Review Article

Rosacea and associated systemic diseases: Epidemiological evidence and shared mechanisms

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Abstract

Rosacea is a chronic inflammatory dermatosis that predominantly affects the facial skin and is characterized by erythema, inflammatory lesions, phymatous changes, and frequent ocular involvement. Advances in clinical understanding have led to a transition from traditional subtype-based classification toward a phenotype-based approach, reflecting the heterogeneity of clinical manifestations and the complexity of its underlying pathophysiology. Rosacea is increasingly recognized as a systemic inflammatory condition involving immune dysregulation, neurovascular alterations, and barrier dysfunction, rather than a disease confined to the skin. A growing body of epidemiological evidence has demonstrated significant associations between rosacea and multiple systemic diseases. Cohort studies, case–control studies, and meta-analyses consistently report links with cardiovascular disorders, including hypertension, dyslipidemia, coronary artery disease, and subclinical atherosclerosis, likely mediated by chronic inflammation and endothelial dysfunction. Metabolic associations, such as obesity, metabolic syndrome, and type 2 diabetes mellitus, further highlight the role of immunometabolic alterations and chronic low-grade inflammation in rosacea. Gastrointestinal comorbidities, particularly inflammatory bowel disease, small intestinal bacterial overgrowth, and functional gastrointestinal disorders, support the relevance of the gut–skin axis in disease expression. Additionally, autoimmune associations, including autoimmune thyroid diseases and other immune-mediated conditions, underscore shared mechanisms of immune dysregulation involving both innate and adaptive immunity. Despite consistent associations, methodological

limitations such as heterogeneous study designs, variable diagnostic criteria, and potential confounding factors limit causal inference. Nonetheless, current evidence supports the concept of rosacea as a multisystem inflammatory disorder. Recognizing its systemic associations has important clinical implications, emphasizing the need for a holistic, multidisciplinary approach to patient evaluation and management. Future prospective and mechanistic studies are required to clarify causality, refine risk stratification, and guide integrated therapeutic strategies aimed at improving long-term outcomes in patients with rosacea.

Key words

Rosacea, Systemic inflammation, Cardiovascular comorbidity, Metabolic syndrome, Gut–skin axis, Autoimmune disease.

Introduction

Rosacea has been increasingly linked to systemic inflammation, a mechanism that may partially explain its association with cardiovascular disease. Elevated circulating levels of proinflammatory cytokines, including interleukin-1 beta, interleukin-6, and tumor necrosis factor alpha, have been consistently reported in patients with rosacea. These mediators are well recognized markers of cardiovascular risk and support the concept that rosacea is not solely a localized cutaneous disorder but rather a condition with systemic inflammatory involvement. From a vascular perspective, the impact of rosacea on carotid intima–media thickness appears to be limited when traditional cardiovascular risk factors are absent. However, evidence suggests that patients with moderate to severe disease or those with ocular involvement may exhibit features of increased subclinical atherosclerosis, indicating a potential stratification of cardiovascular risk according to disease severity [1]. This relationship is further reinforced by data from retrospective cohort studies, which propose that the chronic inflammatory milieu characteristic of rosacea may predispose affected individuals to the development of cardiovascular conditions over time [2].

Beyond cardiovascular involvement, rosacea has also been associated with a broad spectrum of gastrointestinal disorders, including inflammatory bowel disease, celiac disease, and irritable bowel syndrome. These associations have been interpreted within the framework of the gut–skin axis, which suggests that shared genetic susceptibility, alterations in the microbiota, and overlapping immunological pathways may contribute to the coexistence of cutaneous and gastrointestinal inflammation [3]. Supporting this concept, a systematic review and meta-analysis demonstrated a bidirectional relationship between rosacea and inflammatory bowel disease, showing an increased prevalence of rosacea among patients with inflammatory bowel disease and, conversely, a higher prevalence of inflammatory bowel disease among patients with rosacea [4]. Additional interest has focused on the potential contribution of Helicobacter pylori infection and small intestine bacterial overgrowth to rosacea pathogenesis. Therapeutic strategies targeting these conditions have shown promise in improving rosacea symptoms, further underscoring the relevance of gastrointestinal inflammation in disease expression [3].

Ocular involvement represents another important dimension of rosacea-associated comorbidity. Patients frequently present with conditions such as blepharitis, conjunctivitis, and dry eye syndrome. Case–control studies have identified a significant association between rosacea and a variety of ocular disorders, highlighting the need for systematic ophthalmologic assessment in this patient population. These findings suggest that the inflammatory processes underlying rosacea may extend beyond the skin to involve the ocular

surface, reinforcing the importance of a multidisciplinary approach to achieve effective control of both dermatological and ocular manifestations [5].

