ROSACEA AND CARDIOVASCULAR RISK FACTORS

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Summary

Introduction: *Although the relationship of rosacea to the cardiovascular system is well known, facial flushing and telangiectasias being two of the primary skin symptoms of rosacea, recent data indicate a potential connection between rosacea and cardiovascular disease.*

Aim*: Cardiovascular disease risk assessment by identifying cardiovascular risk factors in rosacea patients.*

Material and method: *We conducted a case-control study involving 46 patients with rosacea (37 women and 9 males, mean age 49.8±15.18 years) and 39 control non-rosacea subjects (31 women and 8 males, mean age 47.87±15.11 years) with similar age and gender characteristics to those in the study group. Demographic and anthropometric data, medical history and the presence of cardiovascular risk factors were recorded. Data on the age of the disease and the clinical subtype of rosacea have been collected in rosacea patients. Laboratory investigations including fasting blood glucose, insulin, C-reactive protein, lipid profile, were performed. The HOMA-IR index and the Framingham risk score were calculated.*

Results*: 27 (58.69%) of patients with rosacea had the erythematotelangiectatic subtype and 19 (41.31%) had papulopustular subtype. Mean disease duration in the rosacea group was 10.85±9.08 years. A higher frequency of HTA (p=0.004), low HDL cholesterol (p=0.037), CRP (p=0.028) and metabolic syndrome (p=0.047) were observed in rosacea compared to control group, results that were associated with a higher risk of cardiovascular disease and death according to the Framingham risk score (p=0.001). No correlation of rosacea subtypes with cardiovascular risk factors has been identified.*

Conclusions*: Rosacea patients more commonly associate cardiovascular risk factors compared to control subjects, requiring a systematic assessment of these due to increased risk for cardiovascular disease and death.*

Key words: *rosacea, hypertension, dyslipidemia, metabolic syndrome, reactive C protein.*

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Introduction

Classic, rosacea is considered a strictly cutaneous condition, but a number of studies have noted a frequent association of rosacea with specific symptoms or gastrointestinal disorders [1, 2, 3, 4], cardiovascular disease (CVD), depression [5] or migraine [1]. Although the relationship of rosacea to the cardiovascular system is well known, facial flushing and telangiectasias being two of the primary skin symptoms of rosacea, recent data indicate a potential connection between rosacea and cardiovascular disease.

Aim

In this study, we proposed to evaluate the risk of CVD by identifying cardiovascular risk factors in rosacea patients.

Material and method

We conducted a case-control study involving 46 patients with rosacea and 39 non-rosacea controls matched for age and gender. Subjects of the two groups were recruited from the outpatients of the Clinical Emergency County Hospital from Brașov, between January 2018 and November 2018, men and women aged over 18 years who met the inclusion/exclusion criteria.

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The study protocol was approved by the hospital ethics committee. Enrollment in the study was performed with the written consent of the subjects.

Diagnosis of rosacea was based on clinical aspects according to the National Rosacea Society criteria [6]. For diagnosis of rosacea, at least one of the primary criteria with centrofacial localization is required: history of frequent flushing, permanent erythema, papules and pustules, telangiectasia. Secondary criteria include burning or stinging sensation, edema, plaque, dry skin appearance, ocular manifestations, and hypertrophic changes.

Exclusion criteria

- The subject did not give his written consent for participation in the study;
- Age under 18;
- Pregnant or breastfeeding women;
- Use of lipid-lowering therapies, non-steroidal anti-inflammatory drugs, systemic corticotherapy in the last month;
- Current therapy with oral contraceptives;
- Severe renal function abnormalities;
- Acute or chronic severe liver disease;
- Clinical or subclinical thyroid dysfunctions;
- Other chronic or systemic inflammatory diseases, autoimmune diseases or active infection at enrollment;
- History of severe immunodeficiency syndromes.

Demographic features, personal and familial medical history, cigarette smoking, alcohol consumption, concomitant and recent medication, data on physical examination and anthropometric data (height, weight, waist circumference, BMI) were recorded in a first step. In addition, data on duration of the disease and the clinical subtype of rosacea have been collected in rosacea patients.

Eligible subjects in the first step continued with the following procedures. For women with procreation potential, a urinary pregnancy test was performed. For diagnosis of comorbidities and identification of cardiovascular risk factors, in addition to medical history and physical examination, screening laboratory investigations were performed in both groups. Blood samples were taken by venipuncture (7-10 ml) to perform: blood cell counts, fasting blood glucose (FBG), insulin, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, urea, creatinine, TGO, TGP, uric acid and highly sensitive reactive C-protein (hs-CRP).

