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The Effect of Quercetin, Alpha Lipoic Acid and Thiazolidine Treatment on Metabolic Syndrome and Resistin Level in Rat Model

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Objective: The metabolic syndrome (MetS) is a common and important public health problem. High resistin levels may be associated with MetS, and practices to reduce resistin levels may be effective in the treatment of MetS. The current study was aimed to compare the effects of different treatment methods applied in metabolic syndrome on resistin and biochemical parameters.

Materials and Methods: A total of 60 rats weighing 250±20 grams were divided into 6 groups. Group 1 (n=10, control group), Group 2 (n=10, MetS group), Group 3 (n=10, MetS+ quercetin treatment), Group 4 (n=10, MetS+ Alpha lipoic acid (ALA) treatment), Group 5 (n=10, MetS+ quercetin + ALA treatment), Group 6 (n=10, MetS+ Tiazolidindion (TZD) treatment). The experiment was terminated at the end of 55 days and blood samples were taken from all rats.

Results: Serum resistin levels increased significantly in rats with MetS ($p<0.001$) and decreased in quercetin ($p<0.001$), ALA ($p<0.001$) quercetin + ALA ($p<0.001$) and TZD ($p<0.001$) groups. Serum glucose, insulin and HOMA-IR values were lower in treated groups than in MetS group. Quercetin and quercetin+ALA treatments had a much more positive effect on lipid and uric acid levels compared to the treatment with TZD.

Conclusions: Resistin level increased in rats with metabolic syndrome. All of the different treatment methods applied were found to be associated with a decrease in resistin levels and improvement in biochemical parameters. We believe that reduction in resistin levels and success in the management of MetS can be achieved with the treatment agents used in our study.

Key Words: *Metabolic syndrome, resistin, quercetin, alpha lipoic acid, tiazolidindion*

Metabolik Sendrom Tedavisi ve Resistin Düzeylerine, Quercetin, Alfa Lipoik Asid ve Tioglitazon Tedavisinin Etkisi. Rat Çalışması

Amaç: Bu çalışmada metabolik sendromda uygulanan farklı tedavi yöntemlerinin rezistin ve biyokimyasal parametreler üzerindeki etkilerinin karşılaştırılması amaçlandı.

Gereç ve Yöntem: 250±20 gram ağırlığında toplam 60 rat 6 gruba ayrıldı. Grup 1 (n= 10, kontrol grubu), Grup 2 (n= 10, MetS grubu), Grup 3 (n= 10, MetS+ quercetin tedavi grubu), Grup 4 (n= 10, MetS+ Alfa lipoik asit (ALA) tedavisi grup), Grup 5 (n= 10, MetS+ quercetin + ALA tedavi grubu), Grup 6 (n= 10, MetS+ Tiazolidindion (TZD) tedavi grubu). 55 günün sonunda deney sonlandırıldı ve tüm ratlardan kan örnekleri alındı.

Bulgular: MetS'li ratlarda serum resistin düzeyleri anlamlı olarak arttı ($p<0.001$) ve quercetin ($p<0.001$), ALA ($p<0.001$)), quercetin + ALA ($p<0.001$) ve TZD ($p<0.001$) gruplarında azaldı. Tedavi edilen gruplarda serum glukoz, insülin ve HOMA-IR değerleri MetS grubuna göre daha düşüktü. Quercetin ve quercetin + ALA tedavilerinin lipid ve ürik asit düzeylerine TZD tedavisine göre çok daha olumlu etkisi oldu.

Sonuç: Metabolik sendromlu ratlarda resistin düzeyi yüksek saptandı. Uygulanan tüm farklı tedavi yöntemlerinin resistin seviyelerinde azalma ve biyokimyasal parametrelerde iyileşme ile ilişkili olduğu bulundu. Çalışmamızda kullanılan tedavi ajanları ile resistin düzeylerinde azalma ve MetS yönetiminde başarı sağlanabileceğine inanıyoruz.

