Eur J Dermatol 2016; 26(3): 260-4

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Article accepted on 15/12/2016

The relationship between rosacea and insulin resistance and metabolic syndrome

Background: Rosacea is a chronic inflammatory skin disease affecting the face. A positive correlation has been found between rosacea and cardiovascular diseases. *Objectives:* We sought to investigate the relation between rosacea and metabolic syndrome (MS) and insulin resistance (IR). *Materials and methods:* Between January and June 2015, a case-control study including 47 age-, gender-, and body mass index (BMI)-matched rosacea patients and 50 controls was conducted. Demographic data, clinical features of rosacea patients, anthropometric measures, laboratory findings, blood pressure levels, BMI, smoking history, alcohol consumption, sports life, family history of cardiovascular disease, and presence of MS and IR were recorded. *Results:* Forty-seven rosacea patients (12 men and 35 women; age range: 35-68 years) and 50 controls (11 men and 39 women; age range: 38-78 years) were included in our study. Of 47 rosacea patients, 24 had erythematotelangiectatic type, 22 had papulopustular type, and one had phymatous type. Whereas the rate of IR was significantly higher in the rosacea group, there was no significant difference in the rate of MS between rosacea and the control group ($p = 0.009$ and $p = 0.186$, respectively). In addition, the rosacea group had significantly higher fasting blood glucose, total cholesterol, and systolic and diastolic blood pressure levels ($p<0.05$). Mean levels of LDL, triglyceride, total cholesterol and CRP were significantly higher than in the control group ($p<0.05$). *Conclusion:* Our findings suggest that there is a relationship between rosacea and IR and some parameters of cardiovascular risk factors. We recommend investigation of IR in rosacea patients.

Key words: cardiovascular diseases, insulin resistance, metabolic syndrome, rosacea

Rosacea is a chronic inflammatory cutaneous disease characterised by telangiectasia, erythema, papules and pustules that particularly affect the face. Rosacea most often occurs in people aged 20-50 years and the incidence is about 10% [1]. There are mainly four subtypes of the disease: erythematotelangiectatic, papulopustular, phymatous and ocular. Besides these subtypes, the variants of rosacea are granulomatous rosacea, periorificial dermatitis, pyoderma faciale and steroid rosacea [2-4].

A number of different causes of the development of rosacea have been proposed, such as vascular hyperreactivity, hyperirritability of the skin, ultraviolet (UV) light exposure, pilosebaceous unit abnormalities, *Helicobacter pylori* infection, and *Demodex folliculorum* infestation [4, 5]. However, the main pathophysiological mechanism is still unclear. Recently, it was stated that an excessive inflammatory response associated with cathelicidins played the main role in the pathogenesis of rosacea [6]. Moreover, stress of the endoplasmic reticulum (ER) has been emphasized as a key promoter in the pathogenesis of rosacea. After induction of ER stress by various triggers, toll-like receptor-2 expression increases. This increase enhances the production of cathelicidins and kallikrein 5-mediated inflammation [7, 8]. It has been shown that ER stress alone can induce IL-1β expression by activating inflammasome pathways [9]. Similar to rosacea, ER stress-mediated NLRP3 (nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing-3) inflammasome activation plays an important role in chronic inflammatory diseases involving atherosclerosis and type 2 diabetes mellitus [10].

Several studies have investigated the relationship with inflammatory skin diseases, such as psoriasis and lichen planus with metabolic syndrome (MS), cardiovascular risk factors, and insulin resistance (IR) [11, 12]. Rosacea is also a chronic inflammatory cutaneous disease and pathways that play a role in the pathogenesis of rosacea are similar to those associated with metabolic disorders. To the best of our knowledge, the relationship between rosacea and MS and IR has not previously been investigated. We sought to investigate whether there exists such a relationship between rosacea and MS, as well as IR.