The following were considered as risk factors for cardiovascular disease: age >45 years in men and >55 years in women, family history of early CVD, waist circumference >94 cm in men and >80 cm in women, BMI >25 kg/m^2, pre-diabetes (defined as fasting blood glucose values between 100-125 mg/dL), diabetes mellitus, hypertension, smoking, alcohol consumption, total cholesterol >200 mg/dL, LDL-cholesterol >130 mg/dL, HDL-cholesterol <40 mg/dL in men and <50 mg/dL in women, triglyceride values >150 mg/dL, hsCRP ≥1 mg/L. The metabolic syndrome was defined by the presence of more than three of the criteria established by the International Diabetes Federation (2005) [7]. To quantify insulin resistance, HOMA-IR (HOmeostasis Model Assessment of Insulin-Resitance) (HOMA-IR = [glucose (mg/dL) x insulin (mg/dL)/405) was used. We considered a value >2 of the HOMA index as representing insulin resistance. Subjects from both groups aged 30-79 years were assigned the Framingham 10-Year Risk (FRS) for myocardial infarction and death including age, sex, total cholesterol, HDL-cholesterol, systolic blood pressure, and smoking. Individually calculated FRS was considered to be of low risk (risk <10%), intermediate risk (10-20% risk) and high risk (> 20%).

Statistical analysis

The data was recorded in a Microsoft Excel database and then subjected to a statistical analysis using SPSS 20.0 for Windows. Continuous, normally distributed data was presented as mean ± standard deviation. The ANOVA test was used for comparisons between the groups of continuous variables. The chi-square test was used to compare the categorical variables. The continuous variables were

dichotomized based on the previously defined cut off values and the independent test was applied. Estimated relative risk was calculated by odds ratio using bivariate logistic regression. Correlations between clinical and paraclinical parameters were calculated using the Spearman correlation analysis. The accepted statistical significance threshold was p <0.05.

Results

Demographic features

46 subjects with rosacea (37 women and 9 men, sex ratio F/M 4.11/1, mean age 49.8±15.18 years) and 39 controls (31 women and 8 men, sex ratio F/M 3.88/1, mean age 47.87±15.11 years) were included in study. The age and gender characteristics of the two groups were similar (p=0.949/0.541). 23 (50%) of the rosacea patients had skin phototype 2 and 23 (50%) phototype 3. In control group 12 (30.77%) subjects had phototype 2, 25 (64.1%) phototype 3 and 2 (5.13%) phototype 4. 27 (58.69%) of patients with rosacea had the erythematotelangiectatic subtype and 19 (41.31%) had papulopustular subtype. The duration of evolution of rosacea ranged from 1 to 40 years with a mean of 10.85±9.08 years (Table I).

Cardiovascular risk factors

An age >45 years in men and >55 years in women had 39.13% of rosacea patients and 30.77% of controls (p=0.671). Mean waist circumference was 85.87±15.25 cm in the rosacea group and 83.62±16.99 cm in the control group (p=0.098). An waist circumference >94 cm in men and >80 cm in women was observed in 58.70% of rosacea patients and 46.15% of controls (OR 1.185; 90% CI: 0.765-4.307; p=0.490). Mean BMI was similar in the two groups (26.79±3.29 kg/m^2 and 25.75±5.04 kg/m^2 respectively, p=0.374). A BMI >25 kg/m^2 was calculated in 69.56% of rosacea patients and 48.72% of controls (OR 2.175; 90% CI: 0.902-5.244; p=0.595). The smoking frequency (10.87% vs. 25.64%; p=0.765) and alcohol consumption (10.87% vs. 5.13%; p=0.589) in the two groups did not have statistically significant differences. In the rosacea group the mean total cholesterol level was 213.65±52.47 mg/dL (50% of which had values >200 mg/dL), whereas in the control group the mean cholesterol level was 198,63 ± 38.59 mg/dL (43.59% with values >200 mg/dL) (OR 1.294; 90% CI: 0.549-3.049; p=0.313). The mean LDL level was 126.95±45.94 mg/dL in rosacea patients (36.96% with values >130 mg/dL) and 117.05±29.23 mg/dL in controls (43.59% having values >130 mg/dL) (OR 0.759; 90% CI: 0.317-1.813; p=0.987). In rosacea patients the mean HDL was 53.48±17.48 mg/dL (39.13% below baseline) compared to 57.40±16.71 mg/dL in the control group (33.33% with values below the normal range) (OR 1.286; 90% CI: 0.527-3.134; p=0.037). The mean serum level of triglycerides was 136.51±70.85 mg/dL in rosacea patients (28.26% with values >150 mg/dL) and 128.55±56.63 mg/dL in controls (30.77% with values >150 mg/dL) (OR 0.886; 90% CI: 0.348-2.258; p=0.298). The mean blood glucose level

