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Effect of quercetin on perirenal adipose tissue adiponectin and resistin levels in rats with metabolic syndrome induced by high fructose-diet

Yüksek fruktozlu diyet ile metabolik sendrom oluşturulmuş sıçanlarda quercetinin perirenal yağ dokusu, adiponektin ve resistin düzeyleri üzerine etkisi

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Abstract

Purpose: Metabolic syndrome (MetS) is a cluster of risk factors for developing heart disease, stroke, and type 2 diabetes. Visceral adiposity and insulin resistance are crucial mechanisms of MetS. The increase in adipose tissue observed in MetS causes proinflammatory and anti-inflammatory cytokine imbalance. Accumulating evidence on quercetin, one of the antioxidants frequently used in MetS treatment, suggests that quercetin has significant anti-obesity and lipid-lowering effects simultaneously. Our aim is to investigate the effects of quercetin supplementation on MetS parameters and adipose tissue adipokine levels in rats fed high fructose.

Materials and methods: Sprague Dawley rats, 8-10 weeks of age, were divided into 4 groups, including a control group (C), high fructose (HF) group, quercetin (Q) group, and high fructose+quercetin (HF+Q) group. Fructose was administered to HF groups as a 20% solution in drinking water for 10 weeks. The rats in the Q groups were given 50 mg quercetin per kg BW by gavage for the last 4 weeks of experiment. The body weight, triglyceride (TG), high density lipoprotein (HDL), fasting insulin, fasting glucose, and HOMA-IR were determined in rats. Adiponectin and resistin levels were determined by ELISA assay from perirenal adipose tissue homogenates.

Results: We showed that quercetin acts to improve TG, fasting glucose and insulin resistance in high fructose-fed rats. In this study, we found no effect of quercetin on perirenal adipose tissue adiponectin and resistin levels.

Conclusion: These results showed that high fructose could induce MetS in rats, while quercetin could favorably affect these parameters.

Keywords: Metabolic syndrome, quercetin, perirenal adipose tissue, adiponectin, resistin.

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Öz

Amaç: Metabolik sendrom (MetS) kalp hastalığı, inme ve tip 2 diyabet gelişimi için bir risk faktörleri kümesidir. Visseral adipozite ve insülin direnci MetS'in önemli mekanizmalarıdır. MetS'de gözlenen yağ dokusu artışı proinflamatuar ve antiinflamatuar sitokin dengesizliğine neden olur. MetS tedavisinde sıklıkla kullanılan antioksidanlardan biri olan quercetin hakkındaki kanıtlar, quercetin'in önemli anti-obezite ve lipid düşürücü etkilerinin eş zamanlı olduğu gösterilmiştir. Amacımız, yüksek fruktozla beslenen sıçanlarda quercetin takviyesinin MetS parametreleri ve yağ doku adipokin düzeyleri üzerindeki etkilerini araştırmaktır.

Gereç ve yöntem: 8-10 haftalık Sprague Dawley sıçanlar, kontrol grubu (C), yüksek fruktoz (HF) grubu, quercetin (Q) grubu ve yüksek fruktoz+quercetin (HF+Q) grubu olmak üzere 4 gruba ayrıldı. Fruktoz, HF grup sıçanlarına içme suyunda %20'lik çözelti halinde 10 hafta süreyle uygulandı. Quercetin grubundaki sıçanlara deneyin son 4 haftasında vücut ağırlığı kg başına 50 mg quercetin gavaj yoluyla verildi. Sıçanlarda vücut ağırlığı, trigliserit (TG), yüksk dansiteli lipoprotein (HDL), açlık insülini, açlık glukozu ve HOMA-IR belirlendi. Adiponektin ve resistin seviyeleri perirenal yağ dokusu homojenatlarından ELISA yöntemi ile belirlendi.

Bulgular: Yüksek fruktozla beslenen sıçanlarda quercetin'in TG'yi, açlık glikozunu ve insülin direncini iyileştirdiğini gösterdik. Bu çalışmada quercetin'in, perirenal yağ dokusu adiponektin ve resistin düzeylerine etkisi bulunmadı.

Sonuç: Bu sonuçlar, yüksek fruktozun sıçanlarda MetS'i indükleyebileceğini, quercetin'in ise bu parametreleri olumlu yönde etkileyebileceğini göstermektedir.