***Anahtar Kelimeler*:** *Metabolik sendrom, resistin, quercetin, alfa-lipoik asid, tiazolidon*

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Introduction

Metabolic Syndrome has become a major public health problem today as an inevitable result of lifestyle changes and high prevalence of obesity. Metabolic syndrome, which affects 20-25% of the adult population worldwide, is associated with an increased risk of cardiovascular disease as it causes an increase in the incidence of hypertension, obesity, type 2 diabetes mellitus (T2DM), and dyslipidemia (1, 2).

Visceral adipose tissue, which is the source of adipokine, is accepted as an endocrine organ today. Adipokines secreted from visceral adipose tissue are thought to play an important role in the pathogenesis of MetS (3). Literature data indicated that Adipokines are associated with biological processes that determine cardiovascular risk, based on their roles in inflammation, adipogenesis, lipid metabolism and oxidative stress mechanisms (3). Resistin, an adipokine, has been associated with inflammation and insulin resistance (4). Literature data showed that resistin level is associated with

obesity, insulin resistance and diabetes mellitus and that antidiabetic drugs can increase insulin sensitivity by decreasing resistin levels (5, 6).

The increase in resistinin level in people with insulin resistance and T2DM has increased the need for studies to reduce resistin levels in treatment. Some literature studies have shown that antioxidants such as folic acid and quercetin may be effective in reducing the level of resistin (7, 8). Studies with tiaglitazone have reported a decrease in resistin levels in diet-induced obese rat and obese mice models (9). Studies on humans have shown that thiazolidinedione (TZD) reduces resistin mRNA expression and serum resistin levels by binding to PPAR gamma in adipose tissue (10). It is known that, lipoic acid which is used in the treatment of many diseases, especially diabetes, increases insulin sensitivity. It has been reported that alpha lipoic acid (ALA) administration provides a decrease in insulin resistance in rats with hyperinsulinemia and insulin resistance (11). Although the effects of quercetin, alpha lipoic acid and thiazolidinedione on insulin resistance are known, but their effects on resistin levels have not been explained.

The current study was aimed to investigate the effects of quercetin, alpha lipoic acid and thiazolidinedione administration on serum resistin levels and biochemical parameters in rats with metabolic syndrome.

Materials and Methods

Research and Publication Ethics: This study was approved by Firat University Animal Experiments Local Ethics Committee (date 29 June 2005 and number: 2005/09-02). The minimum sample size required to detect a significance difference using this test should be at least 3 in each group, (18 in total), considering type I error (alfa) of 0.05, power (1-beta) of 0.8, and effect size of 1.4.

Setting of the Experimental Groups: The current study was carried out in Fırat University Experimental Research Unit. Sixty male, five-week-old Wistar albino rats weighing 250±20 gram used in the study were obtained from Fırat University Experimental Research Center. The experimental animals were followed in cages before and during the experiment with a temperature range of 22-24 °C, 12 hours of daylight and 12 hours of darkness, and regularly ventilated room. Drinking water and 8 mm rat pellet feed supplied from Elazig feed factory were given daily without any restrictions.

The rats were divided into 6 equal groups, and study (five group) and control groups were formed. Metabolic syndrome was created in 50 of the 60 rats included in the study. Ten rats formed the control group. In order to cause metabolic syndrome in rats, 10% fructose was added to drinking water for 45 days. After 45 days, 50 rats with metabolic syndrome were divided into 5 groups. One group of rats with metabolic syndrome to been followed up without treatment and the other 4 groups constituted the group to be given quercetin, ALA, quercetin + ALA and pioglitazone, respectively. Duration of treatment was 10 days in all treatment groups. The all experiment period was 55 days. During the experiment, the control group was kept in the same environment with the other groups. In order to compensate for the injection stress, 1 mL/kg/day saline was injected intraperitoneally to the control group, untreated MetS group and piaglitazone treatment group for 10 days.

