ORIGINAL ARTICLE

Rosacea is associated with chronic systemic diseases in a skin severity–dependent manner: Results of a case-control study

Barbara M. Rainer, MD, Alexander H. Fischer, BS, Dimitre Luz Felipe da Silva, Sewon Kang, MD, and Anna L. Chien, MD
Baltimore, Maryland

Rosacea is a chronic inflammatory disease of the skin. It affects up to 15% of the general population with the highest prevalence among adults (>30 years) of Northern European heritage with fair skin.[1] Symptoms present in various combinations and degrees of severity, often fluctuating between periods of exacerbation and

Abbreviations used:

CI:	confidence interval
CVD:	cardiovascular disease
GERD:	gastroesophageal reflux disease
GI:	gastrointestinal
OR:	odds ratio

From the Department of Dermatology, Johns Hopkins University School of Medicine.
Funding sources: None.
Conflicts of interest: None declared.
A portion of this work was presented at the Society for Investigative Dermatology Annual Meeting in Albuquerque, New Mexico, May 7-10, 2014.
Accepted for publication July 6, 2015.

Reprint requests: Barbara M. Rainer, MD, Department of Dermatology, Johns Hopkins University School of Medicine, 1550 Orleans St, Baltimore, MD 21231. E-mail: bm.rainer@gmail.com.
Published online August 6, 2015.
0190-9622/$36.00

http://dx.doi.org/10.1016/j.jaad.2015.07.009

remission. The complex network of the pathophysiology of rosacea is still unclear, and existing therapies only temporarily improve cutaneous symptoms but are not curative.

Traditionally, rosacea is considered a disease that is limited to the skin. A few studies have observed higher risk of specific gastrointestinal (GI) symptoms and disorders,[2-8] cardiovascular disease (CVD),[9] depression,[10,11] and migraine[12] in patients with rosacea. These previous analyses, which yielded conflicting results, were primarily case series, case-control studies with small sample sizes, or retrospective database case-control studies investigating specific comorbidities. Systematic studies to address the association of rosacea with extracutaneous diseases are lacking, and there remains a critical knowledge gap regarding if and to what degree rosacea severity affects the prevalence of systemic comorbidities.

CAPSULE SUMMARY

-
-
-

We therefore enrolled patients with rosacea in a matched case-control study, and investigated the association between rosacea and comorbidities, and whether this association was altered by rosacea severity.

We hypothesized that risk of rosacea, especially in patients with moderate to severe disease, would be associated with the presence of systemic comorbidities.

METHODS

Study design

The study was a single-center case-control study with prospective recruitment of patients with rosacea and matched rosacea-free control subjects. The Johns Hopkins Institutional Review Board approved the study (NA_00078020/October 18, 2012). Study procedures were conducted at the Johns Hopkins Department of Dermatology in Baltimore, MD, between November 2012 and August 2013.

Study cohort

Eligible cases were patients 18 years of age or older with a diagnosis of rosacea. Rosacea-free control subjects were matched to each case by age within 5 years, sex, and race. Participants were recruited from the dermatology clinics at the Johns Hopkins University Hospitals, Baltimore, MD, and through flyers. The study was conducted in accordance with the ethical principles originating from the Declaration of Helsinki and in compliance with local regulatory requirements. Written informed consent was obtained from all patients.

Interview and clinical assessment

A structured interviewer-administered questionnaire collected detailed medical history and current comorbidities, and information on demographics and lifestyle factors, including smoking habits, alcohol use, caffeine intake, and sun exposure. A single study dermatologist assessed rosacea characteristics and rosacea severity using the National Rosacea Society's standard grading system.[13] Rosacea severity was grouped into mild and moderate to severe disease.