Materials and methods

Between January 2015 and June 2015, a case-control study including 47 rosacea patients and 50 age-, gender- and

doi:10.1684/ejd.2016.2748

To cite this article: Belli AA, Gok SO, Akbaba G, Etgu F, Dogan G. The relationship between rosacea and insulin resistance and metabolic syndrome. *Eur J Dermatol* 2016; 26(3): 260-4 doi:10.1684/ejd.2016.2748

body mass index (BMI)-matched participants as a control group was conducted in the Dermatology Outpatient Clinic of Mugla Sitki Kocman University Training and Research Hospital. Ethics committee approval was obtained prior to the study. The diagnosis of rosacea was based on clinical findings according to National Rosacea Society criteria. The controls were selected consecutively from patients who were admitted to our outpatient clinic with various dermatological complaints except rosacea. Exclusion criteria for rosacea patients and controls were: a known disease associated with glucose metabolism, a known coronary artery disease, any other chronic inflammatory disease (including chronic inflammatory skin diseases), and a history of drug use that may affect carbohydrate metabolism.

Demographic data (age and gender), duration of the disease, subtype of rosacea, lesion localisation, triggering factors, current treatments, smoking history, alcohol consumption, sporting activities, history of antihypertensive drug use, and a family history of cardiovascular disease were recorded.

Anthropometric measures (weight, height, and waist circumference [WC]), lipid parameters (total cholesterol, triglyceride, low-density lipoprotein, and high-density lipoprotein), fasting blood glucose (FBG), haemoglobin A1c (Hgb A1c), C-reactive protein (CRP), BMI, and systolic and diastolic blood pressure levels of the participants were evaluated.

WC was defined as the midpoint between the anterior iliac crest and costal margin level and values of >94 cm in men and >80 cm in women were recommended as cut off points for abdominal obesity. BMI was calculated using the formula weight (kg)/height (m^2). Lipid parameters, insulin, and FBG levels were studied after a 12-hour fasting period. Triglyceride value >150 mg/dL, HDL value <40 mg/dL in men and <50 mg/dL in women, LDL value >130 mg/dL, total cholesterol value >200 mg/dL, and Hgb A1c value >5.7% were recommended as cut off levels. FBG value ≥100mg/dL was recommended as the cut off for impaired fasting glycaemia. Systolic BP ≥135 mmHg and diastolic BP ≥85 mm Hg were recommended as cut off points for hypertension.

Based on the diagnostic criteria of the International Diabetes Federation (IDF-2005), WC >94 cm in men and >80 cm in women, plus at least two of the following criteria were accepted as MS: triglyceride value of >150 mg/dL or specific treatment for abnormality of this lipid; high density lipoprotein at <40 mg/dL in men and <50 mg/dL in women or specific treatment for abnormality of this lipid; blood pressure ≥130/85 mmHg or antihypertensive treatment; fasting blood glucose ≥100 mg/dL or diagnosed diabetes mellitus [13].

Insulin resistance was calculated using the homeostasis model assessment of insulin resistance (HOMA-IR) according to the following formula:

$$\text{HOMA-IR} = \text{fasting insulin level (uIU/mL)} \times \text{fasting glucose level (mg/dL)} / 405$$

A value of >2.7 was considered to indicate IR.

For the data analysis, the statistical program "SPSS for windows 20.0" was employed. Mean, standard deviation, ratio and frequency were used for descriptive statistics of the data. The distribution of variables was checked using the Kolmogorov-Smirnov test. The independent samples t test was used for normally distributed variables and the Mann-Whitney U-test for variables not distributed normally. The chi-square test was used for the analysis of qualitative data. $p<0.05$ was considered to be significant.

Results

Forty-seven rosacea patients (12 men and 35 women; age range: 35-68 years; mean: 50.8) and 50 controls (11 men and 39 women; age range: 38-78 years; mean: 50.9) were included in our study. Of 47 rosacea patients, 24 (51.1%) had erythematotelangiectatic type, 22 (46.8%) had papulopustular type, and one (2.1%) had phymatous type rosacea. Thirty-six of the patients (76.6%) had rosacea lesions in the centre of the face, seven (14.9%) on all the face, three (6.4%) on the cheek, and one (2.1%) on the chin (*table 1*). The mean duration of rosacea in the patients was 3.4 ± 3.97 years (range: 3 months to 20 years).

