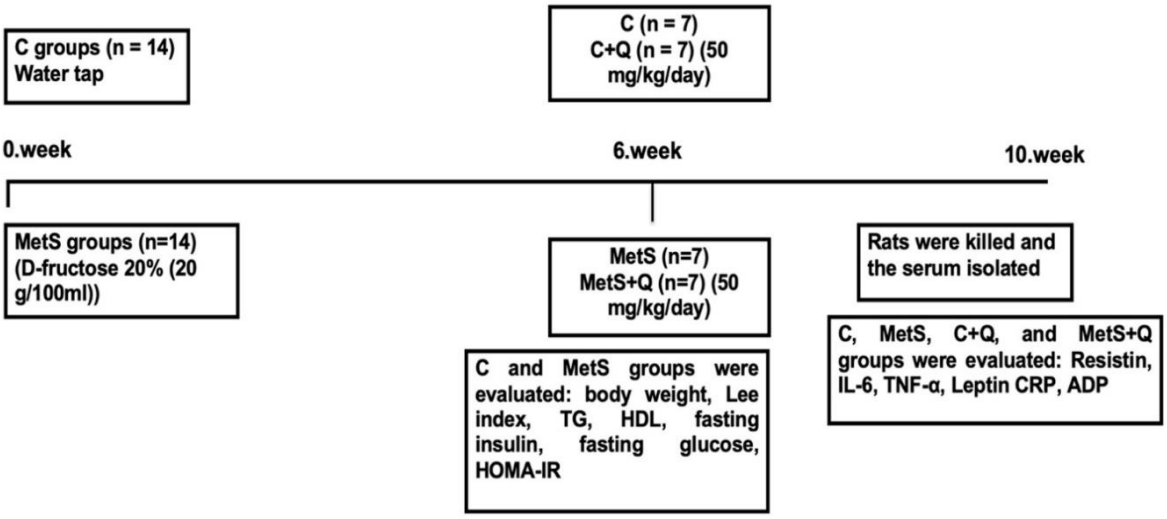

Figure 1. Illustration of experimental design

C rats that received water tap during the experimental period, MetS rats received D-fructose (20% (20 g/ml)), Q was administered 50 mg/kg/day, C: control, MetS: metabolic syndrome, Q: quercetin

Serum biochemical parameters

Following the completion of the experiment, the animals were starved for 8 hours. Serum was obtained by centrifuging blood samples extracted from the abdominal aorta of rats that had been given anesthesia. Samples were kept frozen at -80°C. Commercial kits were used for evaluating the levels of fasting TG (ELISA, BT Lab, E0249Ra, China), HDL (ELISA, Andy gene, AD1756Ra, USA), insulin (ELISA, Elabscience, E-EL-R3034, USA), resistin (ELISA, Andy gene, AD3196Ra, USA), interleukin (IL6) (ELISA, Andy gene, AD2567Ra, USA), TNF-α (ELISA, Andy gene, AD3238Ra, USA), leptin (ELISA, BT Lab, E0561Ra, China), CRP (ELISA, BT Lab, E0053Ra, China) and, ADP (ELISA, Andy gene, AD3187Ra, USA) on the experimental day.

Body weight, Lee index and HOMA-IR measurement

Body weight (BW) was measured and the results were recorded. Lee index was calculated [body weight 1/3 (g) / nasoanal length (cm)] to evaluate the growth performance of the rats

and the development of obesity. Blood samples were collected from the tail of each animal after 8 h of fasting and glucose was measured using a handheld glucometer (ACCU-CHEK Performa Nano). The following formula was used to determine the Homeostatic Model Assessment of Insulin Resistance. (HOMA-IR) index: Fasting glucose (mmol/L) × fasting insulin (mIU/L) / 22.5 is the formula for HOMA-IR.

Statistical analysis

The data were analyzed with the software package SPSS 25.0. Continuous variables are expressed as the mean ± standard error (SEM) and median (minimum- maximum values). The Shapiro-Wilk test was used to determine whether the data had a normal distribution. For parametric tests, we used an independent-sample t-test and one-way analysis of variance (Tukey test for pairwise examinations). Non-parametric testing were performed using the Mann-Whitney U test and the Kruskal-Wallis analysis of variance (Mann-Whitney U test with Bonferroni adjustment for paired analyses). In all analyses, $p \leq 0.05$ was considered statistically significant.