Anahtar kelimeler: Metabolik sendrom, quercetin, perirenal adipoz doku, adiponektin, resistin.

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Introduction

Metabolic syndrome (MetS) is a combination of interrelated conditions that often occur together, including obesity, insulin resistance, glucose intolerance, hypertension, and dyslipidemia [1]. MetS is diagnosed as the presence of at least three of the following five characteristics: insulin resistance, high blood pressure, elevated blood sugar level, increased blood lipids [2]. Central obesity is the main cause of the etiological cascade of MetS. Abnormal fat distribution, rather than adiposity itself, is a more important risk factor for obesity-related disorders [3, 4].

Bioactive substances called adipocytokines which include visfatin, resistin, adiponectin (ADP), tumor necrosis factor alpha (TNF-α) and leptin are secreted by adipocytes. Numerous essential physiological processes, including as inflammation, insulin sensitivity, energy metabolism, and cardiovascular function, are regulated by them [5]. Adipose tissue has a high expression of ADP, which causes the body to become instantly sensitive to insulin [6]. In obese, insulin-resistant mouse models, ADP expression is decreased in contrast to the expression of adipokines that cause insulin resistance, such as resistin and TNF-α [7]. Furthermore, resistin has been shown to preventing insulin-mediated glucose absorption into cells, raise hepatic glucose synthesis, and reduce glucose tolerance, all of which contribute to the development of insulin resistance and the inhibition of adipogenesis in obesity [8].

These adipokines released into the blood attach to specific receptors on the target cells surface to affect the metabolism of tissues and organs. Adipokines can reduce the insulin sensitivity of tissues, leading to inflammation and the development of chronic complications [9]. Consequently, systemic inflammation and ultimately metabolic disorders arise from deregulation of metabolism and adipokine release in adipose tissue [10].

Treatment methods for the control of all these pathologies have not yet provided a complete solution to obesity. Therefore, there is a need for new approaches in the treatment of diseases leading to morbidity caused by MetS. Flavanoids are phytochemicals and have anti-oxidant, anti-inflammatory and anti-diabetic effects that are known protective against obesity-related diseases. An essential flavonoid, quercetin is present in human food and forms combinations with other flavonoids like rutin, hesperidin, and naringenin. Animal and human studies have reported different pharmacological effects of quercetin as attenuation of blood pressure [11], cardiovascular protection [12], loosing of weight [13], improvement of hyperglycemia [13], and hypolipidemic effects [14]. The studies have indicated that quercetin may also help regulate metabolic diseases through a variety of processes, including raising ADP, lowering leptin, antioxidant activity, reducing insulin resistance, raising insulin levels, and inhibiting calcium channels [15].

The aim of this study was to investigate the effect of quercetin on adipocytokine activity from perirenal adipose tissue in MetS rats induced by a high fructose diet, to obtain information about the underlying processes and to identify new therapeutic targets for the treatment of MetS.

Material and methods

Animals

The Pamukkale University Experiments Animal Research Ethics Committee approved all experimental protocols used in our work. Animals were housed in stainless-steel cages in standard conditions (24±2°C and 50±5% humidity) with a 12-h light-dark cycle.

Experiment design

For this study, 24 *Sprague-Dawley male rats* (8-10 weeks old, 135-200 gr) were used. The animals were divided into two groups and were randomly assigned to one of the two following groups: high fructose (HF) (n=12) and control group (C) (n=12). HF had a D-fructose-enriched drink for 10 weeks, while the other group C had tap water for this study. At the end of 6 weeks, the HF and C rats were were randomly separated into four experimental groups as follows:

I: Control (C, n=6) group

II: Quercetin (Q, n=6) group

III: High fructose (HF, n=6) group

IV: High fructose+quercetin (HF+Q, n=6) group

On the other hand, Q and HF+Q group 50 mg/kg/day quercetin was administered by oral gavage. The experimental period is 10 weeks in total (Figure 1).