Group 1 (Control Group; n= 10); 1 mL/kg saline was administered intraperitoneally (ip) for 10 days.

Group 2 (MetS Group; n= 10); Orally 10% fructose 45 days and intraperitoneally 1 mL/kg saline 10 days were administered.

Group 3 (Quercetin Group; n= 10); Quercetin was administered intraperitoneally at a dose of 15 mg/kg/day for 10 days.

Group 4 (ALA Group; n= 10); Alpha Lipoic Acid was administered intraperitoneally at a dose of 100 mg/kg/day for 10 days.

Group 5 (Quercetin + ALA Group; n= 10); Quercetin at a dose of 15 mg/kg/day and ALA at a dose of 100 mg/kg/day were administered intraperitoneally for 10 days.

Group 6 (TZD Group; n= 10); Pioglitazone orally at a dose of 20 mg/kg/day and intraperitoneal 1 mL/kg saline for 10 days were administered

Preparation of Quercetin: Quercetin (Fluka, catalog no: 83370, Germany) was dissolved in 0.5 mL solution of 60% ethanol and made ready for injection.

Preparation of ALA: ALA (Fluka, catalog no: 62320, Switzerland) was dissolved in saline containing 0.5% NaOH and adjusted to pH: 7.4 with HCl.

Collection of Blood Samples: The study was terminated on the 55th day and blood samples were taken into EDTA tubes to evaluate biochemical parameters. All blood samples were centrifuged and separated as serum and plasma. Since many parameters will be examined in the study, the obtained serum and plasmas were placed in polypropylene tubes in small portions and stored at -20 °C until analysis.

Measurements

Measurement of Serum Resistin Levels: Serum resistin levels were studied using rat resistin enzyme-linked immunosorbent assay (ELISA) kit (BioVendor, catalog number: RD391016200, Czech Republic). The test results were multiplied by 20 due to the 1:20 dilution and expressed as ng/mL. (Kit sensitivity: <0.05 ng/mL, measuring range: 0.25-20 ng/mL, intra-assay CV: <5.2% and inter-assay CV: <9.3%).

Measurement of Serum Insulin Levels: Serum insulin levels were studied using the rat insulin ELISA kit (Linco research, catalog no: EZRMI-13K, Missouri, USA) and in accordance with the kit manual. Test results are

reported in ng/mL (Kit sensitivity: <0.2 ng/mL, measuring range: 0.2-100 ng/mL, intra-assay CV: <5% and inter-assay CV: <7.5%).

Measurement of HbA1c Levels: HbA1c levels were measured using Olympus AU 2700 autoanalyzer using Olympus branded commercial kits using whole blood samples taken into EDTA tubes. According to this method, HbA1c value was accepted in a range of 4.0% to 6.2% as normal.

Measurement of Total Antioxidant Capacity: Serum total antioxidant capacity (TAOC) levels were measured on an automated analyzer (Aeorset, Abbott, USA) using a commercially available Randox-TAS kit (Randox, Ireland). Test results are expressed in mmol Trolox equivalan/L.