Results

Results of feeding fructose to rats

The development of MetS in rats fed with fructose was verified by assessing MetS indicators including Lee index, lipid profile, fasting glucose and insulin levels, and HOMA-IR score. The rats in the fructose-treated group exhibited an important rise in body weights and Lee indices, which are used as a measure of obesity, as comparison to the animals in the control group. Based on the lipid profile data, there was no significant difference in the TG level between the two groups. However, the fructose-treated group exhibited a substantial reduction in HDL level compared to the control group. The findings of the insulin metabolism study revealed that the administration of fructose to rats for a duration of 6 weeks caused elevated levels of fasting glucose and insulin, as well as the development of insulin resistance, as indicated in Table 1. The study's findings revealed that the injection of MSG to neonatal rats had a substantial impact on the advancement of MetS throughout their adult lives.

Effect of quercetin on adipocytokine levels

Upon evaluating the impact of orally administering quercetin to rats for a duration of 4 weeks, no notable disparity was found in the levels of adipocytokines (resistin, IL6, TNF-α, leptin, and ADP) and the inflammation marker CRP among the four groups (Figure 2-6). The group in which MetS was generated by fructose administration showed a significant decrease in ADP level compared to the control group. However, the administration of quercetin had no effect on ADP level (Figure 7).

Table 1. Arithmetic mean and the standard error (A.O±S.E) is used to express the results, (n=7)

Parameters	C	MetS	*p* / Test value
Body weight (g)	347±37.18	400±29.55	0.012* (t=-2.953)
Lee index (g/cm)	0.0297±0.0009	0.0317±0.00065	0.008* (t=-2.138)
TGs (mmol/L)	4979.22 (4942.05-6718.86)	5826.74 (4890.01-5945.68)	1 (z=-0.218)
HDL (pg/mL)	234.05±17.14	117.7±26.81	0.0001* (t=-7.313)
Fasting insülin (ng/mL)	43.59±11.48	75.07±14.91	0.016* (t=-1.253)
Fasting glucose (mg/dL)	125.14±24.3	255.14±46.19	0.0001* (t=-6.59)
HOMA-IR	516.06±139.79	1132.95±276	0.011* (t=-3.932)

$p \leq 0.05$ is considered statistically significant
Results for parametric data are expressed as Mean ± Standard error of the mean (SEM)
while for non-parametric data are expressed as median (minimum and maximum values)
Results having statistical significance are represented by *****, t: Independent sample, t-test, z: Mann-Whitney U test, C: Control group
MetS: Metabolic Syndrome group, TGs: Triglyceride, HDL: high-density lipoprotein
HOMA-IR: Homeostatic model assessment of insulin resistance

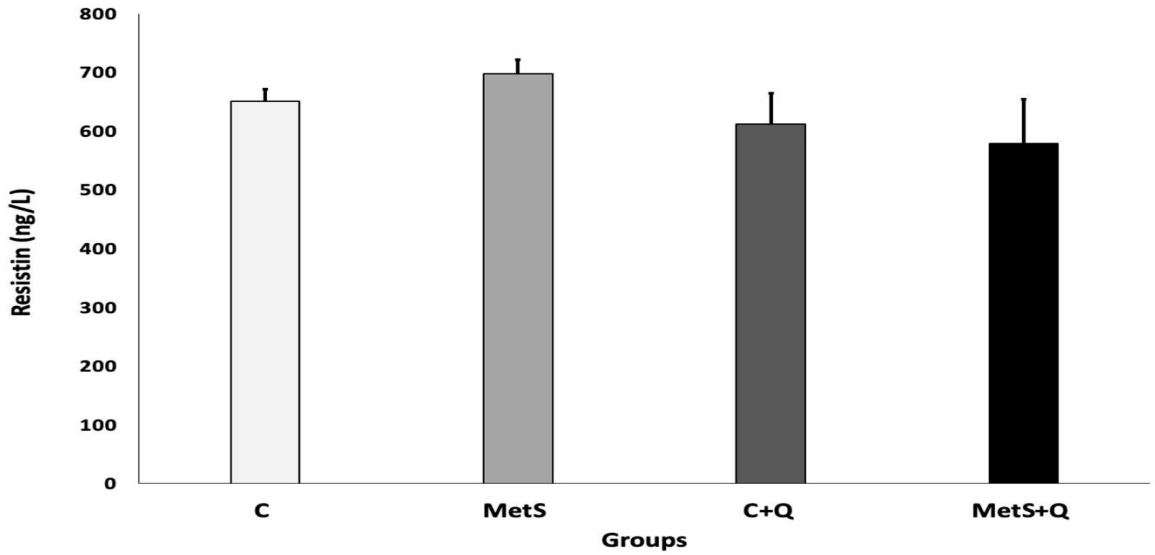

Figure 2. Analysis of resistin following a 10-week experiment, (n=7)