Table I – Demographic and clinical features of study groups

	Rozacea		Controls		p
	n	%	n	%	
Women	37	80.43%	31	79.49%	.541
Men	9	19.57%	8	20.51%	
Age (mean±SD)	49.8±15.18		47.87±15.11		.949
Phototype 2	23	50%	12	30.77%	.453
3	23	50%	25	64.1%	
4	0	0%	2	5.13%	
BMI (mean±SD) (kg/m^2)	26.79±3.29		25.75±5.04		.374
Waist circumference (mean±SD) (cm)	85.87±15.25		83.62±16.99		.098

BMI – body mass index

was 98.16±25.38 mg/dL in the rosacea group (values >100 mg/dL at 36.96%) and 98.92±17.32 mg/dL in the control group (values >100 mg/dL at 30.77%) (OR 1.446; 90% CI: 0.587-3.567; p=0.671). The mean insulin level in the rosacea and control group was 9.062±6.06 µU/mL and 14.9±21.47 µU/mL respectively, and the HOMA-IR index of 2.21±1.59 and 4.25±7.92, respectively. The mean CRP was higher in the rosacea group than in the control group (2.37±4.93 mg/L vs. 1.02±1.3 mg/L, p=0.603), values ≥1 mg/L with 34.78% of patients with rosacea and 23.07% of controls (OR 1.778; 90% CI: 0.680-4.646; p=0.028) (tables II and III). The mean FRS in the rosacea group was 3.307±4.394 and 3.039±3.557 in the control group (p=0.001). A statistically significant correlation between the subtypes of rosacea and cardiovascular risk factors was only observed for the HOMA index (r=-0.364, p=0.017) (Table IV).

Table II – Comparison of laboratory data between study groups

Laboratory variable	Mean value ± SD		p*
Fasting blood glucose (mg/dL)	98.16±25.38	98.92±17.32	.531
Insulin (µUI/mL)	9.062±6.06	14.9±21.47	.328
HOMA-IR index	2.21±1.59	4.25±7.92	.297
Total cholesterol (mg/dL)	213.65±52.47	198.63±38.59	.328
LDL (mg/dL)	126.95±45.94	117.05±29.23	.486
HDL (mg/dL)	53.48±17.48	57.40±16.71	.229
Triglycerides (mg/dL)	136.51±70.85	128.55±56.63	.148
CRP (mg/L)	2.37±4.93	1.02±1.3	.603

** ANOVA test using continuous values of variables; LDL = low-density lipoprotein; HDL = high-density lipoprotein; CRP = C-reactive protein.*

Discussions

In recent years, several inflammatory skin conditions, the most studied being psoriasis, are no longer seen as a simple skin condition but rather as a systemic inflammatory disease associated with an excess of metabolic dysfunction and cardiovascular risk factors. It seems that, in most cases, systemic inflammation is the basis for the relationship between

Table III – Comparison of the rosacea and control groups according to CVD risk factors

	Rozacea (n=46)%	Controls (n=39)%	OR*	95%CI	p**
Age (>45 years in men, > 55 years in women)	18 (39.13%)	12 (30.77%)	1.446	0.587-3.567	.671
Waist circumference (>80 cm in women, >94 cm in men)	27 (58.70%)	18 (46.15%)	1.185	0.765-4.307	.490
BMI (>25 kg/m2)	32 (69.56%)	19 (48.72%)	2.175	0.902-5.244	.595
Smoking	5 (10.87%)	10 (25.64%)	0.354	0.109-1.144	.765
Alcohol consumption	5 (10.87%)	2 (5.13%)	2.256	0.413-12.337	.589
Hypertension	21 (45.65%)	8 (20.51%)	**3.255**	1.234-8.586	**.004**
Fasting blood glucose (>100 mg/dL)	17 (36.96%)	12 (30.77%)	1.319	0.533-3.264	.461
HOMA index (>2)	21 (45.65%)	26 (66.67%)	0.420	0.174-1.016	.658
Total cholesterol (>200 mg/dL)	23 (50%)	17 (43.59%)	1.294	0.549-3.049	.313
LDL (>130 mg/dL)	17 (36.96%)	17 (43.59%)	0.759	0.317-1.813	.987
HDL (<40 mg/dL in men and <50 mg/dL in women)	18 (39.13%)	13 (33.33%)	**1.286**	0.527-3.134	**.037**
Triglycerides (>150 mg/dL)	13 (28.26%)	12 (30.77%)	0.886	0.348-2.258	.298
Metabolic syndrome	14 (30.43%)	10 (25.64%)	**1.269**	0.488-3.295	**.047**
CRP (≥ 1 mg/L)	16 (34.78%)	9 (23.07%)	**1.778**	0.680-4.646	**.028**