Whereas the rate of insulin resistance was significantly higher in the rosacea group, there was no significant difference in the rate of MS between rosacea and control groups (Chi-square test, $p = 0.009$ and $p = 0.186$, respectively) (*table 2*). In addition, the rosacea group had significantly high fasting blood glucose, total cholesterol, systolic blood pressure and diastolic blood pressure levels than the control group ($p<0.05$). The rate of regular exercise and family history of cardiovascular disease were significantly higher in the control group than the rosacea group ($p = 0.025$) (*table 3*).

In the rosacea group, mean levels of LDL, triglyceride, total cholesterol, CRP, and systolic and diastolic blood pressure were significantly higher than in the control group (independent samples t test and Mann-Whitney U-test; $p<0.05$) (*table 4*).

There were no significant differences in the participants' age, gender, weight, height, WC, BMI, smoking history, alcohol consumption, HDL levels or history of antihypertensive drug use between the rosacea and control groups ($p>0.05$). The rates of IR and MS were not significantly different between the patients treated with oral tetracycline and those without a history of oral tetracycline intake ($p = 0.731$ and $p = 0.725$, respectively).

Discussion

Rosacea is a chronic inflammatory skin disease affecting the face. Although several factors have been proposed, the pathogenesis of rosacea still remains unclear. Several studies have investigated the relationship between inflammatory cutaneous diseases and metabolic syndrome (MS), insulin resistance (IR) and cardiovascular risk factors [11, 12]. This study was conducted in the light of the fact that rosacea is a chronic inflammatory skin disease and Duman *et al*. recently found a high risk of cardiovascular disease in rosacea patients [5]. We found a positive relationship between rosacea and IR, as well as some parameters that related to metabolic syndrome and cardiovascular disease risk factors.

Metabolic syndrome is a group of metabolic disorders related to an increased risk of type 2 diabetes mellitus, coronary artery disease, and mortality [14]. These metabolic

Table 1. Characteristics of the rosacea patients.

		Number of patients (%)
Gender	Male	12 (25.5)
	Female	35 (74.5)
Subtype of rosacea	Erythematotelangiectatic	24 (51.1)
	Papulopustular	22 (46.8)
	Phymatous	1 (2.1)
Localization of the lesions	Central face	36 (76.6)
	All the face	7 (14.9)
	Cheek	3 (6.4)
	Chin	1 (2.1)
Triggering factors	UV light	25 (55.3)
	Spicy food	5 (10.6)
	Emotional stress	25 (53.2)
	Heat	6 (12.8)
	Cold	6 (12.8)
	Absent	5 (10.6)
Treatment	Topical metronidazole	39 (83)
	Topical antibiotic (fusidic acid, tetracycline)	7 (14.9)
	Oral tetracycline	11 (23.4)
	Oral isotretinoin	2 (4.3)
	No treatment	4 (8.5)

Table 2. Comparison of the rate of metabolic syndrome and insulin resistance in rosacea and the control group.

		Rosacea group *n* (%)	Control group *n* (%)	*p*
Insulin resistance	Present	21 (44.7)	10 (20)	**0.009**
	Absent	26 (55.3)	40 (80)	
Metabolic syndrome	Present	16 (34.1)	11 (22)	0.186
	Absent	28 (65.9)	39 (78)	

Chi-square test.