Arithmetic mean and the standard error is used to express the results, $p \leq 0.05$ is considered statistically significant
One-way Analysis of Variance (ANOVA) was used to analyze the data (p=0.416; F=1.026, C: 650.94±19.71, MetS: 697.16±23.92
C+Q: 612.03±52.47, MetS+Q: 579.19±75.37). C: Control, MetS: Metabolic Syndrome, C+Q: Control+Quercetin group
MetS+Q: Metabolic Syndrome+Quercetin group

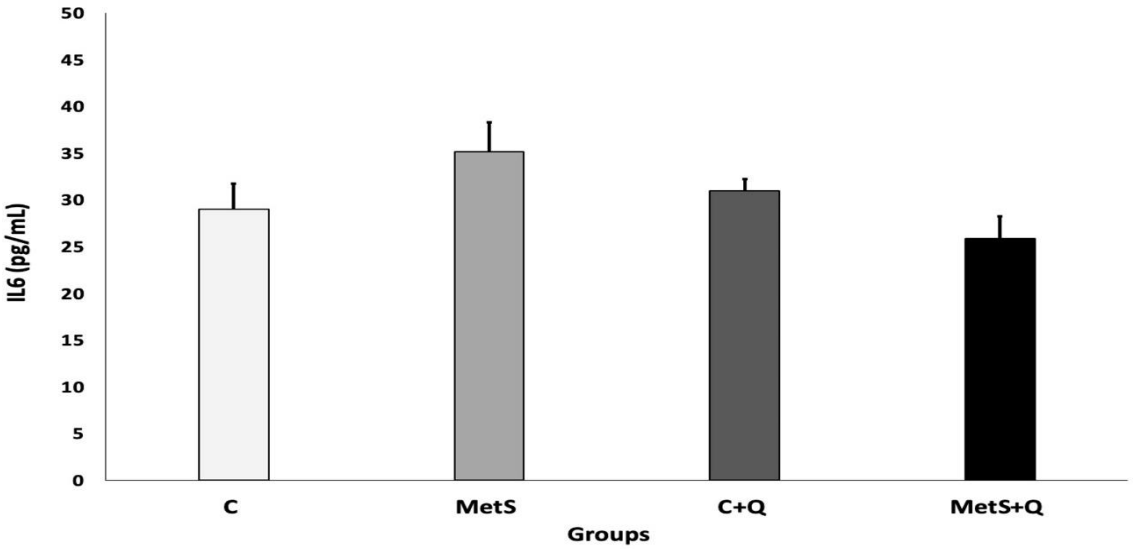

Figure 3. Analysis of IL6 following a 10-week experiment, (n=7)

Arithmetic mean and the standard error is used to express the results, $p \leq 0.05$ is considered statistically significant. Kruskal-Wallis Variance Analysis was used to analyze the data (p=0.09; kw=6.442, C: 29.03±2.71, MetS: 35.20±3.12, C+Q: 30.94±1.30, MetS+Q: 25.86±2.41)
C: Control, MetS: Metabolic Syndrome, C+Q: Control+Quercetin group, MetS+Q: Metabolic Syndrome+Quercetin group

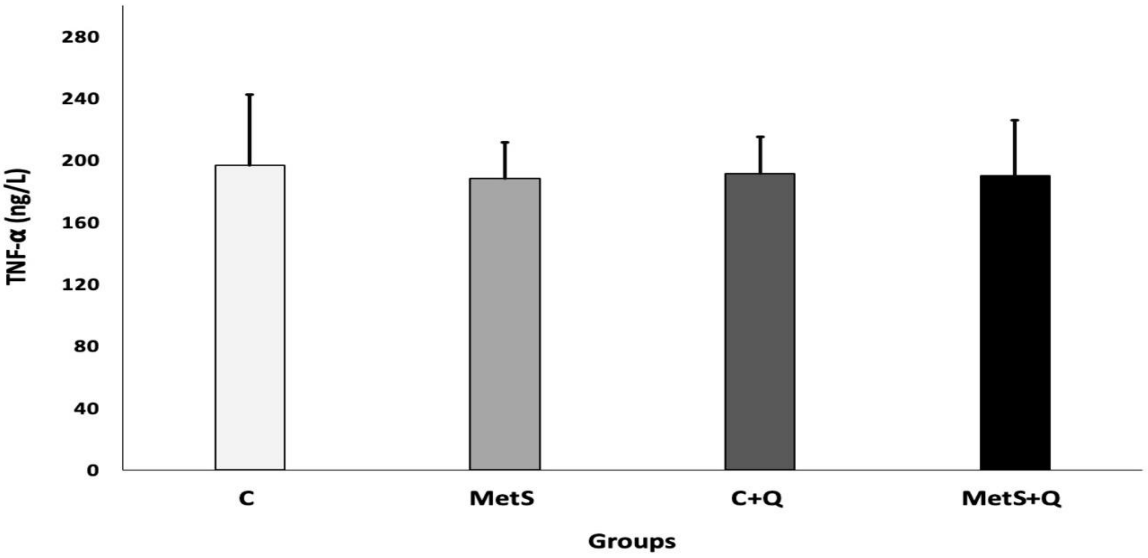

Figure 4. Analysis of TNF-α following a 10-week experiment, (n=7)