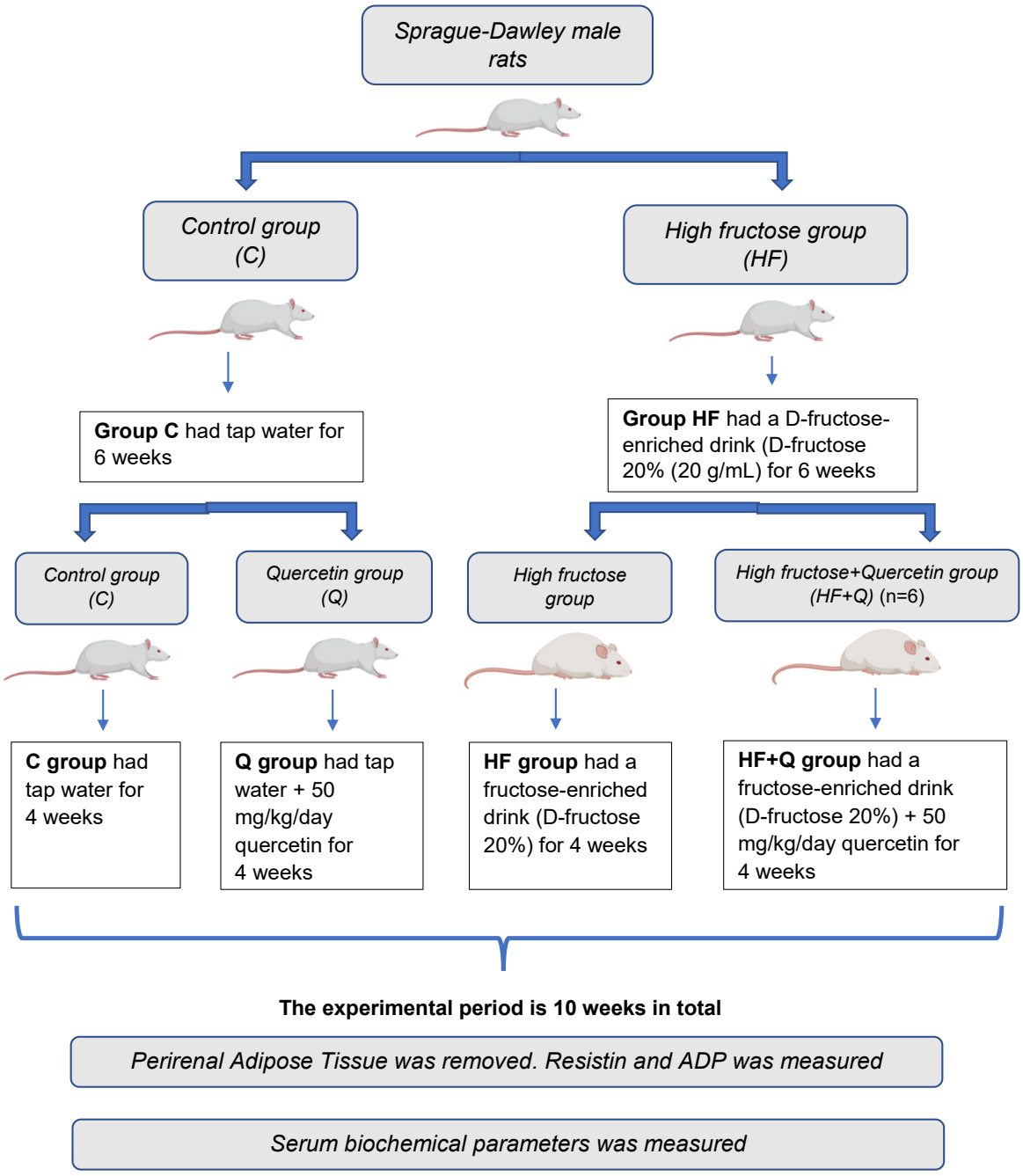

Figure 1. Study design

Preparation of fructose drinking water

The D-Fructose >99% was used in this study to develop a rat model of HF. Rats from groups HF and HF+Q were fed with fructose-enriched drink (D-fructose 20%, Biomatik, CAS:57-48-7, MW: 180.16) (20 g/mL, orally) for 10 weeks. Fructose-enriched drinks were prepared fresh every other day, water bottles were sterilized every week. 20 g of fructose were diluted in 100 mL of tap water to make 20% of the fructose-enriched drinks [16]. For 10 weeks, the rats were given the HF beverages on an ad libitum basis every day. Rats in group C were given tap water.