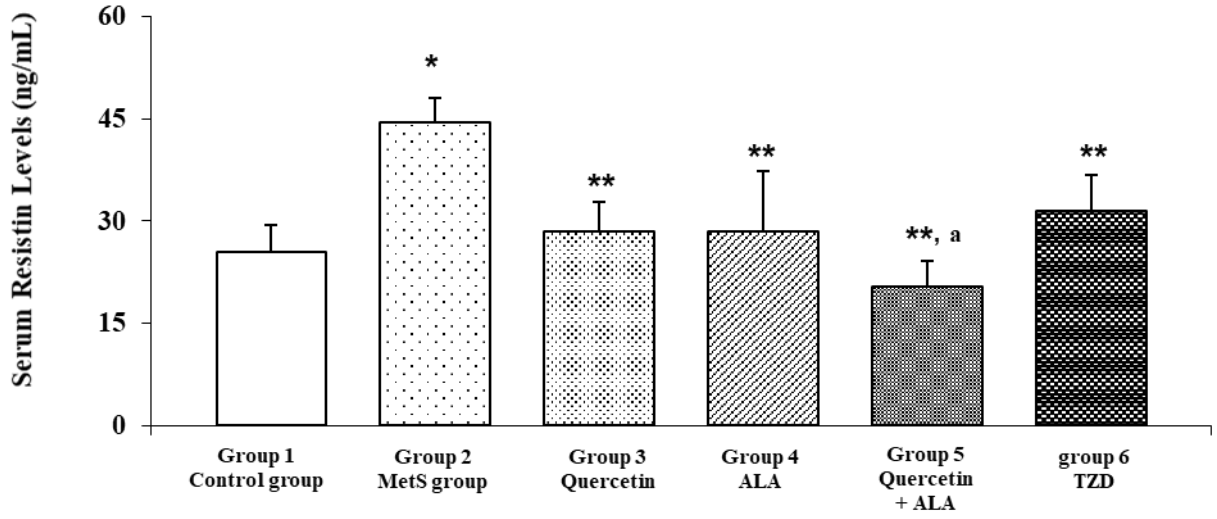
Measurement of Biochemical Parameters: Serum glucose, triglyceride (TG), total cholesterol (TC), HDL-C, LDL-C, VLDL-C and uric acid levels were measured using an Olympus AU 600 autoanalizer and kits. VLDL-C levels were obtained by calculation in the same autoanalyzer.

Fasting blood glucose and insulin values were used to determine insulin resistance with the help of the HOMA test. Fasting serum insulin levels were multiplied by 24.15 constant and fasting serum glucose levels by 0.055 for HOMA-IR, which is used to determine insulin resistance.

Statistical Analyses: Statistical analysis of the data was done by using IBM SPSS 22 statistical package program. The distribution of continuous data was evaluated with the Shapiro-Wilk test before further analysis. Continuous data conforming to normal distribution are expressed as mean±SD and categorical variables as frequency, percentage [n (%)] in the text and table. One-Way ANOVA test was used to compare more than two independent groups for continuous data conforming to normal distribution. Post-Hoc Tukey test was used to compare differences between groups. Categorical variables were compared using Chi-square and Fisher's exact tests as appropriate. Pearson's correlation coefficient was used to evaluate the relationship between two continuous data conforming to normal distribution. The level of significance was $p<0.05$.

Results

Resistin levels were significantly higher in the metabolic syndrome group (Group 2) (44.3793.59 ng/mL) compared to the control group (Group 1) (25.51±3.78 ng/mL) ($p<0.001$). Groups, receiving treatment were; quercetin (28.46±4.35 ng/mL), ALA (28.53±8.83 ng/mL), quercetin + ALA (20.34±3.82 ng/mL) and TZD group (31.49±5.23 ng/mL), resistin levels are lower than metabolic syndrome group ($p<0.001$). The resistin level of quercetin + ALA group was lower than the resistin levels of quercetin and ALA groups ($p<0.05$). The resistin level of quercetin + ALA group was lower than the resistin levels of TZD groups ($p<0.01$) (Figure 1).



*: p<0.001; Compared to the control group.
**: p<0.001; Compared to the Metabolic Syndrome group.
a: p<0.05; compared to Quercetin and ALA group, p<0.01; compared to TZD group
MetS: Metabolic syndrome; **ALA**: Alpha lipoik acid; **TZD**: Thiazolidinedione

Figure 1. Distribution of serum resistin levels of the groups

The glucose, insulin, HOMA-IR score, total cholesterol, triglyceride, VLDL, LDL, uric acid and Hba1C levels of the MetS group (Group 2) were higher than the control group (Group 1) ($p<0.001$). HDL and total antioxidant capacity (TAOC) levels of the MetS group (Group 1) were lower than the control group (Group 1) ($p<0.001$). Glucose, insulin, HOMA-IR, total cholesterol, triglyceride, VLDL, LDL and uric acid levels of the treatment groups (Group 3, Group 4, Group 5 and Group 6) were statistically lower than the MetS group (Group 2) ($p<0.05$). HDL and TAOC levels of the treatment group (Group 3, Group 4, Group 5 and Group 6) were statistically higher than the MetS group (Group 2) ($p<0.001$) (Table 1).