Arithmetic mean and the standard error is used to express the results, $p \leq 0.05$ is considered statistically significant. One-way Analysis of Variance (ANOVA) was used to analyze the data (p=0.998, F=0.012, C: 196.89±45.69, MetS: 188.50±23.08, C+Q: 191.42±23.78 MetS+Q: 189.9±35.99). C: Control, MetS: Metabolic Syndrome, C+Q: Control+Quercetin group, MetS+Q: Metabolic Syndrome+Quercetin group

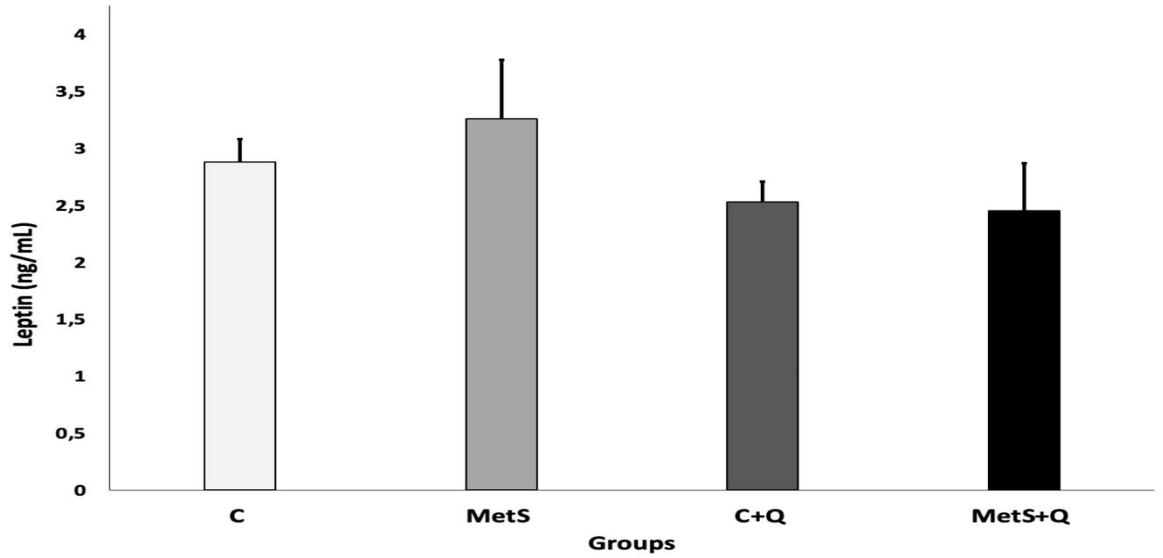

Figure 5. Analysis of leptin following a 10-week experiment, (n=7)

Arithmetic mean and the standard error is used to express the results, $p \leq 0.05$ is considered statistically significant. One-way Analysis of Variance (ANOVA) was used to analyze the data (p=0.494, F=0.841, C: 2.88±0.2, MetS: 3.26±0.515, C+Q: 2.53±0.174413 MetS+Q: 2.45±0.42). C: Control, MetS: Metabolic Syndrome, C+Q: Control+Quercetin group, MetS+Q: Metabolic, Syndrome+Quercetin group