Quercetin application

Quercetin (Lot: SLCC9071, 10G SIGMA) in powder form was dissolved in 1 mL ethanol+4 mL 0.9% serum physiological and administered to Q and HF+Q rats by oral gastric gavage method at a dose of 50 mg/kg/day for last 4 weeks of the study.

Serum biochemical parameters

At the end of experimental period, animals were fasted for 12h. An abdominal cavity incision of 25 mm was made along the ventral midline. The blood samples were obtained from the abdominal aorta of anesthetized rats and were centrifuged to obtain serum. On the experimental day, fasting insulin (E-EL-R3034), triglyceride (TG) (E0249Ra), high density lipoprotein (HDL) levels (AD1756Ra) were measured from serum by ELISA method.

Adipose tissue homogenate

Perirenal adipose tissue was extracted from the abdominal cavity. The perirenal adipose tissue were accessible by retracting the intestines to the side. The samples were immediately frozen in liquid nitrogen and stored at −80^{0}C for later analysis. This fat tissue was resistin (AD3196Ra) and ADP (AD3187Ra) were measured from perirenal adipose tissue homogenates by ELISA method.

Body weight and HOMA-IR measurement

Body weight (BW) was measured, and the results were recorded. Blood samples were collected from the tail of each animal after 12 hr fasting. The tail was cleaned with alcohol and about 1 mm of its end was cut, and a drop of blood was used for the blood glucose test using a handheldglucometer (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). Shapiro-Wilk method was used to determine whether the data were normally distributed. For parametric tests we used one-way analysis of variance (Tukey test for pairwise examinations). For non-parametric tests we used Kruskal-Wallis variance analysis (Bonferroni-corrected Mann-Whitney U test for pairwise examinations). In all analyses, $p \leq 0.05$ was considered statistically significant.

Results

At the end of the 10-week experimental period; body weight and fasting insulin level increased in the HF group due to HF diet, body weight of HF+Q group significantly higher compared to the C+Q group (p=0.012), but no significant difference was observed between the groups for fasting insulin level (p=0.103).

According to the lipid profile results, HDL level did not differ between the groups (p=0.08), whereas TG level increased significantly in the HF group compared to the C group (p=0.009) and HF+Q group TG level significantly lower compared to the HF group (p=0.009). The results showed that this increment in the HF group was normalized by quercetin.

Fasting glucose levels were high in animals given a HF diet. HF and HF+Q group fasting glucose level was significantly higher than the C group (p=0.0001, p=0.011, respectively; C+Q group fasting glucose level was significantly lower than the HF group (p=0.011); HF+Q group fasting glucose level was significantly higher than the C+Q group (p=0.001). Quercetin was observed to have a positive effect on the increased fasting glucose level.

According to HOMA-IR results, HF group results was significantly higher than the C group (p=0.012); C+Q group level was significantly lower than the HF group (p=0.013); HF+Q group level was significantly lower than the HF group (p=0.015); it was observed that insulin resistance occurred in the HF group due to HF. Although quercetin had the effect of reducing insulin resistance in the HF group, this reduction was not significant (Table 1).

When ADP and resistin levels between the groups were analyzed, it was observed that there was no significant difference between the 4 groups (Figure 2, 3).

Table 1. General characteristics of C, HF, Q and HF+Q group rats

Parameters	C (n=6)	HF (n=6)	C+Q (n=6)	HF+Q (n=6)	*p*
Body weight (g)	359.4±14.1	395.5±12.3	355.2±7.4	398.1±7.7$^{\$}$	**0.012**
TG (mmol/L)	4960.6 (4192.0-5026.3)	5945.6 (5856.4-6695.6)*	5566.5 (4630.6-5858.3)	4715.3 (4660.7-5352.8)$^{\#}$	**0.029**
HDL (pg/mL)	237.1 (216.4 - 248.6)	106.9 (100.8-145.2)	295.2 (123.8-396.3)	261.6 (218.7-307.5)	0.08
Fasting insulin (ng/mL)	50.9±4.8	72.3±8.3	54.5±7.4	52.9±1.7	0.103
Fasting glucose (mg/dL)	125.1±9.2	255.1±17.5*	143±10.1$^{\#}$	216±17$^{*\$}$	**0.0001**
HOMA-IR	485.0 (401.1-662.0)	976.7 (913.9-1341.8)*	611.51 (166.3-724.7)$^{\#}$	507.8 (467.1-610.6)$^{\#}$	**0.031**