Medical conditions (lifetime) were self-reported and confirmed by medication use and medical records, where possible. Allergies were grouped as airborne, food, drug, and hymenoptera venom allergy. Respiratory disease included asthma, chronic obstructive pulmonary disease, chronic bronchitis, and chronic rhinosinusitis (≥8 weeks despite treatment). GI disease included gastritis, gastric/duodenal ulcers, malabsorption (lactose, fructose, sucrose, sorbitol), celiac disease, irritable bowel syndrome, small intestinal bacterial overgrowth, colitis (ulcerative, infectious, lymphocytic), and Crohn's disease. Metabolic disease included diabetes, hypertension, hyperlipidemia, and obesity defined by a body mass index >30 kg/m^2. CVD included coronary heart disease, cerebrovascular disease, peripheral artery disease, and heart failure. Urogenital disease included chronic or recurrent urinary tract infections (2 in 6 months or 3 in 1 year), urolithiasis, polycystic kidney disease, nephritis, other unspecified kidney conditions, and urinary incontinence. Female hormone imbalance included premenstrual syndrome, infertility, female sexual dysfunction, endometriosis, polycystic ovarian syndrome (infertility, hirsutism, and oligomenorrhea), ovarian cysts, fibrocystic breast and uterine fibroids, and hormone replacement therapy. Male hormone imbalance included erectile dysfunction, benign prostate hyperplasia, hypogonadism,

and hormone replacement therapy (testosterone). Migraine and other recurrent headaches were grouped together. Musculoskeletal disease included arthropathies, osteopathies, chondropathies, and systemic connective tissue disorders. Hepatobiliary disease included hepatitis, cirrhosis, and liver failure.

Thyroid disease included hyperthyroidism, hypothyroidism, thyroiditis, or other unspecified thyroid conditions. Neurologic disorders included epilepsy, neuropathy, degenerative disc disease, Parkinson disease, Alzheimer disease, brain tumors, and meningitis. Cancer was defined as any malignant tumor and grouped as "cancer including skin cancer" and "cancer other than skin cancer."

Statistical analysis

Deidentified survey data were entered into a REDCap database, which is a secure World Wide Web application designed to support data capture for research studies.[14] We compared the distribution of rosacea cases and controls using paired *t* tests for continuous variables with appropriate transformations, McNemar test for dichotomous and nominal variables, and Wilcoxon signed rank analyses for ordinal variables and continuous variables when transformation did not achieve a normal distribution. The associations between overall rosacea and comorbid diseases were assessed using conditional logistic regression. Adjustment for history of smoking did not substantially change the association of rosacea with CVD, metabolic disease, hypertension, and hyperlipidemia (change in risk estimate <10%). We therefore reported estimates that were not adjusted for smoking.

In a subgroup analysis, we investigated the associations between moderate to severe versus mild rosacea and comorbid diseases using unconditional logistic regression. We further performed sensitivity analyses, controlling the association between rosacea severity and comorbidities separately for age and sex. In analyses where comorbidity categories were specific to a certain sex (for women: female hormone imbalance, hormonal contraception use; for men: male hormone imbalance), we limited analyses to include only members of that sex. All statistical analyses were performed using statistical software (SAS, Version 9.3, SAS Institute Inc, Cary, NC). For all analyses, *P* less than .05 was accepted as significant.

RESULTS

Participant characteristics

A total of 130 participants were recruited for the study, 65 patients and 65 control subjects. Each patient was matched to a control subject by age ($P = .6$), sex ($P = 1.0$), and race ($P = 1.0$). The mean (SD) age of cases was 50.6 (14.1) years, 43 (66.2%) were female, and 62 (95.4%) were Caucasian. Body mass index ($P = .1$), sun exposure ($P = .3$), smoking status ($P = 1.0$), alcohol intake ($P = .5$), and caffeine intake ($P = .3$) were comparable between cases and controls. Cases more frequently had a family history of rosacea ($P < .0001$). Table I provides the distribution of demographics and lifestyle characteristics.

Table I. Demographics and lifestyle characteristics in rosacea cases and controls (n = 130)

