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Original Article

Evaluation of metabolic syndrome and its components in patients with rosacea: a cross-sectional, case-control study

玫瑰痤瘡患者中的代謝綜合徵及其成分的評估：一項橫斷面病例對照研究

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Introduction: Previous studies have suggested an association between cardiovascular disease and rosacea. However, there is still a paucity of data regarding its association with metabolic syndrome (MetS). ***Methods:*** The components of MetS were evaluated in 100 rosacea patients and 100 controls. ***Results:*** MetS was determined in 44% of the rosacea patients and 35% of the controls. Although the difference was not statistically significant (p=0.193), rosacea patients were more likely to have dyslipidaemia (p<0.001), insulin resistance (p=0.035), hypertension (p=0.009), higher atherogenic index (p<0.001) and a higher hypercoagulability (p=0.025) and inflammatory state (p=0.003) compared to controls. ***Conclusion:*** The results of this study support that rosacea patients should be screened routinely for the components of MetS such as dyslipidaemia, insulin resistance, hypertension and other cardiovascular risk factors.

簡介：先前的研究證明心血管疾病和玫瑰痤瘡之間存在關聯。然而，關於其與代謝綜合徵的關聯，仍缺乏數據。**方法**：在各 100 名玫瑰痤瘡患者和對照組人仕中，評估了他們有否代謝綜合徵成分。**結果**：44％的玫瑰痤瘡患者和 35％的對照組人仕被測定為有代謝綜合徵。儘管無統計學意義上的差異（p=0.193），但與對照組相比，玫瑰痤瘡患者較大機會患上血脂異常（p<0.001）、胰島素阻抗（p=0.035）、高血壓（p=0.009）、較高的致動脈粥樣硬化指數（p<0.001）、較高的血液高凝狀態 (p=0.025) 和發炎狀態 (p=0.003)。**結論**：這項研究結果支持玫瑰痤瘡患者應定期篩查有否代謝綜合徵成分，例如血脂異常、胰島素阻抗、高血壓和其他心血管危險因子。

Keywords: Cardiovascular risk factors, metabolic syndrome, rosacea

關鍵詞：心血管危險因子、代謝綜合徵、玫瑰痤瘡

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Introduction

Rosacea is a chronic inflammatory skin condition characterised by persistent or recurrent erythema, telangiectasia, papules, pustules, and sebaceous gland hypertrophy, preferentially affecting the convexities of the face. The prevalence of the condition varies between 1% and 20%, depending on the populations studied. There are four clinical subtypes of rosacea: erythematotelangiectatic, papulopustular, phymatous, and ocular. However, different subtypes can co-exist in the same patient.[1,2]

Metabolic syndrome (MetS) is characterised by a group of interrelated cardiovascular risk factors, including central obesity, atherogenic dyslipidaemia, elevated blood pressure (BP) and raised fasting blood glucose (FBG). Previous studies have extensively documented the association of rosacea with cardiovascular diseases (CVD), but the association between rosacea and MetS has not been adequately examined in the literature.

In the present study, we aimed to evaluate MetS components and the presence of MetS in rosacea patients, and to compare their frequencies with controls.

Materials and methods

Study design

This was a cross-sectional, case-control study of 100 patients with rosacea and 100 age-and gender-matched control subjects who have consecutively admitted to our Department of Dermatology of University Faculty of Medicine, Turkey, between January 2016 and August 2016. The study was approved by the Local Ethical Committee in accordance with the Helsinki declaration. The diagnosis of rosacea was based on the clinical presentation as defined in the National Rosacea Society criteria. The control group included subjects without any chronic inflammatory skin disease. Exclusion criteria were <18 years old and pregnancy. Apart from rosacea, neither rosacea patients nor control participants had any other chronic inflammatory disorder. Each participant gave a written informed consent prior to the examinations. After informed consent, all cases and controls were assessed by a dermatologist (OO) who documented the sociodemographic findings, medical history, biometric measurements and other relevant data.