Taken together, the systemic associations of rosacea have important implications for clinical management. The recognition of these comorbidities supports a holistic approach to patient care, in which clinicians remain vigilant for cardiovascular, gastrointestinal, and ocular involvement and initiate appropriate screening and referrals when indicated [6]. Therapeutic strategies aimed at controlling rosacea may therefore benefit from addressing both cutaneous inflammation and its potential systemic correlates. Systemic treatments such as oral isotretinoin, minocycline, and doxycycline have demonstrated efficacy in reducing inflammatory lesions and may contribute to lowering the overall inflammatory burden associated with the disease [7]. Nevertheless, continued investigation into the pathophysiological links between rosacea and systemic diseases remains essential to refine therapeutic approaches and ultimately improve long-term patient outcomes [8].

The aim of this article is to review the epidemiological evidence of systemic diseases associated with rosacea and to discuss the shared inflammatory mechanisms underlying these associations.

Methodology

For the preparation of this review on rosacea and its association with systemic diseases, a structured analysis of the scientific literature was performed to examine epidemiological links, underlying inflammatory mechanisms, and clinical implications of these comorbidities. The methodological approach was designed to integrate dermatological, immunological, and systemic perspectives, with particular emphasis on cardiovascular, gastrointestinal, and ocular associations, as well as shared pathophysiological pathways.

The literature search was conducted using major biomedical databases, including PubMed, Scopus, and Web of Science, chosen for their broad coverage of dermatology, internal medicine, immunology, and epidemiology. A predefined search strategy was applied using combinations of keywords related to Rosacea, systemic inflammation, cardiovascular comorbidity, metabolic syndrome, gut–skin axis, autoimmune disease. Only articles published between 2021 and 2026 in English or Spanish were considered. Eligible studies included original research articles, cohort and case–control studies, systematic reviews, and meta-analyses that specifically addressed epidemiological associations or mechanistic links between rosacea and systemic diseases. Publications without peer review, with insufficient methodological detail, or with overlapping or duplicated data were excluded.

The initial search yielded a total of 34 relevant publications. These sources were independently reviewed and critically appraised to extract data on prevalence estimates, risk associations, inflammatory markers, and proposed biological mechanisms. Emphasis was placed on studies that provided quantitative measures of association or mechanistic insights supported by clinical or experimental evidence.

Artificial intelligence–based tools were used as supportive instruments for literature organization, thematic clustering, and identification of conceptual relationships among studies. These tools facilitated efficient synthesis of complex data while preserving consistency and logical structure throughout the review.

The analysis followed a qualitative, thematic framework. Findings were grouped into epidemiological associations and shared pathophysiological mechanisms to allow comparative interpretation across disease categories. This approach enabled a coherent evaluation of the current evidence, identification of knowledge gaps, and discussion of the clinical

relevance of rosacea as a potential marker of systemic inflammatory disease.

Rosacea: general concepts

Rosacea is defined as a chronic inflammatory dermatosis that predominantly affects the facial skin and is clinically characterized by transient and persistent erythema, phymatous changes, and possible ocular involvement. Over time, the understanding of rosacea has progressed alongside refinements in its clinical classification. Traditional subtype-based models have evolved toward a phenotype-based classification system, which better reflects the heterogeneity of clinical manifestations and acknowledges the complex and variable underlying pathophysiological processes observed among affected individuals [8, 9].

Within this framework, several main clinical subtypes are recognized, including erythematotelangiectatic, papulopustular, phymatous, and ocular rosacea. Erythematotelangiectatic rosacea is primarily characterized by persistent facial redness accompanied by visible dilated blood vessels, whereas papulopustular rosacea presents with inflammatory lesions resembling acneiform eruptions. Phymatous rosacea is distinguished by progressive skin thickening and tissue enlargement, most commonly involving the nasal area. Ocular rosacea affects the eyes and periocular structures, frequently leading to symptoms such as dryness, irritation, and discomfort, and may occur independently or in association with cutaneous disease [8, 9].

The pathophysiology of rosacea is multifactorial and involves a complex interplay between skin barrier dysfunction, dysregulation of the immune system, and neurovascular alterations. Central mechanisms implicated in disease development include abnormal activation of the cathelicidin pathway, altered signaling through transient receptor potential channels, mast cell activation, and engagement of the NLRP3 inflammasome, all of which contribute to sustained inflammation and vascular reactivity. In addition to these intrinsic mechanisms, genetic predisposition and environmental influences, such as ultraviolet radiation exposure and changes in microbial flora, play important roles in triggering disease onset and exacerbating clinical manifestations [9, 10].