disorders include glucose intolerance, IR, dyslipidemia, central obesity, and hypertension. For the pathogenesis of MS, several factors, such as genetics, IR, obesity, hypertension, dyslipidemia, vascular abnormalities, inflammation, oxidative stress, hyperandrogenism, uric acid deficiency, and vitamin D deficiency, are considered to be responsible. Whereas some of these factors act by causing IR, some play a direct role in the pathogenesis of MS. Increased visceral adipose tissue is also associated with other risk factors, dyslipidaemia, and endothelial dysfunction [14, 15]. Duman *et al.* have reported that some cardiovascular risk factors, such as total cholesterol, LDL, CRP levels, family history of cardiovascular disease, and history of smoking and alcohol consumption, were significantly higher in 60 rosacea patients than in 50 controls. They suggested that rosacea patients should be followed for cardiovascular disease [5]. Moreover, a very recent population-based study from Taiwan has reported that rosacea patients are more likely to have dyslipidaemia and hypertension. In addition, rosacea patients have an increased risk of coronary artery diseases [16]. Rainer *et al*. found a significant association between rosacea and hypertension, metabolic diseases, allergies, respiratory diseases, gastrointestinal diseases and urogenital diseases. They also stated that moderate-to-severe rosacea, relative to mild rosacea, is significantly associated with metabolic diseases, hypertension, hyperlipidaemia, cardiovascular diseases, and gastroesophageal reflux disease [17]. In our study, in addition to a significant positive correlation with IR, some cardiovascular disease risk factors, such as FBG, LDL, total cholesterol, triglyceride, and systolic blood pressure and diastolic blood pressure levels, were significantly higher than in the control group.

For the pathogenesis of rosacea, two main factors have been proposed: vascular and inflammatory factors [18]. Inflammation has been associated with an excessive innate immune system response due to increased activity of proteases and hence cathelicidin peptides. Casas *et al.* showed an overexpression of pro-inflammatory cytokines involving IL-1 beta, TNF-alfa, and IL-8 and inflammasome-related genes involving CASP-1 and NALP-3 in the skin samples of rosacea patients [19]. Various triggers, such as sunlight exposure, bacteria, or parasites can induce this aberrant immune system response in rosacea. Cathelicidins can lead to angiogenesis and inflammatory responses, especially by releasing IL-8. They also enhance the pro-inflammatory and vascular effects of UVB radiation [18-21]. Stimulation of cathelicidin-derived peptide induces IL-1β release via the P2X7 receptor [22]. Similarly, P2X7 receptor expression

Table 3. Comparison of the parameters in rosacea and the control group.

	Patients (n = 47) **n (%)**	**Controls (n = 50)** **n (%)**	***p***
Smoking	6 (12.7)	11 (22)	0.232
Alcohol consumption	3 (6.4)	3 (6)	1.000
Regular exercise	10 (21.3)	20 (40)	**0.046**
LDL >130 mg/dL	23 (48.9)	16 (32)	0.089
TG >150 mg/dL	13 (27.6)	8 (16)	0.163
Total Cholesterol >200 mg/dL	34 (72.3)	22 (44)	**0.005**
HDL <40 mg/dL (men) <50 mg/dL (women)	14 (29.8)	12 (24)	0.520
FBG ≥100 mg/dL	18 (38.2)	7 (14)	**0.006**
CRP >5 mg/dL	7 (14.9)	7 (14)	0.900
HgbA1c >5.7%	23 (48.9)	15 (30)	0.094
Systolic BP ≥135 mmHg	17 (36.2)	8 (16)	**0.023**
Diastolic BP ≥85 mmHg	18 (38.3)	5 (10)	**0.001**
History of antihypertensive drug	6 (12.7)	4 (8)	**0.014**
Family history of CVD	4 (8.5)	14 (28)	0.055
BMI ≥25 kg/m^2	31 (65.9)	36 (72)	0.520

Chi-square test. TG: triglyceride; FBG: fasting blood glucose; CRP: C-reactive protein; BP: blood pressure; CVD: cardiovascular disease; BMI: body mass index.

Table 4. Comparison of the mean levels of parameters in rosacea and the control group.