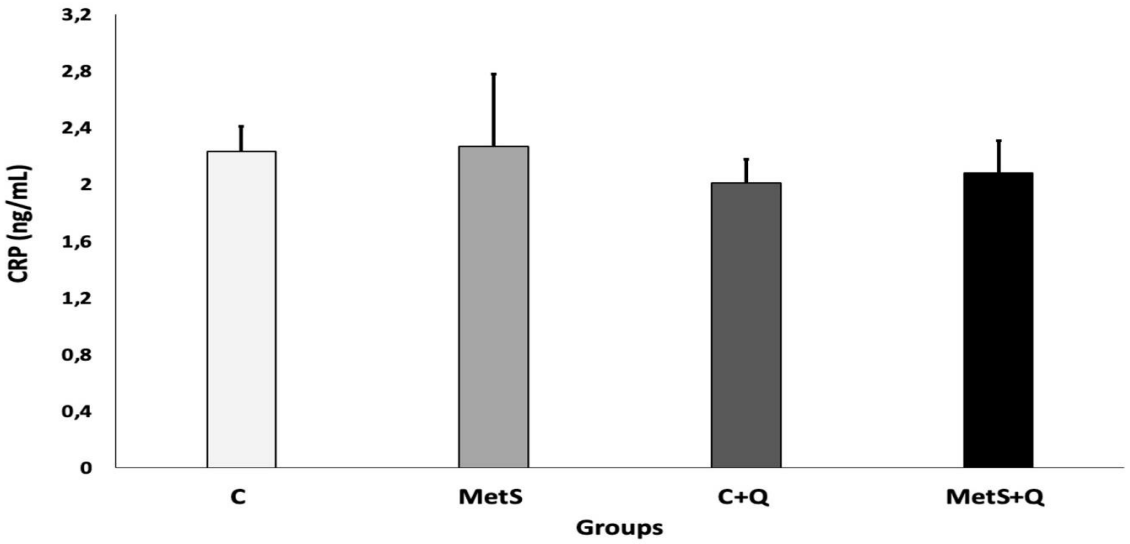

Figure 6. Analysis of CRP following a 10-week experiment, (n=7)

Arithmetic mean and the standard error is used to express the results, $p \leq 0.05$ is considered statistically significant. Kruskal-Wallis Variance Analysis was used to analyze the data (p=0.871, kw=0.708, C: 2.23±0.18, MetS: 2.27±0.51, C+Q: 2.01±0.17, MetS+Q: 2.08±0.23). C: Control MetS: Metabolic Syndrome, C+Q: Control+Quercetin group, MetS+Q: Metabolic Syndrome+Quercetin group

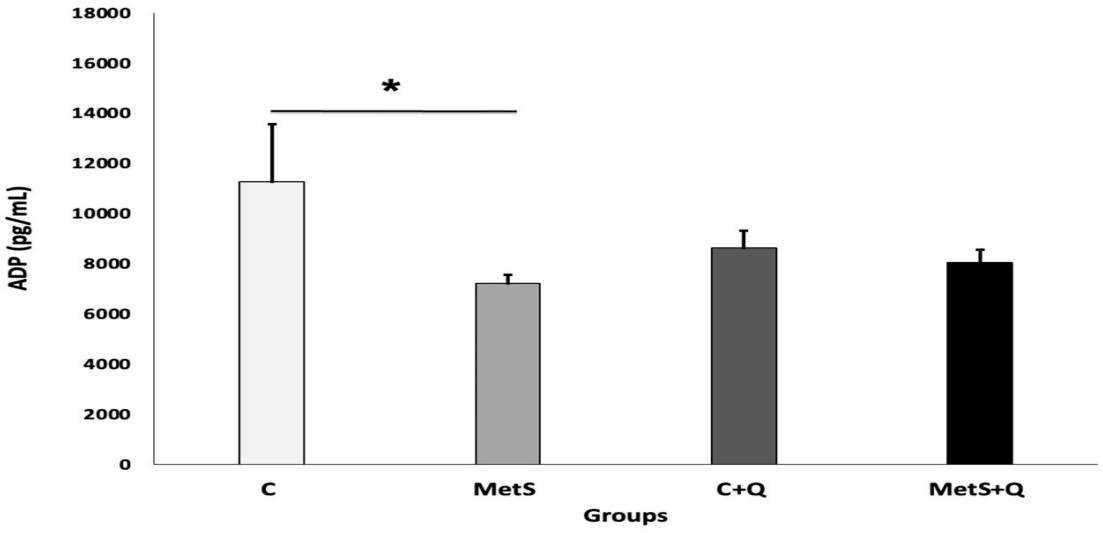

Figure 7. Analysis of ADP following a 10-week experiment, (n=7)

Arithmetic mean and the standard error is used to express the results, $p \leq 0.05$ is considered statistically significant. Kruskal-Wallis Variance Analysis was used to analyze the data (p=0.021, kw=9.725, C: 11272.50±2293.39, MetS: 7202.20±354.41, C+Q: 8629.60±687.67 MetS+Q: 8043.5±521.11). * indicates groups that differ from C group C: Control, MetS: Metabolic Syndrome, C+Q: Control+Quercetin group MetS+Q: Metabolic Syndrome+Quercetin group

Discussion

This study aimed to examine the possible impact of quercetin on adipokine levels in an animal model of MetS induced by fructose. The findings of our study demonstrated that the Lee index, fasting insulin, fasting glucose, and HOMA-IR score exhibited an increase, whereas HDL levels observed a significant reduction in the group treated with fructose, as compared to the control group. The data demonstrated that MetS was successfully induced in these rats 6 weeks following fructose administration. Within this investigation, the fructose-induced MetS model animals exhibited elevated levels of resistin, IL6, and leptin. However, these increases were not statistically significant. The animals exhibited a significant decrease in ADP levels. Furthermore, although not of significant importance, the administration of quercetin to rats with MetS resulted in a reduction in resistin, IL6, and leptin levels.