Epidemiological evidence

The epidemiological evidence linking rosacea with systemic diseases derives from a variety of study designs, including cohort studies, case–control studies, and meta-analyses, each contributing complementary perspectives to the current understanding of these associations. Retrospective cohort studies have played a central role in identifying long-term risks associated with rosacea. One such study demonstrated an association between rosacea and cardiovascular diseases, suggesting that individuals with rosacea may have an increased risk of developing cardiovascular conditions over time [2]. In a similar longitudinal context, another cohort study reported a higher likelihood of type 2 diabetes mellitus among patients with rosacea, underscoring the relevance of metabolic screening and monitoring in this population [11].

Case–control studies have further expanded the scope of investigation by exploring specific systemic and infectious associations. A notable study revealed a significant relationship between rosacea and *Helicobacter pylori* infection, with a higher prevalence of infection observed in rosacea patients compared with matched controls, thereby supporting a potential role of gastrointestinal factors in disease expression [12]. In addition to biological associations, case–control evidence has highlighted gaps in clinical practice, showing that dermatologists may underrecognize or insufficiently address systemic comorbidities in patients with rosacea. These findings emphasize the need for improved awareness, screening, and interdisciplinary management strategies [11].

At a broader level, meta-analytical studies have provided more robust quantitative assessments of these relationships. A comprehensive meta-analysis demonstrated a bidirectional association between rosacea and inflammatory bowel disease, revealing an increased prevalence of rosacea among patients with inflammatory bowel disease and, conversely, a higher prevalence of inflammatory bowel disease among individuals with rosacea [4]. Another meta-analysis corroborated the association between rosacea and *Helicobacter pylori* infection, although it also highlighted variability in results depending on study design, population characteristics, and methodological approaches [12].

In terms of prevalence, rosacea has been associated with a wide range of systemic comorbidities. These include cardiovascular and metabolic conditions such as hypertension and dyslipidemia, as well as inflammatory and psychological disorders, including inflammatory bowel disease, anxiety, and depression [11]. Gastrointestinal comorbidities, such as celiac disease, irritable bowel syndrome, and gastroesophageal reflux disease, have also been linked to rosacea, findings that are frequently interpreted through the concept of the gut–skin axis as a unifying pathophysiological framework [3]. Additionally, an increased risk of actinic keratosis and keratinocyte carcinoma has been reported in patients with rosacea, although evidence regarding the risk of other malignancies remains inconclusive [13].

Several key epidemiological observations emerge from this body of evidence. The prevalence of rosacea is consistently higher among patients with inflammatory bowel disease, with reported odds ratios indicating a statistically significant association [4]. Patients with rosacea also exhibit elevated markers of systemic inflammation, which may contribute to the development of subclinical atherosclerosis, particularly in individuals with moderate to severe disease or ocular involvement [1]. Furthermore, the observed association between rosacea and metabolic disorders, including type 2 diabetes mellitus, reinforces the importance of considering metabolic health as an integral component of rosacea management [6].

Despite these findings, important methodological limitations must be acknowledged. Many studies are constrained by relatively small sample sizes, potential confounding variables, and variability in diagnostic criteria for both rosacea and associated comorbidities, factors that may influence the consistency and generalizability of results. The heterogeneity of study designs, populations, and outcome measures further contributes to inconsistent findings across the literature, highlighting the need for well-designed prospective studies to confirm and clarify these associations [1, 12]. Moreover, the lack of standardized diagnostic criteria and comprehensive data collection frameworks limits comparability between studies, underscoring the importance of methodological harmonization to improve the reliability and interpretability of future epidemiological research [13].

Cardiovascular associations

Rosacea has been associated with hypertension, which represents a major risk factor for cardiovascular disease. The chronic inflammatory state characteristic of rosacea is thought to contribute to endothelial dysfunction, a key early event in the development of hypertension [11]. This relationship is further supported by evidence showing elevated levels of inflammatory markers, such as C-reactive protein, in patients with rosacea. Increased C-reactive protein reflects systemic inflammation and may exacerbate vascular dysfunction, thereby amplifying the risk of hypertension in this population [15].

In addition to blood pressure alterations, dyslipidemia has been identified as another cardiovascular risk factor associated with rosacea. Dyslipidemia, defined by abnormal lipid profiles, may arise as a consequence of the inflammatory processes underlying rosacea,

which can interfere with normal lipid metabolism [11]. Systemic inflammation has been shown to influence lipid levels by promoting proatherogenic changes, including alterations in cholesterol and triglyceride fractions. In this context, the inflammatory milieu observed in rosacea may contribute to unfavorable lipid profiles, thereby increasing overall cardiovascular risk [16].