Body weight, fasting insulin, fasting glucose were described as mean ± standard error (SEM), and determined by One Way Analysis of Variance
Other parameters were described as median and interquartile range and determined by Kruskal Wallis Variance Analysis
$p \leq 0.05$ is considered statistically significant. Results having statistical significance are represented by symbols
*: Groups that differ significantly from group C
$^{\#}$: Groups that differ significantly from group HF
$^{\$}$: Groups that differ significantly from group C+Q
C: Control group, HF: High fructose group, C+Q: Control+Quercetin group, HF+Q: High fructose+Quercetin group
TG: Triglyceride, HDL: high-density lipoprotein, HOMA-IR: Homeostatic model assessment of insulin resistance

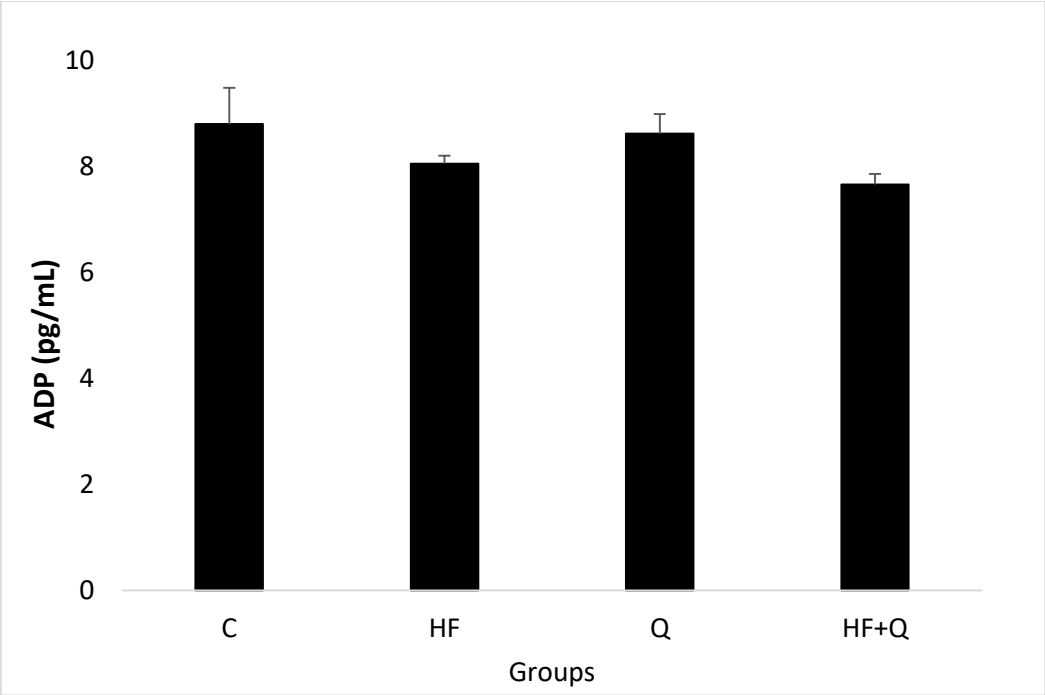

Figure 2. 10th week ADP data of 4 groups. Arithmetic mean and the standard error is used to express the results ($p \leq 0.05$). One-way ANOVA were used to analyze the data

C: control, (n=6); HF: high fructose, (n=6); Q: quercetin, (n=6); HF+Q: high fructose+quercetin, (n=6)