When examining the effects of treatment options applied to rats on biochemical parameters; The insulin level of the quercetin treatment group (Group 3) was statistically higher than the ALA + TZD group (Group 5) ($p<0.05$). Total cholesterol level of the quercetin treatment group (Group 3) was statistically lower than the TZD group (Group 6) ($p<0.01$). VLDL level of the quercetin treatment group (Group 3) was statistically lower than the TZD group (Group 6) ($p<0.05$). LDL and HDL level of the quercetin+ALA treatment group (Group 5) was statistically higher than the TZD group (Group 6) ($p<0.05$) (Table 2).

Table 1. Serum resistin and biochemical parameter levels by groups (n: 10)

	Group 1 (Kontrol Group)	Group 2 (MetS Group)	Group 3 (quercetin Group)	Group 4 (ALA Group)	Group 5 (quercetin+ALA Group)	Group 6 (TZD Group)
Resistin (ng/mL)	25.51±3.78	44.37±3.59***	28.46±4.35†††	28.53±8.83†††	20.34±3.82†††, a, b	31.49±5.23†††
Glucose (mg/dL)	106.00±11.38	143.60±14.89***	104.90±7.46†††	113.70±10.54†††	108.50±9.39†††	112.80±10.04†††
Insulin (ng/mL)	0.54±0.06	0.95±0.08***	0.74±0.10†††, c	0.63±0.04†††	0.67±0.08†††	0.63±0.05†††
HOMA-IR	3.41±0.75	8.06±1.08***	4.60±0.82†††	4.25±0.38†††	4.31±0.73†††	4.25±0.61†††
Uric acid (mg/dL)	1.48±0.11	2.41±0.28***	1.67±0.38†††	1.81±0.42††	1.73±0.26†††	1.78±0.38†
Total cholesterol (mg/dL)	78.10±7.76	109.90±11.89***	79.20±11.14†††, b	89.40±11.82†††	87.30±9.58†††	95.70±7.58††
Triglyceride (mg/dL)	107.70±16.40	173.10±19.24***	122.30±12.53†††	139.40±16.46††	133.80±19.18†††	143.60±19.91†
HDL-C (mg/dL)	32.80±3.64	22.90±7.14**	38.40±4.67†††	37.50±7.04†††	42.90±4.48†††, d	35.20±2.65†††
LDL-C (mg/dL)	29.40±2.24	68.80±9.95***	38.40±7.63†††	37.00±7.81†††	35.20±6.54†††, d	46.60±6.88†††
VLDL-C (mg/dL)	21.80±3.32	34.70±3.88***	24.10±1.79†††, d	28.00±3.23††	26.90±3.98†††	28.80±4.18††
HbA1c (%)	5.00±0.26	5.78±0.64*	5.31±0.29	5.48±0.72	5.57±0.58	5.49±0.61
TAOC (Trolox Eq./L)	1.14±0.12	0.80±0.11***	1.35±0.11†††	1.31±0.08†††	1.32±0.08†††	1.28±0.08†††

*: $p<0.05$; Compared to the control group.
**: $p<0.01$; Compared to the control group.
***: $p<0.001$; Compared to the control group.
†: $p<0.05$; Compared to the Metabolic Syndrome (MetS) group.
††: $p<0.01$; Compared to the Metabolic Syndrome (MetS) group.
†††: $p<0.001$; Compared to the Metabolic Syndrome (MetS) group.