The following were noted: smoking (>5 cigarettes/day), alcohol consumption (>35 g/day), physical activity (physical exercise >30 min/day) and family history of premature CVD (<55 years in father and <65 years in mother). Laboratory examinations and biometric measurements were performed in all subjects. Ophthalmological evaluation was performed in all patients to screen for ocular rosacea.

Biometric and laboratory screenings

Weight and height were measured, and body mass index (BMI) was calculated using the formula weight (kg)/height $(m)^2$. Waist circumference (WC) was measured along the line lying midway between the iliac crest and the costal margin in the mid-axillary line. BP was obtained using the validated device at our center and recordings were made for two times with one-minute intervals, and the average of both values was taken as the true BP of the patients.

Venous blood samples were taken after overnight fasting of 12 h and levels of FBG, insulin, total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), complement reactive protein (CRP), fibrinogen, thyroid stimulating hormone (TSH) and free T4 (fT4) were measured. Subjects with FBG >100 underwent the oral glucose tolerance test (OGTT, 120 minutes after the administration of 75 g of oral glucose).

Insulin resistance (IR) was calculated using the homeostasis model assessment of IR (HOMA-IR) according to the following formula: HOMA-IR = fasting insulin level (μIU/mL) ×FBG (mg/dL) /405.

The presence of dyslipidaemia was defined as serum TG >150 mg/dl, TC >200 mg/dl, LDL-C >130 mg/dl and/or antihyperlipidaemic treatment.[7]

Assessment of MetS

The presence of MetS at study visit was assessed according to the consensus criteria recently approved by Aliberti et al.[8] Patients were diagnosed with MetS if three or more of the following criteria were present: increased waist circumference (≥80 cm for female, ≥94 cm for male), increased TG (≥150 mg/dL or drug treatment for hypertriglyceridaemia), reduced HDL-C (<50 mg/dL for female, <40 mg/dL for male or drug treatment for reduced HDL-C), arterial HT (systolic ≥130 and/or diastolic ≥85 mm Hg or drug treatment for HT), and increased FBG (≥100 mg/dL or drug treatment for DM).[8]

Statistical analyses

Statistical analysis was performed with the SPSS/PC software (Version 23.0 for Windows; SPSS Inc., Chicago, Ill). Constant variables in the data set were expressed as mean±standard deviation, and categorical variables were expressed as frequency and percentage. The Shapiro-Wilk test was used to examine the normality of the distribution of the data. Two samples' Student's t-test was used to compare mean values of normally distributed quantitative variables as the two samples were obtained independently. Mann Whitney U-test was used if the variables were not normally distributed. Qualitative variables were analysed with the Chi-squared test and Fisher's exact test. To evaluate the association between the ophthalmological findings and MetS in rosacea patients, univariate analysis was performed and odds ratios (ORs) for MetS with 95% confidence interval (CI) were obtained. This was followed by logistic regression to determine the influence of MetS on the significant variable using the numerical and categorical variables. P<0.05 was considered significant in all analyses.

Results

The average age of 100 rosacea patients included in this age- and gender-matched controlled study was 46.97±10.02 years old, and the gender of majority was female (female/male: 1.33). The mean time with rosacea was 8.22±7.43 years. Erythematotelangiectatic rosacea was the more common clinical subtype accounting for 64% of cases, and the remainder had papulopustular (27%) and phymatosis subtypes (9%).

In medical history, presence of depression/anxiety was significantly higher in rosacea patients than in the control group (15% vs 6%, p=0.038). CVD was present in 5 (5%) of the rosacea patients (2 had angina, 2 had myocardial infarction and 1 had coronary bypass), and 2 (2%) of the controls (1 had angina and 1 had myocardial infarction) (p=0.248).

MetS was determined in 44% of the rosacea patients and 35% of the control subjects. Although all components of MetS were more prevalent in the rosacea group, the difference in the prevalence of MetS between patients and controls did not reach a statistical significance (p=0.193). Among the MetS components, only hypertriglyceridemia (45% vs. 30%, p=0.028) and increased BP (49% vs. 31%, p=0.009) were found to be significantly higher in the rosacea group (Table 1).