*Bold denotes significant difference (p <0.05); * Bivariate logistic regression; ** t-independent test; BMI = body mass index; LDL = low-density lipoprotein; HDL = high-density lipoprotein; CRP = C-reactive protein.*

Table IV – Comparison of cardiovascular risk factors between subtypes of rosacea

	Erythemato-telangiectatic (n=26)%	Papulo-pustular (n=20)%	OR*	95%CI	p**
Age (>45 years in men, > 55 years in women)	12 (46,15%)	7 (35%)	0.628	0.189-2.085	.447
Waist circumference (>80 cm in women, >94 cm in men)	18 (69.23%)	10 (50%)	0.444	0.133-1.489	.189
BMI (>25 kg/m2)	18 (69.23%)	13 (65%)	0.825	0.239-2.853	.762
Smoking	3 (11.53%)	2 (10%)	0.852	0.128-5.653	.868
Alcohol consumption	2 (7.69%)	3 (15%)	2.118	0.319-14.07	.437
Hypertension	12 (46.15%)	9 (45%)	0.955	0.296-3.078	.939
Fasting blood glucose (>100 mg/dL)	11 (42.31%)	6 (30%)	0.584	0.170-2.005	.398
HOMA index (>2)	16 (61.54%)	5 (25%)	0.208	0.058-0.752	**.017**
Total cholesterol (>200 mg/dL)	13 (50%)	10 (50%)	1.000	0.312-3.209	.999
LDL (>130 mg/dL)	12 (46.15%)	5 (25%)	0.398	0.109-1.388	.146
HDL (<40 mg/dL in men and <50 mg/dL in women)	7 (26.92%)	11 (55%)	3.317	0.964-11.41	.057
Triglycerides (>150 mg/dL)	9 (34.62%)	4 (20%)	0.472	0.121-1.842	.280
Metabolic syndrome	10 (38.46%)	4 (20%)	0.400	0.104-1.544	.184
CRP (≥ 1 mg/L)	10 (38.46%)	6 (30%)	0.686	0.198-2.371	.551

*Bold denotes significant difference (p <0.05); * Bivariate logistic regression; ** t-independent test; BMI = body mass index; LDL = low-density lipoprotein; HDL = high-density lipoprotein; CRP = C-reactive protein.*

cutaneous inflammatory diseases and internal diseases.

Rosacea is a chronic progressive inflammatory skin disorder affecting 5-15% of the general population, particularly individuals with fair skin [8]. Clinical manifestations of rosacea vary in intensity and appearance (erythema, telangiectasia, papules and pustules) with centrofacial localization (cheeks, chin, nose, forehead) and evolution with periods of exacerbation and remission.

The rosacea pathophysiology remains unclear. Several factors involved in the pathogenesis of rosacea have been identified, some based on scientific evidence, others only by clinical observations: genetic predisposition, abnormal vascular reactivity, *Demodex folliculorum* infestation, *Helicobacter pylori* infection, seborrhea, ultraviolet radiation exposure, hypertension, psychological factors, but it is now accepted that rosacea is rather an inflammatory condition than an infectious process [9].

Pathogenic mechanisms of rosacea are related to abnormalities of innate immunity, vascular changes, release of reactive oxygen species by neutrophils, inflammatory mediators, ultraviolet radiation, and microorganisms. Abnormal vascular reactivity appears to be the main phenomenon in the pathogenesis of rosacea and vasodilation is associated with elevated levels of inflammatory mediators, including histamine, prostaglandins and reactive oxygen species [10, 11]. Degeneration of the extracellular dermal matrix caused by degradative proteases released by neutrophils may further damage connective tissue around skin vessels [3]. Recent data indicate that innate immune system dysfunction may play a central role in the development of vascular anomalies and skin inflammation in patients with rosacea [12]. It has been found that rosacea is associated with an exacerbated response of the innate immune system to environmental stimuli by the release of abnormal levels of defensins, a category of antimicrobial peptides (AMPs), such as cathelicidin [13]. In the skin on the face of rosacea patients, 10-fold higher levels of cathelicidin and nearly 1000-fold greater serine protease (kallikrein-5) have been found, a

protease that activates epidermal cathelicidin in its proinflammatory form [14]. Cathelicidin has the role of molecular signaling being involved in angiogenesis, leukocyte migration and scarring. Cathelicidin induces IL-8 release that recruits and activates polymorphonuclear leukocytes, predominant cells in papulo-pustular rosacea [5]. By its proinflammatory and angiogenic properties, LL-37 cathelicidin dysfunction can be considered as the essential factor in the pathogenesis of rosacea [6]. Another factor that appears to interfere with the pathogenesis of rosacea is the hyperexpression of Toll-like-2 receptors (TLR-2), their activation inducing the production of cathelicidin in keratinocytes. A possible ligand for TLR-2 in the skin with rosacea is the chitin of *Demodex* mites [15].