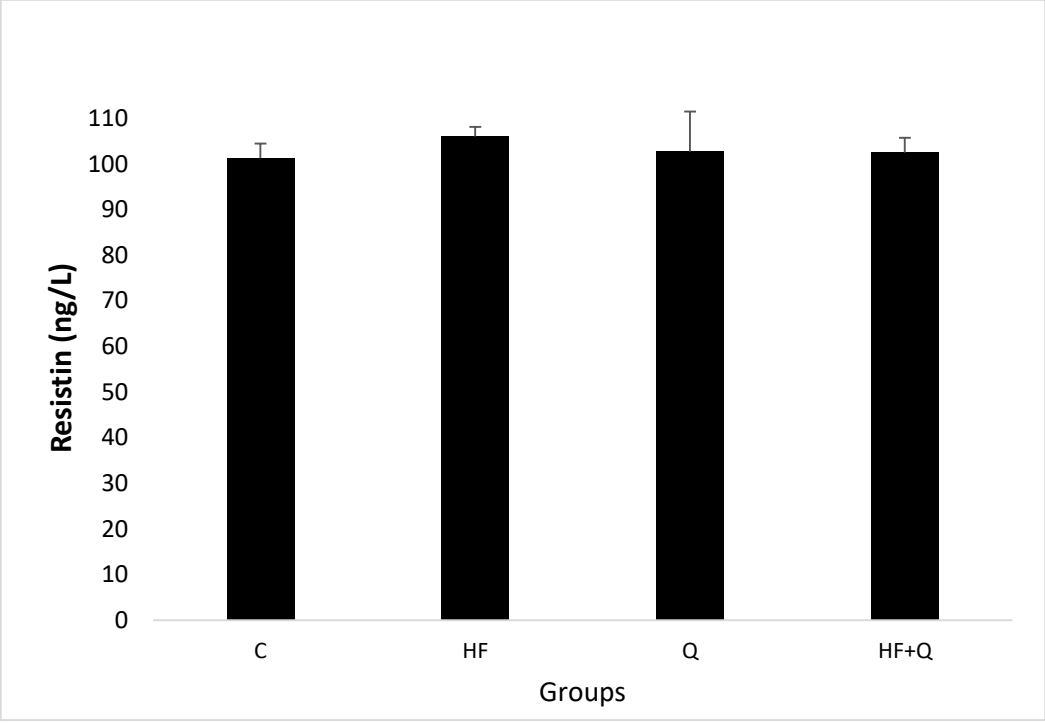

Figure 3. 10th week resistin data of 4 groups. Arithmetic mean and the standard error is used to express the results ($p \leq 0.05$). Kruskal-Wallis test were used to analyze the data

C: control, (n=6); HF: high fructose, (n=6); Q: quercetin, (n=6); HF+Q: high fructose+quercetin, (n=6)

Discussion

MetS is considered an epidemic and is a complex and heterogeneous disease. Clinical signs of a complicated illness include hypertension, insulin resistance, dyslipidemia, abdominal obesity, and hyperglycemia [2]. Various therapeutic strategies used to control MetS include lifestyle changes (such as increased physical activity and calorie restriction), pharmacological agents, and natural compounds [17]. Nevertheless, pharmaceutical drugs have occasionally been linked to cytotoxic effects. Because of this, accumulating evidence showed that several natural polyphenols (resveratrol, quercetin, procyanidins, curcumin, etc.) were beneficial to obesity and other metabolic disorders [17, 18].

As a significant flavonoid, quercetin offers a number of benefits, including lowering blood pressure, preventing hyperlipidemia and hyperglycemia, and having anti-oxidant, antiviral, anticancer, anti-inflammatory, antimicrobial, neuroprotective, and cardioprotective qualities [16]. In the present work, we analyzed the effects of quercetin, on body fat, serum insulin, glucose, TG, HDL parameters; ADP and resistin levels of perirenal adipose tissue in rats fed a high fructose-diet. The current study demonstrated TG, fasting glucose level and HOMA-IR increased in HF group compared to the C group, and these levels were normalized by quercetin treatment, while HDL, ADP and resistin levels were found to be similar all groups. Evaluation of this effect may help us to provide a better understanding of the pathophysiology and treatment of MetS. In recent years, there has been an increasing emphasis on the study of adipocyte biology due to the rising prevalence of adipose tissue-related health issues on a global scale.