In means of lipid parameters, mean TG, TC and LDL-C values, mean TC / HDL-C ratio (Castelli's atherogenic index) (Table 2), and the prevalence of dyslipidemia (77% vs. 52%, p<0.001, OR = 3.09, 95% CI = 1.68-5.68] were significantly higher in rosacea patients compared to controls.

Table 1. Comparison of sociodemographic features, medical history findings and metabolic syndrome components in study subjects

Characteristics	Rosacea patients	Controls	p value
Age, years, mean±SD	46.97±10.02	46.68±12.02	0.853
Gender, n (%)			
Male	43 (43)	43 (43)	1.000
Female	57 (57)	57 (57)	
Socioeconomic status, n (%)			
Low	7 (7)	9 (9)	0.628
Intermediate	86 (86)	81 (81)	
High	7 (7)	10 (10)	
Current smokers, n (%)	29 (29)	30 (30)	0.877
Packet/year, mean±SD	17.58±15.30	17.05±14.41	0.892
Alcohol use, n (%)	24 (24)	27 (27)	0.626
Diet, n (%)	17 (17)	13 (13)	0.428
Sedantarism, n (%)	68 (68)	64 (64)	0.550
Family history of premature cardiovascular diseases, n (%)	6 (6)	5 (5)	0.756
Medical history, n (%)			
Diabetes mellitus and/or antidiabetic use	12 (12)	11 (11)	0.825
Hypertension and/or antihypertensive use	21 (21)	17 (17)	0.471
Hyperlipidemia/dyslipidemia and/or antihyperlipidemic use	5 (5)	4 (4)	–
Cardiovascular disease	5 (5)	2 (2)	–
Depression and/or anxiety	15 (15)	6 (6)	**0.038***
Hypothyroidism	10 (10%)	10 (10%)	1.000
Dyslipidemia, n (%)	77 (77)	52 (52)	<0.001*
Insulin resistance, n (%)	32 (32)	19 (19)	**0.035***
Metabolic syndrome, n (%)	44 (44)	35(35)	0.193
Increased waist circumference ≥94 cm (male) or ≥80 cm (female)	76(76)	67(67)	0.159
Hypertriglyceridemia ≥150 mg/dL or antihyperlipidemic treatment	45(45)	30(30)	**0.028***
Reduced HDL-cholesterol <50 mg/dL (female) or <40 mg/dL (male)	23(23)	22(22)	0.866
Elevated blood pressure ≥130/85 mmHg or antihypertensive treatment	49(49)	31(31)	**0.009***
Increased fasting blood glucose ≥100 mg/dL or hypoglycemic treatment	34(34)	27(27)	0.282
Number of metabolic syndrome components, mean±SD	2.27±1.32	1.77±1.38	**0.010***

*=statistically significant values, –=chi-square test could not be performed

With regard to glucose metabolism, rosacea patients showed significantly higher mean FBG, insulin and HOMA values, and they were also more likely to have IR as compared to controls (32% vs. 19%, p=0.035). Twelve cases in the rosacea group and 11 cases in the control group had primarily diagnosed DM. With the OGTT, we added five cases with newly diagnosed DM and six cases with newly diagnosed glucose intolerance in the rosacea group, while there were only one case with newly diagnosed DM and five cases with newly diagnosed glucose intolerance in the control group. However, the differences did not show statistical significances (p=0.097 and p=0.756, respectively).

In terms of the other components of MetS, rosacea patients showed significantly higher mean CRP and mean fibrinogen values compared to the controls. Likewise, the proportions of the cases with a high CRP level (28% vs. 15%, p=0.025), and with a high fibrinogen level (56% vs. 35%, p=0.003) were significantly higher in the rosacea group.