Comparisons between treatment groups:
a; $p<0.05$ Compared to quercetin and ALA group.
b: $p<0.01$; Compared to the TZD group.
c: $p<0.05$; Compared to the ALA and TZD group.
d: $p<0.05$; Compared to the TZD group.

MetS: Metabolic syndrome; **ALA:** Alpha lipoik acid; **TZD:** Thiazolidinedione; **TAOC:** Total antioxidant capacity

Table 2. Serum resistin and biochemical parameter levels by groups (n: 10)

	Group 1 (Kontrol Group)	Group 2 (MetS Group)	Group 3 (quercetin Group)	Group 4 (ALA Group)	Group 5 (quercetin+ALA Group)	Group 6 (TZD Group)
Resistin (ng/mL)	25.51±3.78	44.37±3.59***	28.46±4.35†††	28.53±8.83†††	20.34±3.82†††, a, b	31.49±5.23†††
Glucose (mg/dL)	106.00±11.38	143.60±14.89***	104.90±7.46†††	113.70±10.54†††	108.50±9.39†††	112.80±10.04†††
Insulin (ng/mL)	0.54±0.06	0.95±0.08***	0.74±0.10†††, c	0.63±0.04†††	0.67±0.08†††	0.63±0.05†††
HOMA-IR	3.41±0.75	8.06±1.08***	4.60±0.82†††	4.25±0.38†††	4.31±0.73†††	4.25±0.61†††
Uric acid (mg/dL)	1.48±0.11	2.41±0.28***	1.67±0.38†††	1.81±0.42††	1.73±0.26†††	1.78±0.38†
Total cholesterol (mg/dL)	78.10±7.76	109.90±11.89***	79.20±11.14†††, b	89.40±11.82†††	87.30±9.58†††	95.70±7.58††
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HDL-C (mg/dL)	32.80±3.64	22.90±7.14**	38.40±4.67†††	37.50±7.04†††	42.90±4.48†††, d	35.20±2.65†††
LDL-C (mg/dL)	29.40±2.24	68.80±9.95***	38.40±7.63†††	37.00±7.81†††	35.20±6.54†††, d	46.60±6.88†††
VLDL-C (mg/dL)	21.80±3.32	34.70±3.88***	24.10±1.79†††, d	28.00±3.23††	26.90±3.98†††	28.80±4.18††
HbA1c (%)	5.00±0.26	5.78±0.64*	5.31±0.29	5.48±0.72	5.57±0.58	5.49±0.61
TAOC (Trolox Eq./L)	1.14±0.12	0.80±0.11***	1.35±0.11†††	1.31±0.08†††	1.32±0.08†††	1.28±0.08†††

*: p<0.05; Compared to the control group.
**: p<0.01; Compared to the control group.
***: p<0.001; Compared to the control group.
†: p<0.05; Compared to the Metabolic Syndrome (MetS) group.
††: p<0.01; Compared to the Metabolic Syndrome (MetS) group.
†††: p<0.001; Compared to the Metabolic Syndrome (MetS) group.

Comparisons between treatment groups:
a; p<0.05 Compared to quercetin and ALA group.
b: p<0.01; Compared to the TZD group.
c: p<0.05; Compared to the ALA and TZD group.
d: p<0.05; Compared to the TZD group.

MetS: Metabolic syndrome; **ALA:** Alpha lipoik acid; **TZD:** Thiazolidinedione; **TAOC:** Total antioxidant capacity

Discussion

In this current study, we demonstrated that serum resistin level is increased in metabolic syndrome. Previous studies reported that increased resistin levels are associated with obesity and insulin resistance (6). An another study reported that intraperitoneal resistin infusion caused increased insulin and glucose levels in rats (12). Some studies in literature reported that, similar to rat studies, serum resistin levels were increased in individuals with MetS in people (13, 14). The current study's findigs were found to be compatible with the literature data.

