Received: 19 July 2022 | Accepted: 3 October 2022

DOI: 10.1111/jocd.15447

JCD Journal of Cosmetic Dermatology WILEY

ORIGINAL ARTICLE

Serum zinc-alpha-2 glycoprotein and insulin levels and their correlation with metabolic syndrome in patients with rosacea

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Abstract

Background: Metabolic syndrome and insulin resistance may accompany rosacea. Zinc-alpha-2 glycoprotein (ZAG) is an adipokine involved in lipid, glucose, and insulin metabolism and might be associated with metabolic syndrome and insulin resistance.

Aims: To investigate the serum ZAG levels, presence of metabolic syndrome, insulin resistance, and the correlation between ZAG levels, rosacea severity, and metabolic syndrome in patients with rosacea.

Patients/Methods: Seventy-nine patients with rosacea and 80 healthy volunteers were included. Anthropometric and demographic features, personal and family histories, clinical data, the subtype, severity, and duration of rosacea were recorded. Metabolic syndrome, insulin resistance, and dyslipidemia were evaluated in both groups. Fasting blood sugar, lipid panel, C-reactive protein, sedimentation rate, insulin, and serum ZAG levels were investigated.

Results: Frequency of metabolic syndrome, systolic and diastolic blood pressures, and C-reactive protein levels were significantly higher in the rosacea group ($p < 0.001$ and $p = 0.001$, respectively). Frequency of dyslipidemia and insulin resistance did not significantly differ between the groups ($p = 0.175$ and 0.694, respectively). The mean serum ZAG levels were lower in the rosacea group, but no significant difference was evident. In rosacea patients with metabolic syndrome, serum ZAG levels were significantly lower ($p = 0.043$); however, serum ZAG levels, insulin, and the homeostasis model assessment-estimated insulin resistance values were significantly higher ($p = 0.168$, 0.013 and 0.001, respectively).

Conclusion: Metabolic syndrome, high blood pressure, and high C-reactive protein levels were associated with rosacea indicating chronic systemic inflammation. ZAG levels were associated with metabolic syndrome in patients with rosacea but not associated with rosacea subtype and disease severity.

KEYWORDS
insulin resistance, metabolic syndrome, rosacea, systemic inflammation, zinc-alpha-2 glycoprotein

1 | INTRODUCTION

Rosacea, a chronic inflammatory skin disease affecting the central face, is characterized by episodic or persistent erythema, papules-pustules, telangiectasia, and phymatous changes, progressing with remissions and exacerbations.[1] In the classification by the American National Rosacea Society in 2002, four different clinical subtypes of rosacea were defined: Erythematotelangiectatic (ET), papulopustular (PP), phymatous, and ocular.[2] Although rosacea is a very common disease, the pathogenesis is still unclear.[3]

Rosacea was previously known as a chronic inflammatory disease of the skin. Today, it is known that it is not merely a skin disease but rather a multisystem inflammatory disease. Prior publications have reported that rosacea was associated with many systemic conditions including cardiovascular diseases, metabolic syndrome (MS), and insulin resistance.[4–11] The association of rosacea and MS might be attributed to shared pathogenesis. In the literature, there exists only a limited number of studies focusing on the coexistence of rosacea, MS, and adipokine levels.[12,13]

Zinc-alpha-2 glycoprotein (ZAG) is a proteinaceous adipokine with anti-inflammatory features affecting lipid and glucose metabolism.[12–16] Many prior studies investigated the association of ZAG with various diseases including obesity, coronary artery diseases, MS, type 2 diabetes mellitus, hypertension, and insulin resistance[14,17–26]; however, to the best of our knowledge, ZAG levels in patients with rosacea have not been studied.

This study aimed to investigate the association of rosacea with MS, insulin resistance, lipid profile parameters, and serum ZAG levels, and to evaluate the correlation between serum ZAG levels and metabolic syndrome components.

2 | MATERIAL AND THE METHOD

This cross-sectional investigation was conducted in the outpatient clinic of the Skin and Venereal Diseases Department of Balikesir University (Number: 94025189–050.03) between August 2020 and April 2021. Seventy-nine patients (59 females, 20 males) with rosacea and 80 healthy controls (60 females, 20 males) were included in the study. Informed consents of the patient and control groups were obtained. Pregnant patients, patients who have malignancy, infectious, and autoimmune diseases, which might affect the levels of serum ZAG, and patients treated systemically for rosacea for the previous 3 months were excluded.