Of note, ocular findings related with rosacea was detected in 88 (88%) patients including blepharitis (76%), meibomitis (57%), dry eye (41%), foreign body sensation (30%), lid margin telangiectasia (20%), conjunctival hyperemia (16%), keratitis (8%), chalazia/hordeolum (8%), blurred vision (3%), corneal vascularisation (1%) and corneal oedema (1%). Among those, only the difference in the prevalence of meibomitis was significantly higher in patients with MetS compared to the patients without MetS [68.2% vs 48.2%, p=0.045, OR = 2.30, 95% CI = 1.01-5.24].

Table 2. Laboratory characteristics and anthropometric measurements in study subjects

Characteristics, mean±SD	Rosacea patients	Controls	p value
Waist circumference (cm)	98.14±9.80	95.30±13.45	0.218
Body mass index	28.08±3.84	27.01±4.69	0.061
Glucose (mg/dL)	95.75±21.83	90.75±11.57	0.016*
Insulin (µIU/mL)	8.02±3.87	6.25±3.57	<0.001*
HOMA	1.96±1.16	1.43±0.95	<0.001*
Triglycerides (mg/dL)	168.38±94.26	116.56±59.26	<0.001*
Total cholesterol (mg/dL)	220.17±44.54	190.72±34.83	<0.001*
LDL-cholesterol (mg/dL)	136.42±37.79	114.84±27.24	<0.001*
HDL-cholesterol (mg/dL)	51.22±10.67	52.56±13.56	0.509
Castelli's atherogenic index	4.39±0.92	3.80±1.02	<0.001*
CRP (mg/L)	4.21±4.95	2.77±2.85	0.006*
Fibrinogen (g/L)	3.62±0.88	3.28±0.70	0.001*
TSH (µIU/mL)	2.16±2.85	1.75±1.04	0.118
fT4 (ng/dL)	0.85±0.22	0.82±0.16	0.585
Systolic blood pressure (mmHg)	117.33±14.79	112.79±17.11	0.044*
Diastolic blood pressure (mmHg)	81.58±10.04	77.53±10.37	0.018*

*=statistically significant values

Discussion

In the present study, we examined the prevalence of MetS and its individual components in a sample of rosacea patients and their age and gender matched controls. Although a statistically significant difference has not been determined in the prevalence of MetS between patients and controls, higher rates of atherogenic dyslipidemia, HT, hyperglycaemia and IR with a higher proinflammatory and procoagulant state have been found to exist in rosacea patients.

The association of rosacea with CVD and cardiovascular risk factors has been clearly demonstrated in previous studies. In this context, the first study was published by Duman et al, high TC, LDL-C and CRP levels, a family history of premature CVD, and a history of smoking and alcohol consumption were reported in rosacea patients compared to controls.[4] Subsequently, a nationwide case-control study from Taiwan confirmed that patients with rosacea are more likely to have dyslipidemia, coronary artery disease and HT.[5] In the light of the results of such studies, the first report of the association of rosacea with MetS and IR was published in 2016 by Akin et al. In a case-control study including 47 age-, gender-, and BMI- matched rosacea patients and 50 controls.[6] In that study, whereas the rosacea group was more likely to have MetS compared to the controls (34.1% vs. 22%), no significant association was found between rosacea and MetS, as in our study. However, in addition to higher mean levels of FBG, LDL-C, TG, TC, CRP, and systolic and diastolic BP, they found a higher prevalence of IR in rosacea patients. Our results are highly consistent with those obtained in this study. Systemic inflammatory component and secretion of proinflammatory cytokines have been proposed to explain the underlying mechanism for the predisposition to such disturbances in these patients.[9,10]

Although the exact mechanisms involved in the pathogenesis of rosacea are largely unknown, recent scientific interest focuses on abnormally high facial skin levels of the antimicrobial peptide cathelicidin LL-37 as well as cathelicidin's processing enzyme, a serine protease called kallikrein 5 in rosacea patients. Apart from the antimicrobial activity, LL-37 has additional functions in the activation and the control of immune responses such as cytokine and chemokine release from local cells and leucocytes, and chemotactic effects on a large number of immune cells.[1,11] Because of the role of LL-37 in the inflammatory processes, it has been hypothesised that it might also contribute to the innate immunity involved in atherosclerosis. In this context, Edfeldt et al. have first demonstrated the expression of the cathelicidin LL-37 in atherosclerotic lesions.[12] In the following years, the LL-37 gene expression was demonstrated to be significantly higher in peripheral blood mononuclear cells from obese women compared to lean and overweight women, and LL-37 mRNA level was shown to significantly correlate with CVD risk factors in men independently of BMI and WC.[13] These findings have also supported that the expression of the cathelicidin LL-37 may be modulated as part of the processes that lead to CVD and metabolic disturbances in rosacea patients.