Over the past few years, there has been an increase in the body of research demonstrating the health advantages of polyphenols. Several of these polyphenols have demonstrated a definite anti-obesity effect in animal models in the field of MetS. The well-known polyphenolic flavonoid molecule quercetin (3,5,7,3',4'-pe ntahydroxyflavone) is found in berries, onions, broccoli, tomatoes, and apples. It has hepatoprotective, anti-inflammatory, and anti-oxidant qualities [16]. Numerous studies have examined its advantageous impacts on obesity, insulin resistance, and MetS [19, 20]. A lot of investigations have exhibited the advantageous impacts of quercetin in decreasing body fat and enhancing insulin sensitivity [21]. According to earlier research by Vazquez Prieto et al. [22], adipose tissue mass was significantly reduced after 6 weeks of treatment with a combination of resveratrol and quercetin at doses that did not significantly reduce body fat when given separately (15 mg/kg/day and 30 mg/kg/day, respectively). The other study, Panchal et al. [23] showed that rats given a high-fat diet supplemented with 0.08% quercetin for eight weeks had reduced abdominal obesity (-37%). On the other hand, Wein et al. [24] demonstrated that quercetin feeding over 4 weeks did not affect body weight gain, body composition, or plasma leptin levels compared to other groups (high-fat diet and low-fat diet without quercetin). Similar to these results, Aranaz et al. [25] showed that no effects were observed on body weight during quercetin supplementation for 8 weeks. In our study, consistent with Wein et al. [24] and Aranaz et al. [25], when the effect of quercetin on body weight was analyzed, these parameters were increased in the HF group, but there was no significant change between the groups. Our results are supported by research conducted in the literature on the impact of the effects of polyphenols, which are dependent on the dose and the time of treatment. These variable results of quercetin on body weight may probably be due to the differences in the models used.

There are several studies in the literature showing alterations in lipid profile in rats with a high-fructose diet [25-27]. Fructose consumption for 6 weeks led to the development of metabolic alterations characteristic of MetS. In our study, according to the lipid profile results, TG level increased significantly in the HF group compared to the C group. The results showed that this increment in the HF group was normalized by quercetin. HDL level did not significantly differ between the groups, whereas HDL level was decreased in the HF group compared to the other groups; Q and HF+Q levels were higher than the HF group, but these changes were not significant. According to several studies, quercetin prevented mice fed a high-fat and high-sucrose diet from accumulating hepatic fat [25, 28]. Similarly, Jung et al. [26] showed that mice given a diet supplemented with 0.025%

quercetin for 9 weeks showed significant reductions in serum TG, TC, and epididymal adipose tissue weight. In another investigation, Peredo Escárcega et al. [29] found that, in comparison to control animals, MetS rats developed dyslipidemia with lower levels of HDL-C and elevated levels of non-HDL-C and triglycerides. Conversely, in the MetS group, the maximum dose of resveratrol+quercetin was effective in lowering triglycerides and non-HDL-C, but in the control group, only the highest dose was able to lower the concentration of non-HDL-C. In line with previous investigations, Wang et al. [30] demonstrated that the percentage of abdominal fat was considerably reduced when quercetin intake increased, with the greatest outcome occurring at 0.06% dietary quercetin supplementation when compared to the control group. Concurrently, quercetin at concentrations of 0.04% and 0.06% dramatically lowered serum levels of TG, TC, and LDL. Taken together, our data show that quercetin may improve lipid profile, and these different results of quercetin on lipid profile, may probably be due to the distinct dose and the time of treatment.

Our investigation found that animals given a HF diet had high fasting glucose levels. Quercetin was observed to have a positive effect on the increased fasting glucose level. Studies have shown quercetin to boost ADP expression and secretion while lowering blood levels of insulin, TG, cholesterol, and glucose [30]. As previously noted, obesity increases the mass and functionality of adipose tissue, which can result in elevated levels of free fatty acids in the blood, which can obstruct the transmission of insulin signals and induce glucose intolerance. Because of this, we set out to find out if quercetin supplementation may enhance the MetS rats' insulin sensitivity and glucose tolerance. According to our study's HOMA-IR results, it was observed that insulin resistance occurred in the HF group due to HF diet. Like our result, Henagan et al. [31] have demonstrated that quercetin supplementation at low levels (50 mg/day for 8 weeks) had positive effects on body fat and diet-induced insulin resistance in rats, but not at higher dosages (600 mg/day). Similarly, Vazquez Prieto et al. [22] showed that rats given high fructose for six weeks experienced lower plasma ADP, dyslipidemia, insulin resistance, obesity, and inflammation of the adipose tissue. All of these indicators were enhanced by dietary supplementation with 20 mg/kg/d of quercetin. In line with these findings, we recently observed that a 50 mg/kg dose of quercetin supplementation dramatically lowered the HOMA-IR score, pointing to a possible function in preventing diet-induced insulin resistance. Although quercetin had the effect of reducing insulin resistance in the HF group, this reduction was not significant.