The development of MetS is influenced by both genetic and environmental variables, which are equally significant. Studies have indicated that dietary fructose is associated with a rise in visceral fat tissue. Unlike glucose, fructose does not quickly induce the release of leptin or insulin, which means it does not activate the typical feeling of satiety (satiety) [15]. Research findings from both randomized clinical trials and observational studies show that consuming high amounts of fructose is associated with an increase in energy intake, weight gain, and a higher risk of obesity [16]. Research indicates that these illnesses may be associated with oxidative stress and endoplasmic reticulum stress [17, 18]. Kumar et al. [19] discovered that introducing a 20% fructose solution into the rats' drinking water for a duration of 12 weeks resulted in elevated body weight, increased body fat, and negatively affected their lipid profile. Sánchez Lozada et al. [20] identified a metabolic abnormality in Sprague-Dawley rats after two weeks of consuming drinking water containing 10% fructose. According to these findings, a diet high in fructose was found to be efficient in creating a MetS model in rats.

In obesity, adipose tissues become dysfunctional, pro-inflammatory molecules increase and anti-inflammatory adipokines decrease. The disorder is marked by reduced levels of ADP and leptin, elevated levels of inflammatory adipo/cytokines, increased digestion of fats, and a low response to insulin. Clinical study has demonstrated that reduced levels of ADP contribute to insulin resistance, while elevated levels of resistin in obesity are associated with insulin resistance and the development of type 2 diabetes in mice [21]. Researchers discovered that individuals who are morbidly obese have elevated levels of resistin compared to individuals of normal weight. While there may be inconsistencies in certain animal models indicating that resistin levels are low in obesity, it is widely accepted that resistin levels are up in obesity. Several human studies failed to demonstrate a significant correlation between resistin levels and obesity or insulin resistance [22, 23]. There is a direct relationship between the amount of IL6 produced in adipose tissue and its presence in the bloodstream, and both of these factors are associated with obesity and insulin resistance. Our investigation did not find a statistically significant rise in IL6 levels, although observing a gradual increase in relation to MetS. The level of leptin is directly correlated with the quantity of adipose tissue [24]. The study demonstrated a substantial elevation in leptin levels in obese rats as compared to control animals [25]. The observed elevation in IL6 and leptin levels in the MetS group in our study may be attributed to the increase in adipose tissue mass in these animals.

Various investigations have indicated that some medicinal plants and active compounds can potentially regulate MetS by decreasing blood glucose levels, blood pressure, and fat buildup [26]. Quercetin, a significant flavonoid, is present in the human diet and is a constituent of other flavonoids such hesperidin, naringenin, and rutin. Quercetin has been found to have several pharmacological effects in both animals and humans. These effects include reducing blood pressure [10], protecting the cardiovascular system [11], promoting weight reduction, improving high blood sugar levels [12], and reducing lipid levels [27]. Quercetin supplementation is believed to possess antidiabetic characteristics by promoting glucose uptake through a process involving mitogen-activated protein kinase (MAPK), which is dependent on insulin. It also decreases the activity of enzymes involved in gluconeogenesis and reduces the generation of glucose in liver cells (hepatocytes) [28]. MAPK has been

identified as a stimulator of adipogenesis through the activation of adipogenic and inflammatory factors such as Nuclear Factor kappa B (NF-κB), TNF-α, IL-1β, and IL-6. Research shown that quercetin effectively suppressed the activity of MAPK in adipocytes and decreased the production of adipogenic and inflammatory cytokines in a cell line model using 3T3-L1 cells [29]. Quercetin treatment at a dosage of 10 mg/kg in obese Zucker rats effectively decreased inflammation by inhibiting TNF-α and ADP stimulation [30]. The observed decline in resistin, IL6, and leptin levels in MetS mice following quercetin administration may be attributed to the actions of quercetin. When TNF-α was present, the administration of 1 and 10 micromolar quercetin to 3T3-L1 adipocytes resulted in an increase in ADP levels and a decrease in resistin levels. A study demonstrated that giving 20 mg/kg of quercetin three times a week to male Wistar rats aged 30 days, after six weeks of consuming drinking water with 10% fructose, resulted in an increase in ADP levels and a decrease in TNF-α and resistin levels [31]. After consuming 10% fructose drinking water for 45 days, 5-week-old Wistar albino rats were given a daily intraperitoneal dose of 15 mg/kg quercetin for 10 days. This resulted in a notable variation in resistin levels compared to the MetS group [32]. Based on this data, we believe that the outcomes of our study may be influenced by factors such as the initial age of the rats, the species, and the number of subjects involved. This study attempted to explain the effects of quercetin on adipokine levels in MetS. This study has some limitations. Confirmation of the obtained adipokine levels using different molecular assays would have increased the reliability of the results. The study of the effect of quercetin on the parameters of MetS could have contributed to the evaluation of this polyphenol in MetS as a whole.