The association between rosacea and coronary artery disease further supports the concept of rosacea as a condition with systemic vascular implications. Epidemiological data indicate an increased risk of coronary artery disease among patients with rosacea, a relationship that is likely mediated by chronic inflammation and its role in atherogenesis [2]. Proinflammatory cytokines commonly elevated in rosacea have been implicated in the acceleration of atherosclerotic plaque formation, suggesting a plausible biological link between cutaneous inflammation and coronary artery disease development [1].

Evidence of subclinical atherosclerosis provides additional insight into the cardiovascular burden associated with rosacea. Increased carotid intima–media thickness, a well-established marker of early atherosclerotic changes, has been observed in patients with rosacea, indicating the presence of vascular alterations before the onset of clinically overt cardiovascular disease. This finding appears to be particularly pronounced in individuals with moderate to severe rosacea or with ocular involvement, who demonstrate greater increases in carotid intima–media thickness and, consequently, a higher risk of subclinical atherosclerosis [1].

Taken together, the coexistence of hypertension, dyslipidemia, and systemic inflammation in patients with rosacea suggests an elevation in global cardiovascular risk. This multifactorial risk profile highlights the importance of comprehensive cardiovascular assessment and screening in the management of rosacea [16]. In this regard, the monocyte-to-high-density lipoprotein ratio has been proposed as a useful biomarker for cardiovascular risk assessment in inflammatory conditions such as rosacea, as it integrates both inflammatory and metabolic components into a single parameter [17].

Metabolic associations

Obesity is characterized by the expansion and remodeling of adipose tissue, processes that are accompanied by profound immunometabolic shifts and altered cytokine signaling, ultimately leading to a state of chronic low-grade inflammation [18]. This persistent inflammatory milieu is closely linked to the development of multiple metabolic comorbidities, including insulin resistance and metabolic syndrome, and may progressively extend its effects to involve several organ systems [18, 19].

Within this context, metabolic syndrome represents a constellation of metabolic disturbances, including insulin resistance, dyslipidemia, and hypertension, which are frequently associated with obesity [20]. Insulin resistance, a central component of metabolic syndrome, is amplified by obesity-related inflammation, with macrophages playing a pivotal role in sustaining inflammatory signaling within adipose tissue and peripheral organs [21]. The clinical relevance of this syndrome lies in its strong association with an increased risk of type 2 diabetes mellitus and cardiovascular diseases, underscoring the importance of early identification and comprehensive management of these metabolic abnormalities [20].

Dietary factors have emerged as important modulators of metabolic inflammation. Nutritional interventions, particularly adherence to dietary patterns such as the Mediterranean diet, have been shown to reduce systemic inflammatory markers and improve insulin sensitivity, thereby exerting beneficial effects on metabolic health. In addition, pomegranate extract has demonstrated the ability to enhance energy expenditure and attenuate inflammatory responses, suggesting a potential complementary

role in mitigating obesity-related metabolic stress [22].

At the molecular level, obesity and metabolic syndrome are associated with dysregulation of key metabolic pathways, particularly those involved in lipid metabolism. Alterations in specific metabolites, including sphingomyelins, have been identified in individuals with these conditions, and their differential expression has been shown to correlate with clinical parameters such as glucose and lipid concentrations. These findings highlight the close interplay between metabolic dysfunction and inflammation in the pathogenesis of obesity-related disorders [22].

Gastrointestinal associations

A growing body of evidence supports a close relationship between rosacea and inflammatory bowel disease. Systematic reviews and meta-analyses have demonstrated a bidirectional association between these conditions, showing a higher prevalence of rosacea among patients with inflammatory bowel disease and, conversely, an increased prevalence of inflammatory bowel disease in individuals with rosacea. In this context, the reported odds ratio of 1.86 for rosacea in patients with inflammatory bowel disease indicates a statistically significant association, reinforcing the concept of shared pathogenic mechanisms [4]. Further insight has been provided by Mendelian randomization studies, which suggest a potential causal relationship whereby inflammatory bowel disease, particularly Crohn's disease and ulcerative colitis, increases the risk of developing rosacea. These studies have highlighted the possible involvement of the interleukin-23 signaling pathway, pointing toward common immunological pathways and suggesting potential therapeutic targets relevant to both conditions [21, 23].