2.1 | Compiling data and evaluation

Previous diseases and operations, smoking, alcohol, and drug use history of all participants were recorded. Fitzpatrick skin phototype, body weight, height, body mass index (BMI), systolic and diastolic blood pressures, and comorbidities including hypertension, diabetes mellitus, and cardiovascular disease of both groups were also recorded. Waist circumference was measured and recorded at the midpoint of the distance between the arch rib and the anterior superior iliac spine. The rosacea subtype, disease duration, and severity of rosacea patients were recorded as well. The rosacea classification and grading system defined by the American National Rosacea Society Expert Committee was used to determine the type and severity of rosacea disease.[27] For each subtype, disease severity was evaluated as "mild: 1 point, moderate: 2 points, severe: 3 points." The evaluation of the patient and control groups in terms of MS and dyslipidemia was made based on the NCEP ATP III diagnostic criteria.[28,29] According to BMI (kg/m^2) calculation; participants with a BMI <18.5 kg/m^2 were considered underweight, those between 18.5–24.99 kg/m^2 were considered normal weight, those between 25–29.99 kg/m^2 were overweight, and those ≥30 kg/m^2 were obese. A HOMA-IR (Homeostatic Model of Assessment-Insulin Resistance) score of more than 2.7 was accepted as an indicator of insulin resistance.[30]

2.2 | Statistical analysis

The Pearson Chi-squared and Fisher exact Chi-squared test, Shapiro–Wilk test, Mann–Whitney U test, and Kruskal–Wallis H test were used in our study. The Spearman correlation analysis was used to determine the correlation between the variables.

3 | RESULTS

A total of 159 patients were included in our study, 79 patients with rosacea, [59 females and 20 males, mean age: 48.2 ± 12.1 (range: 23–74)] and 80 healthy individuals [60 females and 20 males, mean age: 46.6 ± 12.2 (range: 25–71)] as the control group. Isolated erythematotelangiectatic rosacea (ETR) in 48 (60.8%), papulopustular rosacea (PPR) in 20 (25.3%), and phymatous rosacea subtype in 2 (2.5%) rosacea patients were observed. Seven (8.9%) patients had both ETR and PPR, 1 (1.3%) patient had ETR, ocular, and PPR, and 1 patient (1.3%) had phymatous and ocular rosacea subtypes. Of 79 patients with rosacea, 62 (78.5%) had a disease duration of less than 5 years, and 17 (21.5%) had more than 5 years.

The mean systolic and diastolic blood pressure levels of the rosacea group were significantly higher compared to that of the control group ($p < 0.001$).

Metabolic syndrome (MS) was detected in 30 (38%) patients from the rosacea group and 9 (11.2%) individuals from the control group ($p < 0.001$). Total cholesterol, triglyceride, LDL and HDL levels, and the frequency of dyslipidemia and insulin resistance did not significantly differ between the groups ($p = 0.0638$; 0.057; 0.821; 0.453; 0.175; 0.694, respectively) (Table 1).

CRP levels were found significantly higher in the rosacea group compared to that in the control groups; however, no significant difference in erythrocyte sedimentation rate (ESR) levels was evident between the groups ($p = 0.001$; 0.658).

The mean serum ZAG levels were 23.498 ± 7.16 (12.659–48.737) ng/ml in the rosacea group, and 24.263 ± 6.750 (14.165–57.933) ng/ml in the control group. Although the mean serum ZAG levels were found lower in patients with rosacea compared to that of the control group, no statistically significant difference was evident ($p = 0.168$). Serum ZAG levels were lower in patients with severe rosacea compared to that in the patients with mild rosacea. However, no statistically significant difference was detected in serum ZAG levels in terms of rosacea severity and subtypes ($p = 0.37$, 0.431, respectively). Significant difference was detected in median ZAG levels between rosacea patients with MS and patients without MS ($p = 0.043$) while no significant difference was observed in median ZAG values between patients with dyslipidemia and s without dyslipidemia ($p = 0.2$). A significant association between rosacea disease severity and BMI was found ($p = 0.008$). BMI was significantly higher in patients with severe rosacea compared to that in patients with mild rosacea ($p = 0.01$). A significant association was found between the severity of rosacea disease and fasting blood sugar (FBS) ($p = 0.041$). The FBS value was significantly higher in patients with severe rosacea compared to that in patients with mild rosacea ($p = 0.026$). FBS was significantly higher in the group with rosacea disease duration of more than 5 years compared to that in the group with less than 5 years ($p = 0.013$). No significant correlation was found between the severity of rosacea and median ZAG, insulin, and HOMA-IR values ($p = 0.37$; 0.11; 0.07, respectively). Median insulin and HOMA-IR levels were found to be significantly higher in rosacea patients with MS than in those without. In patients with rosacea having dyslipidemia, median insulin and HOMA-IR values were found to be significantly higher than in those without dyslipidemia (Table 2).

