Evidence-based update on rosacea comorbidities and their common physiologic pathways

Anna D. Holmes, PhD,[a] Julia Spoendlin, PhD,[b] Anna L. Chien, MD,[c] Hilary Baldwin, MD,[d] and Anne Lynn S. Chang, MD[e]
Fort Worth, Texas; Boston, Massachusetts; Baltimore, Maryland; Morristown, New Jersey; and Redwood City, California

Rosacea is a common chronic inflammatory disease affecting the facial skin whose etiology and pathophysiology are the subject of much investigation. Risk factors include genetic and environmental elements that may predispose individuals to localized inflammation and abnormal neurovascular responses to stimuli. Recent studies have introduced an array of systemic rosacea comorbidities, such as inflammatory bowel disease and neurologic conditions, that can be challenging to synthesize. We critically review the current data behind reported rosacea comorbidities and identify and highlight underrecognized physiologic mediators shared among rosacea and associated comorbidities. This information may be helpful in addressing patient questions about potential systemic implications of rosacea and can serve as a candidate platform for future research to understand rosacea and improve treatments. (J Am Acad Dermatol 2018;78:156-66.)

Key words: cardiovascular; comorbidity; environment; gastrointestinal; genetics; immune; microbiome; neurologic; pathophysiology; rosacea.

Rosacea is a chronic cutaneous disease clinically characterized by erythema, telangiectasia, papules, or pustules on the central face. Ocular and phymatous symptoms are also common. The medical literature suggests the underlying pathophysiology is mediated by abnormal inflammatory and neurovascular processes. Rosacea prevalence reports vary, with rates from 2% to 22% in the United States and Europe, respectively.[1-4] Onset typically occurs after 30 years of age and has been most commonly reported in more photosensitive skin types.[5,6]

In 2015 and 2016, several observational studies reported potential associations of rosacea with

Abbreviations used:

CeD:	celiac disease
CVD:	cardiovascular disease
GST:	glutathione-S-transferase
GWAS:	genome-wide association study
HLA:	human leukocyte antigen
HR:	hazard ratio
IBD:	inflammatory bowel disease
IL:	interleukin
MHC:	major histocompatibility complex
MS:	multiple sclerosis
OR:	odds ratio
RA:	rheumatoid arthritis
ROS:	reactive oxygen species
SIBO:	small intestinal bacterial overgrowth
UC:	ulcerative colitis

From Galderma Laboratories, L.P.,[a] Fort Worth; Division of Pharmacoepidemiology and Pharmacoeconomics,[b] Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston; Department of Dermatology,[c] Johns Hopkins School of Medicine, Baltimore; Acne Treatment and Research Center,[d] Morristown; and the Department of Dermatology,[e] Stanford University School of Medicine, Redwood City.

Funding sources: None.

Dr Holmes is an employee of Galderma Laboratories, L.P., Dr Spoendlin received an independent research grant funded by Galderma as a PhD student at the University of Basel between 2010-2013, Dr Baldwin is a speaker and advisor for Galderma, and Dr Chang has been a clinical investigator for studies sponsored by Galderma. Dr Chien does not have conflicts of interest to declare.

Accepted for publication July 14, 2017.

Reprints not available from the authors.

Correspondence to: Anne Lynn S. Chang, MD, Stanford University School of Medicine, 450 Broadway, Pavilion C, 2nd fl, Redwood City, CA 94063. E-mail: alschang@stanford.edu.

Published online October 28, 2017.

0190-9622/$36.00

http://dx.doi.org/10.1016/j.jaad.2017.07.055

various comorbidities.[2-13] These findings bring into question whether rosacea is a localized skin disease, as previously thought, or a disease with systemic implications. To critically review the data behind reported comorbidities of rosacea, we searched PubMed using the keywords "rosacea," "epidemiology," "comorbidity," "case-control," "cohort," and "risk." We summarized our findings using descriptive tables (Table I) and narrative discussion, excluding case reports. We further examined genetic, environmental, and pathophysiologic factors underlying rosacea and associated comorbidities, and highlight commonalities between rosacea and these seemingly disparate systemic diseases.

