FURGALSKA-KUDŁA, Julia, SUŁAWA, Adrian, TARGOŃSKI, Oskar, TARGOŃSKA, Marta, FEDOROWICZ, Sebastian, BASIAK, Aneta, PTASIŃSKI, Aleksander, NIEKURZAK, Rafał, and BUCZEK, Agnieszka. Association Between Rosacea and Risk Factors – A Literature Review. Quality in Sport. 2024;35:56291. eISSN 2450-3118.
https://dx.doi.org/10.12775/QS.2024.35.56291
https://apcz.umk.pl/QS/article/view/56291

The journal has been 20 points in the Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 19.11.2024. Revised: 26.11.2024. Accepted: 18.12.2024. Published: 18.12.2024.

Association Between Rosacea and Risk Factors – A Literature Review

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ABSTRACT

Introduction and purpose: Rosacea is a common chronic inflammatory disease with four clinical subtypes based on the predominant signs and symptoms. The majority of patients present skin problems like reddening, papules or pustules, swelling of the face and nose, and eye symptoms like dryness, tearing, and redness. Anxiety and depression associated with rosacea deeply affect the quality of patients' lives. Yet, the pathogenesis of rosacea remains poorly understood, with suggestions of involvement from various complex factors like immune dysregulation, genetic factors, neurovascular dysregulation, micro-organisms, and environmental factors as promoting features of rosacea.

Aim of the study: The purpose of this article is to investigate the association between factors like alcohol intake, Helicobacter pylori infection, and cardiovascular diseases and the risk of developing rosacea.

Material and methods: An analysis of papers available in PubMed, Google Scholar, and Springer Link was performed.

Conclusion: The knowledge presented in this review suggests the existence of links between rosacea and various risk factors like alcohol intake, infection of H.pylori, and Cardiovascular diseases. Considering the clinical and pathological differences among rosacea subtypes, it is essential to explore the role of alcohol in each subtype separately. While rosacea may not be directly associated with IHD, stroke, or diabetes, it does show correlations with hypertension and dyslipidemia. Rosacea is significantly associated with a higher prevalence of HP infection, but high-quality prospective studies are needed to ascertain if Helicobacter Pylori is a risk factor for rosacea. Further investigations are warranted to validate these findings and explore underlying mechanisms. The predisposing factors revealed in this study could help us gain insights into rosacea pathophysiology and develop interventions especially targeting modifiable risk factors.

Keywords: rosacea, alcohol, cardiovascular disease, smoking, heliobacter pylori

ROSACEA

Rosacea is a prevalent chronic relapsing immune-mediated inflammatory cutaneous disorder, primarily affecting the central face, characterized by flushing, erythema, papules, pustules, and telangiectasia with different combinations and degrees of clinical symptoms presented in every individual. (1) Eye symptoms like dryness, tearing, redness, foreign-body sensation, and blurred vision are also observed. Anxiety and depression associated with rosacea can affect the quality of patients' lives influencing physical, emotional, and psychological aspects. The visible symptoms of rosacea can make social interactions challenging. In severe cases, the physical discomfort and emotional stress caused by rosacea can affect work performance. Overall, rosacea is more than just a skin condition; it can deeply affect multiple aspects of an individual's life, underscoring the importance of effective support and expanding knowledge on the subject.

There are four clinical subtypes based on the predominant signs and symptoms: papulopustular, erythematotelangiectatic, phymatous, and ocular.

Papulopustular Rosacea - It manifests as red eruptions resembling acne and is often mistaken for common acne. Treatment may include oral antibiotics (e.g., doxycycline) and topical preparations containing metronidazole, azelaic acid, as well as newer agents like ivermectin. (2,3)

Erythematotelangiectatic Rosacea (ETR) - This type is characterized by redness (erythema) and visible blood vessels (telangiectasia). It is often accompanied by burning and skin sensitivity. Treatment includes avoiding triggers, using creams based on metronidazole or azelaic acid, and laser therapy, which can help reduce erythema and telangiectasia (2,4)

Phymatous Rosacea - Characterized by the thickening of the skin and the formation of nodular changes, most commonly on the nose (rhinophyma). Treatment includes laser therapies, surgical procedures, and sometimes oral isotretinoin to reduce symptoms and improve skin appearance (2,3)

Ocular Rosacea - Affects the eyes, causing redness, irritation, dryness, and a foreign body sensation in the eye. Treatment may include the use of moisturizing eye drops, oral antibiotics, and eyelid hygiene to alleviate symptoms (3,4)

Rosacea typically manifests in individuals aged 20 to 50 years. It is notably prevalent among those with lighter skin tones, with estimates ranging from 2% to 22%. (5) Interestingly, it is also commonly observed in individuals with darker complexions, with a prevalence reported as high as 10%. (6)

ALCOHOL

Ethanol is a diminutive compound that dissolves readily in both fats and aqueous solutions. Consequently, the consumption of alcohol impacts virtually all bodily tissues, and the duration required for recuperation from resultant tissue harm varies based on the quantity and period of alcohol ingestion. (7)