In conclusion, although the mechanisms of action of polyphenols remain unclear, it is very important to adjust the duration and dose of these flavonoids in order to obtain beneficial effects. Our findings indicate that quercetin, when given to animals with MetS, may have the ability to control the levels of adipokines. However, additional research is necessary to determine the specific signaling pathways of adipokines originating from adipose tissue.

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Conflict of interest: The authors have no conflicts of interest.

References

1. Huang PL. A comprehensive definition for metabolic syndrome. *Dis Model Mech*. 2009;2(5-6):231-237. doi:10.1242/dmm.001180
2. Kim JE, Kim JS, Jo MJ, et al. The Roles and Associated Mechanisms of Adipokines in Development of Metabolic Syndrome. Molecules. 2022;27(2):334. Published 2022 Jan 6. doi:10.3390/molecules27020334
3. Horwitz A, Birk R. Adipose Tissue Hyperplasia and Hypertrophy in Common and Syndromic Obesity-The Case of BBS Obesity. Nutrients. 2023;15(15):3445. Published 2023 Aug 4. doi:10.3390/nu15153445
4. Zorena K, Jachimowicz Duda O, Wąż P. The cut-off value for interleukin 34 as an additional potential inflammatory biomarker for the prediction of the risk of diabetic complications. Biomarkers. 2016;21(3):276-282. doi:10.3109/1354750X.2016.1138321
5. Bastard JP, Maachi M, Lagathu C, et al. Recent advances in the relationship between obesity, inflammation, and insulin resistance. Eur Cytokine Netw. 2006;17(1):4-12.
6. Pandey G, Shihabudeen MS, David HP, Thirumurugan E, Thirumurugan K. Association between hyperleptinemia and oxidative stress in obese diabetic subjects. J Diabetes Metab Disord. 2015;14:24. Published 2015 Apr 14. doi:10.1186/s40200-015-0159-9
7. Monda V, Polito R, Lovino A, et al. Short-Term Physiological Effects of a Very Low-Calorie Ketogenic Diet: Effects on Adiponectin Levels and Inflammatory States. Int J Mol Sci. 2020;21(9):3228. Published 2020 May 2. doi:10.3390/ijms21093228
8. Ruban A, Stoenchev K, Ashrafian H, Teare J. Current treatments for obesity. Clin Med (Lond). 2019;19(3):205-212. doi:10.7861/clinmedicine.19-3-205