Adipokines related to inflammation, lipid and glucose homeostasis, and adipocyte synthesis have all been demonstrated to occur in adipose tissue. It is proposed that these compounds could be useful therapeutic targets. Adipose tissue in good health is essential to human health. In addition to its other functions, it helps maintain energy homeostasis and isolates interior organs. A metabolically active tissue is the perirenal adipose tissue (PAT), which is a part of visceral adipose tissue. This is because PAT can create a panel of adipokines or cytokines that control renal activity through endocrine or paracrine mechanisms [32, 33]. Thus, PAT is considered to be a very useful cell source in therapeutic aspects. To the best of our knowledge, this is the first study to investigate the effects of quercetin on ADP and resistin levels from perirenal adipose tissue in rats fed HF.

In animal studies showed that obese animals had lower levels of ADP, but calorie restriction increased ADP levels [34]. Reports on changes in ADP levels with quercetin are controversial. Some studies report that there is no change, while others report an increase or decrease. Leptin and ADP concentrations were found to be significantly higher in MetS rats compared to control rats, according to Peredo Escárcega et al. [29]. The MetS rats' ADP levels were only slightly decreased (13% by resveratrol 50 + quercetin 0.95), and leptin concentration was not affected by supplementation with resveratrol + quercetin. Furthermore, it has been demonstrated that supplementing mice with a high-fat diet to create obesity led to decreased levels of glucose, insulin, TG, and cholesterol but increased ADP secretion [35]. Kim et al. [36] found that quercetin-rich onion peel extract supplementation increased ADP mRNA levels in mesenteric adipose tissue but found no differences in ADP mRNA levels from

in the perirenal adipose tissue of rats with diet-induced obesity. In our study, when the effect of quercetin on adipokines was analyzed, there was no significant change in ADP levels between the groups.

Our data revealed that ADP and resistin levels didn't show a significant difference between the groups. The multiple administration periods that were used could be the cause of this disparity with other studies. It is possible that adipokine levels would alter if the duration of the polyphenol treatment interval was extended. Insulin resistance is promoted by elevated levels of resistin, a circulating hormone unique to adipocytes in rodents that is elevated in obesity [35, 37]. Although conflicting data in animal models suggests that resistin levels are low in obesity, it is commonly believed that resistin levels are elevated in obesity [38, 39]. Iqbal et al. [40] found no relationship between the degree of obesity and resistin levels in 71 obese patients. In our study, similar to this result, no significant increase in resistin level was observed in the Q and HF+Q groups compared to the control group. The dosage and timing of treatment have an impact on the effects of polyphenols. More research on the biological role and control of quercetin is necessary because the implications of these discoveries are not entirely obvious.

In conclusion, we effectively created a high-fructose diet rat model by administering 20% fructose and by providing adequate criteria. Administration of quercetin alone improved fasting glucose and insulin resistance. Co-administration of quercetin with fructose normalized TG levels. Quercetin administration did not affect ADP and resistin levels in perirenal fat of high fructose-treated rats. Our study's findings imply that 50 mg/kg of quercetin given for four weeks may be advantageous for fructose-mediated lipid and carbohydrate metabolism. Thus, it will be guiding us to evaluate the antiobesity activity of quercetin and its potential to be developed as a drug in the fight against MetS.

Conflict of interest: The authors declare that they have no conflicts of interest.

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Authors' contributions to the article

E.K.T. and M.T.A. have constructed the main idea and hypothesis of the study. E.K.T. and M.T.A. they developed the theory and arranged/edited the material and method section. E.K.T. and M.T.A. have done the evaluation of the data in the results section. Discussion section of the article. Written by E.K.T. and M.T.A., E.K.T. and M.T.A. reviewed, corrected and approved. In addition, all authors discussed the entire study and approved the final version.