Characteristic	Cases n = 65	Controls n = 65	*P* value
Sex, No. (%)			1.0*
Female	43 (66.2)	43 (66.2)	
Male	22 (33.8)	22 (33.8)	
Race, No. (%)			1.0*
White	62 (95.4)	62 (95.4)	
Asian	2 (3.1)	2 (3.1)	
African American	1 (1.5)	1 (1.5)	
Skin phototype, No. (%)			.1†
1	15 (23.1)	8 (12.3)	
2	42 (64.6)	46 (70.8)	
3	5 (7.7)	9 (13.9)	
4	2 (3.1)	1 (1.5)	
5	1 (1.5)	1 (1.5)	
Age, y, mean (SD; range)	50.6 (14.1; 23-92)	50.4 (14.8; 22-94)	.6‡
BMI, kg/m^2, mean (SD)	27.6 (5.8)	26.0 (5.4)	.1§
Amount of sun, No. (%)			.3†
No exposure	0 (0.0)	1 (1.5)	
Rare, 1 wk/y	10 (15.4)	18 (27.7)	
Medium, 2-4 wk/y	20 (30.8)	11 (16.9)	
Frequent, >4 wk/y	35 (53.9)	35 (53.9)	
Family history of rosacea, No. (%)			<.0001*
Yes	36 (55.4)	8 (12.3)	
No	29 (44.6)	57 (87.7)	
Smoking status, No. (%)			>.99*
Nonsmoker	60 (92.3)	59 (90.8)	
Current smoker	5 (7.7)	6 (9.2)	
Alcohol, drinks/wk, mean (SD)	2.5 (2.5)	2.8 (4.9)	.4†
Caffeine, 8-oz cups/d, mean (SD)	2.4 (2.0)	2.1 (1.6)	.2†

BMI, Body mass index.
*Calculated by McNemar test.
†Calculated by Wilcoxon signed rank analysis.
‡Calculated by paired *t* test.
§Calculated by paired *t* test after log transformation.

Rosacea characteristics

Of 65 patients with rosacea, 38 (58.4%) had mild and 27 (41.5%) had moderate to severe rosacea as

Table II. Distribution of comorbidities in rosacea cases and controls (n = 130)

Comorbid disease	Cases n = 65 No. (%)	Controls n = 65 No. (%)	OR for rosacea (95% CI)	*P* value
Allergy				
Airborne	44 (67.7)	26 (40.0)	4.6 (1.7-12.1)	.002
Food	11 (16.9)	2 (3.1)	10.0 (1.3-78.1)	.03
Respiratory diseases	18 (27.7)	6 (9.2)	4.0 (1.3-12.0)	.01
GERD	32 (49.2)	13 (20.0)	4.2 (1.7-10.2)	.002
Other GI diseases	23 (35.4)	11 (16.9)	3.0 (1.2-7.6)	.02
Hypertension	24 (36.9)	13 (20.0)	2.8 (1.1-7.2)	.03
Metabolic diseases	35 (53.8)	24 (36.9)	2.4 (1.04-5.4)	.04
Urogenital diseases	15 (23.1)	2 (3.1)	7.5 (1.7-32.8)	.007
Female hormone imbalance	21 (48.8)	10 (23.3)	3.2 (1.2-8.7)	.02

CI, Confidence interval; *GERD*, gastroesophageal reflux disease; *GI*, gastrointestinal; *OR*, odds ratio.

defined by a standard grading system for rosacea.[13] Patients presented with erythematotelangiectatic (95.4%), papulopustular (36.9%), and phymatous (15.4%) changes, and nearly half (46.2%) had ocular involvement. Mean (SD) duration of disease was 11.8 (9.6) years.

Rosacea and prevalence of comorbidities

When analyzed by conditional logistic regression for matched case-control pairs, patients with rosacea were more likely to have allergies (airborne [odds ratio {OR} 4.6, 95% confidence interval {CI} 1.7-12.1, $P < .01$], food [OR 10.0, 95% CI 1.3-78.1, $P < .05$]), respiratory diseases (OR 4.0, 95% CI 1.3-12.0, $P < .05$), gastroesophageal reflux disease (GERD) (OR 4.2, 95% CI 1.7-10.2, $P < .01$), other GI diseases (OR 3.0, 95% CI 1.2-7.6, $P < .05$), hypertension (OR 2.8, 95% CI 1.1-7.2, $P < .05$), metabolic diseases (OR 2.4, 95% CI 1.0-5.4, $P < .05$), urogenital diseases (OR 7.5, 95% CI 1.7-32.8, $P < .01$), and female hormone imbalance (OR 3.2, 95% CI 1.2-8.7, $P < .05$) (Table II). Borderline significant associations were observed between rosacea and drug allergy (OR 2.2, 95% CI 1.0-5.2, $P = .06$), migraine (OR 2.3, 95% CI 0.9-5.6, $P = .07$), and musculoskeletal diseases (OR 2.2, 95% CI 1.0-5.2, $P = .06$).