TABLE 1 Comparison of the presence of MS, dyslipidemia, and insulin resistance

	Patient *n* (%)	Control *n* (%)	*p* value
Metabolic Syndrome			
With	30 (%38.0)	9 (%11.2)	<0.001
Without	49 (%62.0)	71 (%88.8)	
Dyslipidemia			
With	46 (%58.2)	38 (%47.5)	0.175
Without	33 (%41.8)	42 (%52.5)	
Insulin Resistance			
With	12 (%15.2)	14 (%17.5)	0.694
Without	67 (%84.8)	66 (%82.5)	

4 | DISCUSSION

The pathogenesis of rosacea is still unclear; however, it has been thought to involve a complex interplay of genetic factors, neurovascular and immune dysregulation, presence of microorganisms, and environmental factors.[3] Rosacea could be considered a systemic inflammatory condition that has been shown to be associated with various systemic diseases. The link between rosacea and systemic diseases including allergic, respiratory diseases, gastrointestinal diseases, metabolic syndrome, diabetes mellitus, and cardiovascular diseases is increasingly being investigated.[4,9,29]

A study by Rainer et al.[4] has found that various systemic diseases were more common in patients with rosacea. Particularly moderate and severe rosacea were reported to be significantly associated with hyperlipidemia, hypertension, gastro-esophageal reflux, metabolic and cardiovascular diseases. In the study by Aksoy et al.,[31] the frequency of obesity, hypertension, and metabolic disease were found significantly higher in the rosacea group compared to that in the control group. While a relationship was found between the duration of rosacea and the presence of metabolic disease, no significant relationship was found between rosacea subtypes and any systemic comorbidity. In our study, comorbidities that existed in patients with rosacea included hypertension, diabetes mellitus, and cardiovascular system diseases. However, no significant difference was detected between the two groups in terms of these comorbidities. We think that this may be because patients with coexisting diseases including autoimmune, allergic, and chronic inflammatory diseases, which may accompany MS and affect serum ZAG and insulin values, were excluded.

In our study, systolic and diastolic blood pressure values were higher in the patient group compared to that in the control group in accordance with the studies of Akin Belli et al.,[32,33] and Aksoy et al.[31] In the meta-analysis study of Li et al.,[34] a significant relationship was found between rosacea and hypertension, but no significant relationship was found between diabetes mellitus. In our study, in accordance with the literature, obesity and FBS levels were found to be higher in patients with severe rosacea than in those with mild disease. Aksoy et al.[31] reported that the duration of the disease was

TABLE 2 Comparison of CRP, ZAG, insulin, and HOMA-IR values

		Min–Max	Mean ± SD	Median	*p* value
CRP (N: 0–5 mg/L)	Rosacea	2.98–34.5	4.774 ± 4.972	21219	0.001
	Control	2.98–10.5	3.619 ± 1.723	2.980	
Serum ZAG (ng/ml)	Rosacea	12.659–48.737	23.498 ± 7.161	21.219	0.168
	Control	14.165–57.933	24.263 ± 6.750	23.676	
Insulin (μIU/ml)	Rosacea	1.820–35.410	7.363 ± 4.791	6.290	0.172
	Control	1.500–23.000	7.250 ± 3.975	6.730	
HOMA-IR	Rosacea	0.359–18.011	2.009 ± 2.128	1.506	0.923
	Control	0.311–5.154	1.752 ± 0,999	1.551	

correlated with metabolic disease (presence of any of one: obesity, hypertension, hyperlipidemia, diabetes mellitus); however, we did not observe a correlation between the duration of rosacea and obesity, hypertension, hyperlipidemia, MS, and presence of dyslipidemia in our study. We found a significant relationship only between disease duration and FBS levels. FBS values were found to be higher in patients with a disease duration of more than 5 years.