The current study demonsrated that glucose, cholestrol, VLDL, LDL, HOMA-IR and insulin levels are increased in MetS. Previous studies showed that serum resistin levels are higher in subjects with MetS, and resistin level was positively associated with plasma glucose and serum TG, TC, VLDL, insulin and insulin resistance, whilst negatively associated with HDL-C (15, 16). Asgary et al reported that, plasma glucose and serum TG, TC, VLDL, insulin and insulin resistance are higher in the metabolic syndrome than in the non-metabolic syndrome group (13). The data we obtained showed once again the relationship between metabolic syndrome and biochemical parameters and was found to be compatible with the literature data.

Literature data and current study data have shown that resistin levels are increased in metabolic syndrome. Therefore, the current study has focused on treatment aimed at reducing resistin levels. The current study showed that serum resistin levels decreased in rats treated with quercetin, ALA, ALA + quercetin and TZD. Sharma et al. showed that pioglitazone used in the treatment of metabolic syndrome and diabetes has an agonistic effect on the PPAR gamma receptor and PPAR gamma reduces the release of resistin (17). In another studies about the effect of quercetin and ALA on the same receptor, it was determined that both agents exhibited agonistic effects (18, 19). It has even been stated that quercetin, when given with rosiglitazone, competes to bind to the PPAR gamma region (20) and can replace TZD group drugs based on this agonistic effect (19). Khorshidi et al. reported that Quercetin supplementation decreased resistin plasma levels and gene expression in overweight or obese women with PCOS (21). In a meta-analysis study conducted by F. Haghighat Doost and M. Hariri, it was reported that alpha lipoic acid reduce inflammatory mediators and caused a decrease in metabolic syndrome parameters

(22). The current study data are consistent with literature data and it show that resistin levels can be reduced with the applied treatments.

The current study showed a positive improvement in biochemical parameters in all treatment groups. It was found that the decrease in the resistin level was associated with the improvement in biochemical parameters. In two different studies in the literature, the relationship between resistin levels and metabolic parameters attention has been drawn. Firstly, it was reported that total cholesterol, TG, LDL, fasting blood glucose and systolic blood pressure were positively correlated with resistin levels (13). In another study, it was reported that resistin levels were high in patients with MetS and that high resistin levels were associated with increased blood pressure, obesity, dyslipidemia and decreased insulin sensitivity (15). The current study and literature data emphasized that therapies to decrease serum resistin levels may be important in the treatment of metabolic syndrome. The current study which four different treatment methods were applied, it was found that all treatment methods caused a decrease in resistin levels and biochemical parameters but there were differences between treatments on biochemical parameters. The data obtained from the study support our hypothesis that the reduction of resistin levels is effective in the treatment of metabolic syndrome and improvement in biochemical parameters.

The current study showed that combined therapy was associated with more effective resistin reduction than monotherapy. Skoczylas et al reported that combined antihypertensive therapy was associated with a greater decrease in resistin than monotherapy (23). A previous study showed that increased resistin levels normalized after treatment of hyperthyroidism (24). Another study reported that statins could reduce resistin levels by controlling the inflammatory response, and the duration and dose of statin treatment was correlated with the reduction in resistin levels (25). Evidence in the previous literature that the strong anti-inflammatory effect is associated with an effective decrease in resistin levels, supports the relationship of the combined therapy obtained in the current study with more reduction in resistin levels.

In conclusion, the current study showed that serum resistin levels are associated with the metabolic syndrome and impaired biochemical parameters. Quercetin, ALA, quercetin + ALA and TZD treatments may reduce serum resistin levels and improve biochemical parameters. We believe that the treatment methods applied in the current study can be effective in the treatment of metabolic syndrome in monotherapy or combined therapy. Combined therapy may be more effective than monotherapy. It is necessary to confirm the findings of our in vitro study by an appropriately designed large-scale clinical study.

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