9. Leiherer A, Stoemmer K, Muendlein A, et al. Quercetin Impacts Expression of Metabolism- and Obesity-Associated Genes in SGBS Adipocytes. Nutrients. 2016;8(5):282. Published 2016 May 12. doi:10.3390/nu8050282
10. Yamamoto Y, Oue E. Antihypertensive effect of quercetin in rats fed with a high-fat high-sucrose diet. Biosci Biotechnol Biochem. 2006;70(4):933-939. doi:10.1271/bbb.70.933
11. Dong Q, Chen L, Lu Q, et al. Quercetin attenuates doxorubicin cardiotoxicity by modulating Bmi-1 expression. Br J Pharmacol. 2014;171(19):4440-4454. doi:10.1111/bph.12795
12. Aguirre L, Arias N, Macarulla MT, Gracia A, Portillo MP. Beneficial effects of quercetin on obesity and diabetes. Open Nutraceuticals J. 2011;4(1):189-198. doi:10.2174/1876396001104010189.
13. Mamikutty N, Thent ZC, Sapri SR, Sahruddin NN, Mohd Yusof MR, Haji Suhaimi F. The establishment of metabolic syndrome model by induction of fructose drinking water in male Wistar rats. Biomed Res Int. 2014;2014:263897. doi:10.1155/2014/263897
14. Rahmani AH, Alsahli MA, Khan AA, Almatroodi SA. Quercetin, a Plant Flavonol Attenuates Diabetic Complications, Renal Tissue Damage, Renal Oxidative Stress and Inflammation in Streptozotocin-Induced Diabetic Rats. Metabolites. 2023;13(1):130. Published 2023 Jan 15. doi:10.3390/metabo13010130
15. Arslan S, Şanlıer N. Fruktoz ve Sağlık. Mersin Univ Saglık Bilim Derg. 2016;9(3):150-158.
16. Kuzma JN, Cromer G, Hagman DK, et al. No difference in ad libitum energy intake in healthy men and women consuming beverages sweetened with fructose, glucose, or high-fructose corn syrup: a randomized trial. Am J Clin Nutr. 2015;102(6):1373-1380. doi:10.3945/ajcn.115.116368
17. Busserolles J, Gueux E, Rock E, Demigné C, Mazur A, Rayssiguier Y. Oligofructose protects against the hypertriglyceridemic and pro-oxidative effects of a high fructose diet in rats. J Nutr. 2003;133(6):1903-1908. doi:10.1093/jn/133.6.1903
18. Mellor K, Ritchie RH, Meredith G, Woodman OL, Morris MJ, Delbridge LM. High-fructose diet elevates myocardial superoxide generation in mice in the absence of cardiac hypertrophy. Nutrition. 2010;26(7-8):842-848. doi:10.1016/j.nut.2009.08.017
19. Kumar SR, Mohd Ramli ES, Abdul Nasir NA, Mohd Ismail N, Mohd Fahami NA. Methanolic Extract of Piper sarmentosum Attenuates Obesity and Hyperlipidemia in Fructose-Induced Metabolic Syndrome Rats. Molecules. 2021;26(13):3985. Published 2021 Jun 29. doi:10.3390/molecules26133985
20. Sánchez Lozada LG, Tapia E, Jiménez A, et al. Fructose-induced metabolic syndrome is associated with glomerular hypertension and renal microvascular damage in rats. *Am J Physiol Renal Physiol*. 2007;292(1):F423-F429. doi:10.1152/ajprenal.00124.2006
21. Demirci Ş, Gün C. Adipoz doku ve adipoz dokudan salgılanan bazı proteinler. Mehmet Akif Ersoy Unıv J Health Sci Ins. 2019;5(2):155-179. doi:10.24998/maeusabed.338105
22. Mohammadzadeh G, Zarghami N, Mobaseri M. Serum resistin concentration in obese diabetic patients: any possible relation to insulin resistance indices? Int J Endocrinol Metab. 2008;4:183-193.
23. Emral R. Adinopektin ve diğer sitokinler. Türkiye Klinikleri J Med Sci. 2006;26:409-420.
24. Koerner A, Kratzsch J, Kiess W. Adipocytokines: Leptin the classical, resistin—the controversical, adiponectin—the promising, and more to come. Best Practice&Research. J Clin Endocrinol Metab. 2005;19:525-546. doi:10.1016/j.beem.2005.07.008
25. El Kafoury BMA, Bahgat NM, Abdel Hady EA, Samad AAAE, Shawky MK, Mohamed FA. Impaired metabolic and hepatic functions following subcutaneous lipectomy in adult obese rats. Exp Physiol. 2019;104(11):1661-1677. doi:10.1113/EP087670
26. Talha J, Priyanka M, Akanksha A. Hypertension and herbal plants. Int Res J Pharm. 2011;2(8):26-30.
27. Bhaskar S, Kumar KS, Krishnan K, Antony H. Quercetin alleviates hypercholesterolemic diet induced inflammation during progression and regression of atherosclerosis in rabbits. Nutrition. 2013;29(1):219-229. doi:10.1016/j.nut.2012.01.019
28. Eid HM, Nachar A, Thong F, Sweeney G, Haddad PS. The molecular basis of the antidiabetic action of quercetin in cultured skeletal muscle cells and hepatocytes. Pharmacogn Mag. 2015;11(41):74-81. doi:10.4103/0973-1296.149708
29. Ahn J, Lee H, Kim S, Park J, Ha T. The anti-obesity effect of quercetin is mediated by the AMPK and MAPK signaling pathways [published correction appears in Biochem Biophys Res Commun. 2011 Jan 7;404(1):579]. Biochem Biophys Res Commun. 2008;373(4):545-549. doi:10.1016/j.bbrc.2008.06.077
30. Rivera L, Morón R, Sánchez M, Zarzuelo A, Galisteo M. Quercetin ameliorates metabolic syndrome and improves the inflammatory status in obese Zucker rats. Obesity (Silver Spring). 2008;16(9):2081-2087. doi:10.1038/oby.2008.315
31. Vazquez Prieto MA, Bettaieb A, Rodriguez Lanzi C, et al. Catechin and quercetin attenuate adipose inflammation in fructose-fed rats and 3T3-L1 adipocytes. Mol Nutr Food Res. 2015;59(4):622-633. doi:10.1002/mnfr.201400631

32. Parmaksız A, Yakar B, Önalan E, Dönder E, Gürsu MF. Metabolik Sendrom Tedavisi ve Resistin Düzeylerine, Quercetin, Alfa Lipoik Asid ve Tioglitazon Tedavisinin Etkisi. Rat Çalışması. Fırat Med J. 2023;37(3):193-199.