Within this gastrointestinal–cutaneous interplay, small intestinal bacterial overgrowth has emerged as a relevant factor. Small intestinal bacterial overgrowth is highly prevalent among patients with inflammatory bowel disease, with pooled analyses indicating a prevalence of approximately 31%, significantly higher than that observed in healthy control populations. This condition appears to be more common in Crohn's disease than in ulcerative colitis, reflecting differences in disease distribution and intestinal involvement [24]. The link between small intestinal bacterial overgrowth and rosacea is supported by clinical observations showing that treatments aimed at eradicating bacterial overgrowth, particularly antibiotic therapies, can lead to improvement in rosacea symptoms. These findings suggest that small intestinal bacterial overgrowth may exacerbate rosacea through mechanisms involving gut dysbiosis and the amplification of systemic inflammatory responses [2, 25].

In addition to inflammatory bowel disease and small intestinal bacterial overgrowth, functional gastrointestinal disorders have also been associated with rosacea. Conditions such as irritable bowel syndrome have been linked to rosacea, and the underlying alterations in the gut microbiome characteristic of these disorders may contribute to systemic inflammation with downstream effects on skin homeostasis [25]. Supporting this association, elevated levels of fecal calprotectin, a biomarker of gastrointestinal inflammation, have been detected in patients with rosacea. This finding provides further evidence of a connection between intestinal inflammatory activity and the severity or presence of rosacea manifestations [26].

These observations are commonly interpreted within the framework of the gut–skin axis, which proposes that intestinal microbiota can influence skin health through immune modulation and systemic inflammatory pathways. Alterations in gut microbiota composition, including reduced microbial diversity and shifts in specific bacterial taxa, have been implicated in the pathophysiology of rosacea, reinforcing the concept of a bidirectional communication between the gut and the skin. In line with this

theory, therapeutic strategies aimed at modulating the gut microbiome, such as the use of probiotics, prebiotics, and targeted dietary interventions, are increasingly being explored as potential adjunctive treatments for rosacea, highlighting the clinical relevance of the gut–skin axis in disease management [21, 27].

Autoimmune associations

Autoimmune thyroid diseases, including Hashimoto's thyroiditis and Graves' disease, have been associated with an increased risk of developing other autoimmune conditions, among them rosacea. These thyroid-specific autoimmune disorders are characterized by immune dysregulation, which may contribute to the inflammatory processes observed in rosacea. The shared involvement of altered immune tolerance and sustained inflammatory signaling suggests that common pathogenic mechanisms may underlie the coexistence of autoimmune thyroid disease and rosacea [32, 33].

In addition to thyroid disorders, rosacea has been linked to a broader spectrum of immune-mediated systemic diseases, including inflammatory bowel disease and rheumatoid arthritis. These conditions share overlapping immunological pathways, particularly those involving dysregulated cytokine signaling and impaired T cell tolerance. Such shared mechanisms may not only facilitate the coexistence of these diseases but also contribute to the exacerbation of rosacea symptoms in affected individuals [3, 32].

At the mechanistic level, the pathophysiology of rosacea is characterized by overactivation of the immune system, involving disturbances in both innate and adaptive immune responses. This dysregulation includes excessive production of proinflammatory cytokines and impaired function of regulatory T cells, features that are also central to the development and progression of autoimmune diseases. The convergence of these immune abnormalities supports the concept of rosacea as part of a broader spectrum of immune-mediated inflammatory conditions. Furthermore, genetic susceptibility and environmental influences, including alterations in the microbiome, play a contributory role in sustaining immune dysregulation in rosacea and other autoimmune disorders, reinforcing the interconnected nature of these conditions [34].

Conclusion

Rosacea is a heterogeneous chronic inflammatory dermatosis whose phenotype-based classification better reflects the complexity of its clinical presentation and underlying pathophysiological mechanisms, including immune dysregulation, neurovascular alterations, and barrier dysfunction. This multifactorial nature supports the concept of rosacea as a systemic inflammatory condition rather than an isolated cutaneous disease.

Accumulating epidemiological evidence demonstrates consistent associations between rosacea and multiple systemic comorbidities, particularly cardiovascular, metabolic, gastrointestinal, and autoimmune diseases. Chronic low-grade systemic inflammation appears to represent a central unifying mechanism linking rosacea to hypertension, dyslipidemia, atherosclerosis, metabolic syndrome, inflammatory bowel disease, and autoimmune disorders.

The recognition of these systemic associations has important clinical implications, highlighting the need for a holistic and multidisciplinary approach to rosacea management. Comprehensive screening for cardiometabolic, gastrointestinal, and immune-mediated comorbidities, along with improved methodological standardization in future studies, is essential to refine risk stratification and optimize long-term patient outcomes.

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