Rosacea severity and prevalence of comorbidities

In a subgroup analysis that compared 27 (41.5%) patients with moderate to severe rosacea to 38 (58.4%) patients with mild rosacea, we detected a dose-response effect regarding rosacea severity and the prevalence of comorbidities. Compared with mild rosacea, moderate to severe rosacea was strongly associated with hyperlipidemia (OR 6.8, 95% CI 1.9-24.6, $P < .01$), hypertension (OR 4.0, 95% CI 1.4-11.7, $P = .01$), metabolic diseases (OR 4.4, 95% CI 1.5-12.9, $P < .01$), CVD (OR 4.3, 95% CI 1.5-12.4, $P < .01$), and GERD (OR 4.6, 95% CI 1.6-13.2, $P < .01$) (Table III). These results remained robust after separate adjustment for age and sex, with 1 notable exception for cancers including skin cancer; here rosacea severity was inversely associated with "cancer including skin cancer" after adjusting for sex (OR 0.2, 95% CI 0.02-0.9, $P < .05$).

Table III. Association between rosacea severity and comorbidities (n = 65)

Comorbid disease	Mild n = 38 No. (%)	Moderate to severe n = 27 No. (%)	OR for moderate to severe rosacea (95% CI)	*P* value
GERD	13 (34.2)	19 (70.4)	4.6 (1.6-13.2)	.005
Hyperlipidemia	4 (10.5)	12 (44.4)	6.8 (1.9-24.6)	.003
Hypertension	9 (23.7)	15 (55.6)	4.0 (1.4-11.7)	.01
Metabolic diseases	15 (39.5)	20 (74.1)	4.4 (1.5-12.9)	.007
Cardiovascular diseases	12 (31.6)	18 (66.7)	4.3 (1.5-12.4)	.006

CI, Confidence interval; *GERD*, gastroesophageal reflux disease; *OR*, odds ratio.

DISCUSSION

Our case-control study reports significant associations between rosacea and several systemic comorbidities. Patients with rosacea have significantly higher odds of experiencing allergies (airborne and food), respiratory diseases, GERD/other GI diseases, hypertension, metabolic diseases, urogenital diseases, and female hormone imbalance compared with age-, sex-, and race-matched control subjects originating from the same population. Moderate to severe rosacea[13] is associated with hyperlipidemia, hypertension, metabolic diseases, CVD, and GERD. These associations remained robust after separate adjustment for age and sex. Interestingly, when we added sex into the regression model, the ORs of "cancer including skin cancer" were decreased in patients with moderate to severe rosacea compared with mild rosacea. Given that no association between "cancer other than skin cancer" and rosacea severity was detected, skin cancer is likely driving the above-mentioned association. Considering that there was no difference in sun-exposing behaviors between groups, it is conceivable that patients with more severe rosacea may visit their dermatologists

more often; hence, skin cancer precursors might be detected and treated earlier.

Previous studies suggested a link between rosacea and GI disorders such as malabsorption, celiac disease,[2] inflammatory bowel disease,[3,4] small intestinal bacterial overgrowth,[6,7] and *Helicobacter pylori* risk,[7,8] but these studies yielded conflicting results in some cases. Our study confirmed a significant association of rosacea and GERD/other GI diseases. The risk of GERD was significantly higher in more severe rosacea (OR 4.6, 95% CI 1.6-13.2, $P < .01$) independent of doxycycline use.

Another interesting finding is the strong association of rosacea with cardiovascular risk factors and CVD. Rosacea has been associated with biomarkers of CVD risk, such as total cholesterol, low-density lipoprotein, and C-reactive protein.[9] The current study indicates that rosacea disease activity matters, and demonstrates that moderate to severe rosacea is associated with hyperlipidemia, hypertension, metabolic diseases, and CVD. Thus, assessing cardiovascular risk factors and the overall CVD risk in patients with rosacea seems prudent.

Although our study establishes associations between rosacea and chronic systemic diseases, the pathophysiological connections are complex and remain unclear. It is likely that these connections involve mechanisms that underlie chronic inflammatory conditions including inflammatory cytokines, and metabolic, immune, and endocrine changes. The associations between rosacea and diseases involving barrier tissues such as the respiratory, GI, and urogenital tracts, which are constitutively colonized by a greatly diverse and site-specific flora, raises suspicion that dysbiosis might be a factor in the pathogenesis of rosacea, as well.