Another proposed mechanism of the inflammatory processes in rosacea is the oxidative modification of proteins and lipids by reactive oxygen species (ROS). As it has been well-known for many years, that ultraviolet (UV) exposure and photodamage play an important role in the pathophysiology of rosacea. In general, UV radiation generates ROS, which have a pro-inflammatory effect on the skin. ROS bind to toll-like receptor 2 (TLR2) on keratinocytes, and further aggravates the inflammatory cascade existing in rosacea. The epidermis in patients with rosacea has shown to expresses higher amounts of both ROS and TLR2.[14,15] Considerable data indicate that oxidative stress is one of the main factors associated with IR, CVD and HT, and an overproduction of ROS is clearly one of the key factors of MetS.[16] Additionally, recent studies have

demonstrated significantly increased surface expression and activity of TLR2 on monocytes of the subjects with MetS compared to controls.[17] Higher levels of ROS and TLR2 in rosacea may also lead to a higher rate of metabolic disturbance in these patients.

Furthermore, endoplasmic reticulum (ER) stress are also hypothesised to play a critical role in the pathophysiology of rosacea in recent studies. ER stress is a condition that is accelerated by the accumulation of unfolded/misfolded proteins after a disturbance in the ER quality control due to a variety of physiological and pathological conditions. Triggers such as UV radiation, heat, cold, psychological stress, certain foods, skin irritants, *Demodex* mites may represent ER stressors and increase ER stress.[18] More recently, ER stress and the unfolded protein response have been found to play an important role in diseases associated with CVD such as IR, DM, obesity, non-alcoholic fatty liver disease and atherosclerosis have been discovered.[19] Moreover, emerging evidence suggests that pharmacological modulators of ER stress can be developed as novel treatments of these metabolic disorders.[20] Thus, the mechanisms of rosacea and metabolic diseases suggest that ER stress may be a key link between rosacea and metabolic conditions.

Although not specific, rosacea also commonly affects the eyes including meibomian gland dysfunction (MGD). In this study, rosacea patients with MetS had a higher prevalence of meibomitis compared to the patients without MetS. In the literature, patients with MGD have a significantly higher rate of cardiovascular risk factors compared to controls without MGD. Thus, meibomitis may serve as an early indicator for metabolic disturbances in also rosacea patients.

The present study has some limitations such as being a hospital-based, cross-sectional design and lack of follow-up data. Additionally, the rosacea patients were composed of different subtypes. Thus, more long-term, prospective studies using large cohorts are needed.

In conclusion, whereas a statistically significant association between rosacea and MetS was not found in this study, the results have revealed that rosacea patients have various parameters of MetS such as atherogenic dyslipiaemia, HT, hyperglycaemia, IR, proinflammatory and procoagulant state. In order to provide comprehensive care in rosacea patients, we recommend that physicians be aware of these findings. Further studies with larger cohorts are required to assess the impact of rosacea on these risk factors.

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Conflicts of interest

The authors declare that there is no conflict of interest.