Inflammatory neurogenic reaction is also discussed in the pathogenesis of rosacea. Rosacea patients are hypersensitive to physiological stimuli that cause recurrent facial flushing. In the normal dermis, blood vessels, mast cells and sensory nerves interact closely, but a significantly higher number of mast cells have been reported in the skin of rosacea patients [8], hence, the possibility that mast cells play a role in regulating the mechanisms of neuroimmunological and neurovascular communication in the initial stages of rosacea.

Hua et al. [16], in a study conducted in Taiwan on 33,553 patients with rosacea compared to a control group of 67,106 without rosacea individuals with the same age and gender characteristics, observed that rosacea patients had a 41% higher risk for dyslipidemia, 35% higher for coronary heart disease, and 17% higher for HTA than for non-rosacea patients. The risk of cardiovascular disease was higher in men with rosacea compared to women, and also men with rosacea presented a higher risk for diabetes and stroke. Patients with an older history of rosacea have a higher risk of CVD. Another study in a smaller number of patients led in Turkey also demonstrated a higher frequency of dyslipidemia and CVD in rosacea patients [5]. The pathophysiological connections between rosacea and CVD are complex and remain unclear, possibly involving mechanisms underlying chronic inflammatory conditions, including proinflammatory cytokines, metabolic, immunological and endocrine changes. Studies have reported the presence of cathelicidin in the atheroma plaque [17] and even an association between the expression of the human cathelicidin gene and CVD risk factors [18]. Similarly, serine protease appears to play a role in the atherosclerotic process, and blocking its activity prevents the atherosclerotic plaque extension [19].

Currently the systemic inflammation is known to lead to structural changes of cholesterol carrying lipoproteins adversely affecting their ability to remove cholesterol from the body. When released into the systemic circulation, immune cells and cytokines alter the function of endothelial and hematopoietic cells, increasing the risk of insulin resistance and atherosclerosis. Many evidences indicate that inflammation, both focal and systemic, plays a key role in the destabilization and breakage of atherosclerotic plaques leading to acute cardiovascular events [20]. Given the important role that inflammatory processes play in determining the stability of the atheromatous plaque, recent research has focused on the determination of biomarkers of inflammation (fibrinogen, ESR, CRP, serum amyloid A, IL-6, TNFα, t-PA-PAI-1 complex, E-selectin, P-selectin etc.) helping to improve risk stratification and identifying groups of patients who may benefit from special treatment strategies. Among these markers, CRP is considered the prototype marker of the systemic inflammatory process, being the most studied both as a causal factor and in the prediction of coronary artery disease [21]. In contrast to other markers of inflammation, CRP levels are stable over long periods, have no diurnal variation, and can be measured inexpensively with high sensitivity assays [22]. In our study, the mean CRP was higher in the rosacea group compared to the controls (2.37±4.93 vs. 1.02±1.3 mg/L), and 34.78% of the rosacea patients had CRP values ≥1 mg/L.

Systemic inflammatory cascade is considered to favor the development of metabolic syndrome (MS) [23]. MS is a group of classical cardiovascular risk factors including central obesity, dyslipidemia, glucose intolerance and hypertension, and is identified as a strong predictor of CVD, stroke and type 2 DM [21]. According to the

latest scientific evidence, visceral adipose tissue not only serves to store energy but is also an important player in the immune system and is an active endocrine organ that also produces pro-inflammatory cytokines [24].

In our study there was a higher frequency of hypertension and MS, low levels of HDL cholesterol and higher values of CRP in patients with rosacea compared to the controls, results that were associated with a higher risk of CVD and death as shown by the FRS calculation (p=0.001).

In conclusion, rosacea patients more often associate cardiovascular risk factors in comparison with controls, requiring a systematic assessment of these risk factors due to the increased risk for cardiovascular disease and death.

Study limitations

Due to the small size of the studied group, our results should be considered preliminary and should be reproduced on a larger sample of subjects.

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Conflict of interest
NONE DECLARED

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