	Rosacea group **Mean ± SD**	**Control group** **Mean ± SD**	***p***
Age	50.81 ± 8.22	50.90 ± 9.69	0.960
Weight (kg)	73.89 ± 10.21	71.58 ± 8.87	0.236
Height (cm)	162.93 ± 6.89	162.16 ± 7.20	0.598
Waist circumference (cm)	90.00 ± 10.41	87.42 ± 9.88	0.213
LDL (mg/dL)	132.96 ± 31.21	119.84 ± 27.46	**0.030**
Triglyceride (mg/dL)	131.49 ± 69.60	103.26 ± 50.25	**0.001***
Total cholesterol (mg/dL)	218.53 ± 33.37	201.80 ± 36.48	**0.021**
HDL (mg/dL)	58.96 ± 15.75	59.20 ± 17.22	0.837*
FBG (mg/dL)	96.57 ± 13.05	92.48 ± 6.89	0.060
CRP (mg/dL)	4.86 ± 12.86	2.78 ± 4.93	**0.024***
HgbA1c (%)	5.76 ± 0.45	5.64 ± 0.33	0.146
Systolic BP (mmHg)	127.45 ± 17.35	118.60 ± 15.25	**0.012***
Diastolic BP (mmHg)	81.49 ± 8.34	76.00 ± 8.81	**0.001***
BMI (kg/m^2)	27.98 ± 4.18	27.17 ± 3.36	0.293

**Independent samples t test, Mann-Whitney U test. TG: triglyceride; FBG: fasting blood glucose; CRP: C-reactive protein; BP: blood pressure; BMI: body mass index.*

in peripheral blood monocytes has been related to plasma levels of C-reactive protein and inflammatory cytokines (TNF-α and IL-1β) in patients with type 2 diabetes mellitus. Wu *et al.* noted that the P2X7 receptor could be involved in pathological alterations of type 2 diabetes mellitus, especially in patients with high CRP levels [23]. Kim *et al.* stated that hepatic ER stress and inflammation give rise to hepatic insulin resistance in obese people [24]. Consequently, IR and some metabolic parameters which were increased in our patients may have resulted in rosacea-derived induction of ER stress pathways, expression of LL-37 and inflammasome activation, similar to other inflammatory skin diseases, such as psoriasis.

Edfeldt *et al*. reported that cathelicidin LL-37 is generated in atherosclerotic lesions and modulates the immune system by increasing adhesion molecule and chemokine expression [15]. In another study, Benachour *et al.* found a relationship between cathelicidin LL-37 gene expression and cardiovascular disease risk factors. In this study, BMI, WC, systolic blood pressure, and triglyceride

levels were positively correlated, and HDL levels negatively correlated, with LL-37 gene expression [25]. Detection of cathelicidins in atherosclerotic plaques and the relation of cathelicidin gene expression to cardiovascular risk factors may also elucidate the high rates of IR in our rosacea patients.

Furthermore, Takci *et al.* found decreased paraoxone-1 (PON1) activity, which is an antioxidant enzyme, and increased oxidative stress in 39 rosacea patients. They suggested that oxidative stress may have a role in the pathophysiology of rosacea [26]. Systemic oxidative stress is also associated with insulin resistance and atherosclerosis [27, 28].

In conclusion, our findings suggest that there is a relationship between rosacea and IR, as well as some parameters related to metabolic syndrome. This relationship may be explained by the fact that similar factors, such as increased cathelicidin LL-37 levels, ER stress, inflammatory cytokines, and oxidative stress, are present during the pathogenesis of rosacea and metabolic disorders. We recommend investigation of IR in rosacea patients. However, the pathophysiological connection between these diseases has not been completely elucidated. A limitation of this study is the small number of patients in each subtype. Further studies should be conducted with large numbers of rosacea patients to duplicate our results. ■

Disclosure. *Acknowledgements: The authors thank Prof. Dr. Ercan Baldemir, Mugla Sitki Kocman University, Department of Biostatistics, Mugla, Turkey for statistical analysis of the study. Financial support: none. Conflict of interest: none.*

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