In the study conducted by Akin Belli et al.,[32,33] insulin resistance was found to be significantly higher in patients with rosacea, and in the study of Li et al.,[34] a higher rate of MS was found in patients with rosacea. In our study, the rate of MS was found to be higher in the patient group, in accordance with the current literature. No difference was detected in the components of MS diagnostic criteria including waist circumference, FBS levels, triglyceride, and HDL levels, between the groups.

Investigation of the various lipid parameters revealed no significant difference in total cholesterol, triglyceride, LDL, and HDL levels, unlike the studies conducted by Akin Belli et al.[32,33] In addition, no difference was observed in terms of insulin, HOMA-IR levels and insulin resistance in our rosacea and control groups.

Consistent with the studies of Akin Belli et al.,[32,33] Duman et al.,[35] and Sinikumpu et al.,[36] CRP levels were also found to be high in patients with rosacea in our study. This supports the hypothesis of the presence of low-grade systemic inflammation in rosacea.

In our study, systolic and diastolic blood pressures, presence of MS, and CRP levels, which are among the cardiovascular disease risk factors, were found to be statistically significantly higher in the rosacea group. Accordingly, we suppose that rosacea is not an independent risk factor for cardiovascular disease but is associated with cardiovascular disease risk factors, as stated in the studies of Duman et al.[35] and Egeberg et al.[37]

Although the mean serum ZAG levels in patients with rosacea were lower than in the control group, we did not find a significant difference between the two groups. We think that this may be because the vast majority of patients with rosacea have mild to moderate disease activity in our study and also the meticulous study inclusion criteria of rosacea patients and the exclusion of the patients having malignancy, infectious and autoimmune diseases, which might affect serum ZAG levels. We found a negative correlation between ZAG levels, waist circumference, and BMI in patients with rosacea. Our findings in our study, in accordance with the studies of Yang et al.,[38] Marrades et al.,[39] and Liu et al.,[40] support the negative correlation between adipose tissue increase and serum ZAG levels.

Although, ZAG, an adipokine and a lipid mobilizing protein, there still exists conflicting results in studies evaluating the relationship between MS and serum ZAG levels. While some authors have found lower serum ZAG levels; others detected just the opposite, higher levels. Therefore, there exists an obscurity of how ZAG levels are affected in MS.[16,17,40–43] Like the findings in the studies of Lei et al.[41] and Wang et al.,[17] our study supports that the presence of MS and serum ZAG levels are negatively correlated. The median ZAG values were found to be lower in rosacea patients with MS than in patients without MS.

In most of the studies, ZAG has been shown to be negatively correlated with insulin resistance, and few studies have found a positive correlation or no relationship at all.[23,42–44] Consistent with the current literature, a positive correlation was found between MS and dyslipidemia, and between insulin and HOMA-IR levels. No correlation was detected between ZAG values and insulin, HOMA-IR, FBS, triglyceride, total cholesterol, LDL, and HDL levels in the patient group.

Recently, ZAG levels in various skin diseases are being investigated, and a few studies on vitiligo and atopic dermatitis draw attention.[45–47] However, no study so far has investigated the serum adipokine levels and the correlation between rosacea, accompanying comorbidities and adipokine levels. We think that our study is pioneering one evaluating a novel marker, ZAG levels, for use to detect MS in rosacea and may be in other chronic inflammatory skin diseases associated with comorbidities.

The main limitation of our study was the small sample size. In addition, since it was a cross-sectional study, multicenter, prospective studies with larger sample groups are needed to establish a clear cause–effect association.

FUNDING INFORMATION

This project was funded by the Scientific Research Project Unit of Balikesir University.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICAL APPROVAL

All procedures performed in this study were in accordance with the ethical standards of the local ethical committee of Balikesir University (Number: 94025189–050.03).

PRESENTATION

This work has been presented as an oral presentation at 7th INDERCOS Meeting 2022 and awarded the best oral presentation first prize

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How to cite this article: Sahin RB, Kilic FA, Hizli P, Baykan O. Serum zinc-alpha-2 glycoprotein and insulin levels and their correlation with metabolic syndrome in patients with rosacea. *J Cosmet Dermatol*. 2023;22:645-650. doi: 10.1111/jocd.15447