References

1. van Zuuren EJ, Fedorowicz Z, Carter B, van der Linden MM, Charland L. Interventions for rosacea. Cochrane Database Syst Rev 2015;4:CD003262.
2. Tan J, Berg M. Rosacea: current state of epidemiology. J Am Acad Dermatol 2013;69:27-35.
3. Wilson PW, D'Agostino RB, Parise H, Sullivan L, Meigs JB. Metabolic syndrome as a precursor of cardiovascular disease and type 2 diabetes mellitus. Circulation 2005;112:3066-72.
4. Duman N, Ersoy Evans S, Atakan N. Rosacea and cardiovascular risk factors: a case control study. J Eur Acad Dermatol Venereol 2014;28:1165-9.
5. Hua TC, Chung PI, Chen YJ, Wu LC, Chen YD, Hwang CY, et al. Cardiovascular comorbidities in patients with rosacea: A nationwide case-control study from Taiwan. J Am Acad Dermatol 2015;73:249-54.

6. Akin Belli A, Ozbas Gok S, Akbaba G, Etgu F, Dogan G. The relationship between rosacea and insulin resistance and metabolic syndrome. Eur J Dermatol 2016;26:260-4.
7. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NECP) expert panel on detection, evaluation and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA 2010;285:2486-97.
8. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association;World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 2009; 120:1640-5.
9. Padhi T, Garima. Metabolic syndrome and skin: psoriasis and beyond. Indian J Dermatol 2013;58: 299-305.
10. Esser N, Legrand-Poels S, Piette J, Scheen AJ, Paquot N. Inflammation as a link between obesity, metabolic syndrome and type 2 diabetes. Diabetes Res Clin Pract 2014;105:141-50.
11. Two AM, Wu W, Gallo RL, Hata TR. Rosacea: part I. Introduction, categorization, histology, pathogenesis, and risk factors. J Am Acad Dermatol 2015;72:749-58.
12. Edfeldt K, Agerberth B, Rottenberg ME, Gudmundsson GH, Wang XB, Mandal K, et al. Involvement of the antimicrobial peptide LL-37 in human atherosclerosis. Arterioscler Thromb Vasc Biol 2006;26:1551-7.
13. Benachour H, Zaiou M, Samara A, Herbeth B, Pfister M, Lambert D, et al. Association of human cathelicidin (hCAP-18/LL-37) gene expression with cardiovascular disease risk factors. Nutr Metab Cardiovasc Dis 2009; 19:720-8.
14. Woo YR, Lim JH, Cho DH, Park HJ. Rosacea: Molecular Mechanisms and Management of a Chronic Cutaneous Inflammatory Condition. Int J Mol Sci 2016;17:1562.
15. Jones D. Reactive oxygen species and rosacea. Cutis 2004;74:17-20, 32-4.
16. Ando K, Fujita T. Metabolic syndrome and oxidative stress. Free Radic Biol Med 2009;47:213-8.
17. Jialal I, Kaur H, Devaraj S. Toll-like Receptor Status in Obesity and Metabolic Syndrome: A Translational Perspective. J Clin Endocrinol Metab 2014;99:39-48.
18. Melnik BC. Endoplasmic reticulum stress: key promoter of rosacea pathogenesis. Exp Dermatol 2014;23:868-73.
19. Schröder M, Sutcliffe L. Consequences of stress in the secretory pathway: The ER stress response and its role in the metabolic syndrome. Methods Mol Biol 2010; 648:43-62.
20. Cao SS, Kaufman RJ. Targeting endoplasmic reticulum stress in metabolic disease. Expert Opin Ther Targets 2013;17:437-48.
21. Awais M, Anwar M, Iftikhar R, Iqbal Z, Shehzad N, Akbar B. Rosacea - the ophthalmic perspective. Cutan Ocul Toxicol 2015;34:161-6.
22. Barton K, Monroy DC, Nava A, Pflugfelder SC. Inflammatory cytokines in the tears of patients with ocular rosacea. Ophthalmology 1997;104:1868-74.
23. Braich PS, Howard MK, Singh JS. Dyslipidemia and its association with meibomian gland dysfunction. Int Ophthalmol 2016;36:469-76.
24. Chen A, Chen HT, Chen HC, Chen YT, Hwang YH, Sun CC, et al. Asymptomatic Meibomian Gland Dysfunction and Cardiovascular Disease Risk Factors in a Middle-Aged Population in Taiwan - A Cross-sectional Analysis. Sci Rep 2017;7:4935.