

REVIEW

Comorbidities in rosacea: A systematic review and update

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Background: Rosacea is linked to abnormalities of cutaneous vasculature and dysregulation of the inflammatory response. Recent reports on rosacea have shown a significant association with cardiovascular, gastrointestinal, and psychiatric diseases, all of which may affect morbidity and mortality among these patients.

Objective: To review available data regarding comorbidities associated with rosacea, discuss their pathogenesis, and highlight the evaluation of affected patients.

Methods: We performed a complete and systematic literature review in PubMed/Medline, Embase, and the Cochrane Collaboration databases, searching for all articles on possible associated diseases that have been reported with rosacea, with no limits on publication date, participant age, sex, or nationality.

Results: A total of 29 studies were included in this systematic review, including 14 case-control, 8 cross-sectional, and 7 cohort studies. Statistically significant association with rosacea has been mostly demonstrated with depression (n = 117,848 patients), hypertension (n = 18,176), cardiovascular diseases (n = 9739), anxiety disorder (n = 9079), dyslipidemia (n = 7004), diabetes mellitus (n = 6306), migraine (n = 6136), rheumatoid arthritis (n = 4192), *Helicobacter pylori* infection (n = 1722), ulcerative colitis (n = 1424), and dementia (n = 1194).

Limitations: Limitations included the accuracy of the published data, potential patient selection, and possible confounding factors. The true nature of the drawn correlations is uncertain, and causality cannot be established.

Conclusions: Rosacea is associated with a number of systemic disorders. Recognition of these conditions is critical to providing appropriate screening and management of affected patients. (J Am Acad Dermatol <https://doi.org/10.1016/j.jaad.2017.09.016>.)

Key Words: comorbidity; inflammation; morbidity; mortality; rosacea; screening; systemic.

The presence of a mixed inflammatory infiltrate in rosacea skin and the success of anti-inflammatory medications support the hypothesis that rosacea is primarily an inflammatory disorder.^{1,2} It is known that chronic inflammation plays a prominent role in atherosclerosis and that patients with various inflammatory diseases, including rheumatoid arthritis and psoriasis, have a

Abbreviations used:

CAD:	coronary artery disease
CVD:	cardiovascular disease
DM:	diabetes mellitus
GI:	gastrointestinal
IBD:	irritable bowel disease
MMP:	matrix metalloproteinase

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high risk for development of systemic diseases.³ Because rosacea is generally linked to abnormalities of cutaneous vasculature and dysregulation of the inflammatory response^{1,2} and because the chronic inflammatory nature of rosacea is similar to psoriasis,⁴ recent data have shown that rosacea may be associated with systemic comorbidities that may affect morbidity and mortality among these patients. Recognizing and addressing these diseases are critical to improve outcomes. These disorders have been well identified and studied in psoriasis, but data on diseases associated with rosacea are still relatively sparse and not thoroughly evaluated. The aim of this article is to review these data to discuss their pathogenesis and highlight the specific work-up for these patients.

METHODS

Two reviewers (R.H. and M.G.) independently performed a systematic literature review in the Pubmed/Medline, Embase and Cochrane collaboration databases. The search included all articles on possible comorbidities that have been reported with rosacea. The corresponding authors of unavailable articles were contacted by e-mail.

Articles published in English or French and dated between January 1955 and January 2017 were included in this study. To determine eligibility for inclusion in this review, we screened titles and abstracts by using the criteria of case-control, cross-sectional, or cohort studies with no limits on publication date, participant age, sex, or nationality. Case reports, letters to the editor, and abstracts were not included in this review. After exclusion of repeated articles, a manual review of the citations from these articles was performed to identify additional articles. Disagreements between reviewers (R.H. and M.G.) were resolved by discussion to reach a consensus; Cohen's κ statistic for the inclusion of studies was 0.8.

RESULTS

Our initial search yielded a total of 552 articles. Of those, 54 were duplicates and 286 records were excluded after title and abstract revision. In all, 29 articles were included in the systematic review: 14 case-control, 8 cross-sectional, and 7 cohort studies. The stepwise approach for study selection is summarized in Fig 1, and the characteristics of the

included studies can be found in Supplemental Table I⁵⁻³² (available at: <http://www.jaad.org>). Table I shows (1) the number of studies on comorbidities that revealed a positive correlation with rosacea and (2) the total number of cases that have been reported with rosacea in all the included studies. The most important statistically significant

association with rosacea was demonstrated with depression (n = 117,848 patients), hypertension (n = 18,176), cardiovascular disease (CVD) (n = 9739), anxiety disorder (n = 9079), dyslipidemia (n = 7004), diabetes mellitus (DM) (n = 6306), and migraine (n = 6136). The total number of reported cases of comorbidities is shown in Fig 2.

DISCUSSION

Rosacea is a common facial skin disorder with poorly understood pathogenesis. Recent data show that it involves proinflammatory mediators and activation of the adaptive immune system.^{1,33,34} To the best of our knowledge, our study is the first review analyzing available data regarding the diseases associated with rosacea. We also discussed the possible underlying disease mechanisms and made recommendations for early monitoring and prevention of those comorbidities.

CVD

In this review, rosacea was significantly associated with CVD risk factors, including coronary artery disease (CAD), CVD, peripheral artery disease, heart failure, DM, hypertension, dyslipidemia, and metabolic syndrome.^{5-8,35} Notably, the association between rosacea and CAD was still significant after adjustment for hypertension, DM, and dyslipidemia. Chronic inflammation in rosacea can be systemic. Interestingly, recently published data have shown a reduced risk for vascular events with tetracycline treatment in patients with rosacea. It is stipulated that through the inhibition of metalloproteinases, the anti-inflammatory properties of tetracyclines may have beneficial secondary effects on the cardiovascular system in these patients.^{36,37} Similarly to psoriasis, rosacea should be considered an independent risk factor for CAD,⁵ and clinicians should screen patients with rosacea for cardiovascular disease. We suggest that practitioners refer these patients for appropriate work-up. For primary

CAPSULE SUMMARY

- Recent reports suggest a significant association of rosacea with certain systemic disorders.
- This systematic review demonstrates that rosacea is associated with cardiovascular, gastrointestinal, neurologic, and psychiatric comorbidities.
- Screening for, recognizing, and addressing these conditions are critical aspects of patient management.

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