CAPSULE SUMMARY

- Rosacea is a common inflammatory skin condition that has been associated with increasing numbers of systemic diseases.
- This article analyzes the latest literature on common genetic, environmental, and pathophysiologic factors that underlie both rosacea and associated comorbidities.
- Rosacea may be a sign of concurrent or future comorbid medical conditions.

ROSACEA COMORBIDITIES

Gastrointestinal

Prevailing literature suggests comorbidity associations between rosacea and disorders of the gastrointestinal tract (Table I).[7,8] The strongest evidence from recent observational studies suggest a link between rosacea and inflammatory bowel disease (IBD). For instance, a large retrospective case-control study from the United Kingdom Clinical Practice Research Datalink of 80,957 outpatient rosacea cases treated in primary care observed an increased risk of rosacea in patients with ulcerative colitis (odds ratio [OR] = 1.65; 95% confidence interval [CI], 1.43-1.90) and Crohn's disease (OR = 1.49 [95% CI, 1.25-1.77]) compared to patients without rosacea. Stronger associations occurred in patients with more severe IBD.[9] A US-based observational cohort study among women reported a significant association between rosacea and subsequent development of Crohn's disease (hazard ratio [HR] = 2.20 [95% CI, 1.15-4.18]) but not ulcerative colitis (adjusted for antibiotic use).[10] Because IBD usually develops at an earlier age than rosacea, the latter study may reflect only a subset of IBD patients with concurrent rosacea. Studies from Taiwan, Korea, and Denmark further substantiate a rosacea–IBD association,[11-13] with younger patients exhibiting the highest comorbidity risk.[9,11,12]

A Danish nationwide cohort study (n = 4,312,213) reported a significant association between rosacea and subsequently diagnosed celiac disease (CeD) ($P < .001$),[13] a finding that was specific to women in a related case-control study.[14] The authors further reported a significant association between irritable bowel syndrome and rosacea, although the study did not adjust for IBD, a possible confounder with overlapping symptoms.[25]

A gastrointestinal microbial contribution to rosacea pathogenesis has been hypothesized, with evidence for the bacteria *Helicobacter pylori*, and possibly small intestinal bacterial overgrowth (SIBO), as associated factors.[26-28] A small prospective cohort study (n = 88) reported a 21.6% and 25% prevalence of *H pylori* and SIBO, respectively, in patients with rosacea.[29] Although *H pylori* is known to cause peptic ulcers, an increased risk of rosacea among peptic ulcer patients was not found in a UK-based observational study.[9] Notably, there is a significant coincidence but not a higher rate of new *H pylori* infection in patients with existing rosacea[13]; therefore, these bacteria may instead predispose individuals or act as a trigger factor for rosacea onset.

Neurologic

The greatest number of recent rosacea comorbidity associations pertain to neurologic diseases, with the strongest evidence associating rosacea and depression. Data from 2 national ambulatory care surveys collected between 1995 and 2002 in the United States found that depression accounted for 65.1% of psychiatric comorbidities in patients with rosacea compared with 29.9% in the general population (temporality not assessed).[17] Similarly, the incidence rates for anxiety and depression were more than double in a Danish rosacea cohort compared to the reference population.[15] These findings are concordant with survey-based studies reporting decreased quality of life,[30,31] depression, and anxiety[32] in patients with rosacea; however, the underlying impact of altered physical appearance requires additional study. Case-control data from the United Kingdom suggests that individuals with preexisting depression are not at increased risk for rosacea.[16]

Multiple reports also link rosacea with migraine.[19,33-36] For instance, a retrospective case-control study of 53,927 patients with rosacea in the United Kingdom from 1995 to 2009 reported a higher incidence of rosacea in women with a history of