Limitations that affect case-control studies need to be taken into account. These include recall and response bias in self-reported checklists, moderate sample sizes impacting the ability to analyze low-prevalence conditions, and the cross-sectional nature of the study, which precludes detection of cause-effect relationships and their directionality. Finally, we did not control for some potential confounders, such as physical activity, nutrition, or family history of disease, including atopy. Therefore, our results should be considered hypothesis generating and require confirmation in prospective studies. The associations with several comorbid diseases in addition to the role of rosacea disease severity raise numerous new questions. To understand the link between comorbidities and rosacea, we need to investigate if pre-existing comorbidities affect the risk and phenotype of rosacea or if rosacea precedes the manifestation of comorbid diseases. Do comorbidities affect treatment response, and accordingly, should we use different treatment strategies in the presence of certain comorbidities? Lastly, given the involvement of tissues that interface with the microbial environment, such as the intestinal, respiratory, reproductive, and urinary tracts and the skin, future research needs to investigate how the tissue-environment interface is altered in patients with rosacea.

In conclusion, our study provides evidence supporting the link between rosacea and systemic comorbidities. Moderate to severe rosacea is associated with hyperlipidemia, hypertension, metabolic diseases, CVD, and GERD. Physicians should be aware of these associations to provide comprehensive care to patients with rosacea, especially to those presenting with more severe disease.

REFERENCES

1. Spoendlin J, Voegel JJ, Jick SS, et al. A study on the epidemiology of rosacea in the U.K. *Br J Dermatol*. 2012;167:598-605.
2. Watson WC, Paton E, Murray D. Small-bowel disease in rosacea. *Lancet*. 1965;1:47-50.
3. Walton S, Sheth M, Wyatt EH. Rosacea and ulcerative colitis: a possible association. *J Clin Gastroenterol*. 1990;12:513-515.
4. Romiti R, Jansen T, Heldwein W, et al. Rosacea fulminans in a patient with Crohn's disease: a case report and review of the literature. *Acta Derm Venereol*. 2000;80:127-129.
5. Kendall SN. Remission of rosacea induced by reduction of gut transit time. *Clin Exp Dermatol*. 2004;29:297-299.
6. Parodi A, Paolino S, Greco A, et al. Small intestinal bacterial overgrowth in rosacea: clinical effectiveness of its eradication. *Clin Gastroenterol Hepatol*. 2008;6:759-764.
7. Gravina A, Federico A, Ruocco E, et al. *Helicobacter pylori* infection but not small intestinal bacterial overgrowth may play a pathogenic role in rosacea. *United European Gastroenterol J*. 2015;3:17-24.
8. Jones MP, Knable AL Jr, White MJ, et al. *Helicobacter pylori* in rosacea: lack of an association. *Arch Dermatol*. 1998;134:511.
9. Duman N, Ersoy Evans S, Atakan N. Rosacea and cardiovascular risk factors: a case control study. *J Eur Acad Dermatol Venereol*. 2014;28:1165-1169.
10. Gupta MA, Gupta AK, Chen SJ, et al. Comorbidity of rosacea and depression: an analysis of the National Ambulatory Medical Care Survey and National Hospital Ambulatory Care Survey—outpatient department data collected by the U.S. National Center for Health Statistics from 1995 to 2002. *Br J Dermatol*. 2005;153:1176-1181.
11. Spoendlin J, Bichsel F, Voegel JJ, et al. The association between psychiatric diseases, psychotropic drugs and the risk of incident rosacea. *Br J Dermatol*. 2014;170:878-883.
12. Spoendlin J, Voegel JJ, Jick SS, et al. Migraine, triptans, and the risk of developing rosacea: a population-based study within the United Kingdom. *J Am Acad Dermatol*. 2013;69:399-406.
13. Wilkin J, Dahl M, Detmar M, et al. Standard grading system for rosacea: report of the National Rosacea Society Expert Committee on the classification and staging of rosacea. *J Am Acad Dermatol*. 2004;50:907-912.
14. Klipin M, Mare I, Hazelhurst S, et al. The process of installing REDCap, a web-based database supporting biomedical research: the first year. *Applied Clin Inform*. 2014;5:916-929.