Although the influence of alcohol intake on the skin is comparatively insignificant when contrasted with its effects on the liver, gastrointestinal tract, and nervous system (8)
it still warrants attention, considering the skin's status as the largest organ in the human body. Ethanol consumed orally undergoes oxidation to acetaldehyde by alcohol dehydrogenase and is eventually transformed into acetic acid. Alcohol and its byproducts have the potential to instigate and exacerbate specific skin conditions. (9)
The impact of alcohol on skin conditions potentially includes the following mechanisms: The skin-intestinal axis: Alcohol consumption can affect the intestinal microbiota, and numerous individuals with skin ailments, such as rosacea, concurrently experience gastrointestinal disorders, like small intestine bacterial overgrowth and Helicobacter pylori infection. (10) Induction of skin inflammation: alcohol encourages the generation of inflammatory cytokines in keratinocytes and fosters the multiplication of lymphocytes, intensifying inflammatory skin conditions like psoriasis. (11)
Encouragement of vascular permeability: Alcohol heightens microvascular permeability, which could directly lead to skin flushing post-consumption. Elevated vascular permeability also prompts tissue inflammation in the skin; and Harm from metabolites: Throughout metabolism, alcohol yields acetaldehyde and produces reactive oxygen species, impacting DNA's typical biological functions via oxidative stress and epigenetic influences. (7)
This might lead to harm to the immune system or even carcinogenesis. In this chapter, we will examine recent advancements in studies exploring the correlation between alcohol intake and rosacea
In recent years, significant progress has been made in understanding the relation
ship between alcohol intake and rosacea.

The relationship between alcohol consumption and the aggravation of rosacea remains a topic of debate. Epidemiological studies conducted separately in the United States and the United Kingdom have suggested that alcohol intake exacerbates rosacea, with a significant association between increased alcohol consumption and a higher risk of developing the condition (12,13). The mechanisms by which alcohol might worsen rosacea include alcohol-induced capillary dilation, heightened inflammatory responses, and alterations in the gut microbiome(14,15). Ethanol from alcoholic beverages can be metabolized by gut microbiota, leading to higher levels of acetaldehyde, a toxic byproduct that disrupts microbiota balance. Research has shown that patients with rosacea have a notably higher incidence of small intestinal bacterial

overgrowth compared to controls. (16) Conversely, some case-control studies have found no significant correlation between alcohol consumption and rosacea. (17) Considering the clinical and pathological differences among rosacea subtypes, it is essential to explore the role of alcohol in each subtype separately. For example, a study by Second et al. found that alcohol consumption was specifically linked to the phymatous subtype. (18) Further research is necessary to clarify the precise mechanisms involved.

CARDIOVASCULAR DISEASES

Cardiovascular diseases (CVDs) encompass a range of disorders affecting the heart and blood vessels. They are the leading cause of morbidity and mortality worldwide, significantly impacting both individual health and healthcare systems.

Types of Cardiovascular Diseases

1. Coronary Artery Disease (CAD): This is the most common type of CVD, caused by the build-up of plaque in the coronary arteries, which can lead to heart attacks. CAD is characterized by angina (chest pain), shortness of breath, and other symptoms due to reduced blood flow to the heart muscle.
2. Hypertension (High Blood Pressure): Persistent high blood pressure can damage blood vessels and the heart, increasing the risk of heart attacks, strokes, and other problems.
3. Heart Failure: This condition occurs when the heart cannot pump blood efficiently, leading to symptoms such as fatigue, shortness of breath, and fluid retention.
4. Arrhythmias: These are irregular heartbeats, which can be harmless or life-threatening. Common types include atrial fibrillation and ventricular tachycardia.
5. Stroke: A stroke happens when the blood supply to part of the brain is interrupted or reduced, preventing brain tissue from getting oxygen and nutrients. Strokes can cause lasting brain damage, long-term disability, or death.
6. Peripheral Artery Disease (PAD): This occurs when plaque builds up in the arteries that supply blood to the limbs, most commonly the legs, leading to pain and mobility issues.

Effective management and prevention strategies for CVDs involve lifestyle modifications, medical treatments, and sometimes surgical interventions. Key preventive measures include maintaining a healthy diet, regular physical activity, avoiding tobacco use, and managing stress. Medications such as antihypertensives, statins, and antiplatelet agents are commonly used to

manage risk factors and symptoms. In severe cases, surgical procedures like angioplasty, stent placement, or bypass surgery may be necessary.

Several factors increase the risk of developing CVDs, including lifestyle (poor diet, physical inactivity, and smoking are significant contributors), medical conditions (hypertension, high cholesterol, diabetes, and obesity), genetic predisposition (family history of CVD), age and gender (the risk increases with age, and men are generally at higher risk earlier in life compared to women). Some of them such as smoking, alcohol consumption, and diet, along with chronic inflammation activated by immune dysregulation, are shared in the pathogenesis of both rosacea and CMD, hence exploring their relationship can be beneficial for acquiring knowledge

The systematic review and meta-analysis conducted by Qi Chen et al. (19) aimed to investigate the association between rosacea and cardiometabolic disease (CMD). They meticulously followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines, conducting a thorough search of various electronic databases. Thirteen studies meeting their inclusion criteria were analyzed, encompassing a total of 50,442 patients with rosacea and 1,525,864 control individuals.

The results revealed several key findings:

1. Ischemic Heart Disease (IHD) and Stroke: Rosacea did not show a significant association with IHD or stroke based on the analysis of multiple studies, indicating that rosacea may not be a risk factor for these conditions.
2. Diabetes: While the prevalence of diabetes among individuals with rosacea did not show a significant difference compared to controls, patients with rosacea demonstrated higher fasting blood glucose (FBG) levels. This suggests a potential link between rosacea and elevated FBG levels, indicating a predisposition to diabetes.
3. Hypertension: Patients with rosacea were found to have a significantly higher risk of hypertension compared to controls. This association may be attributed to neurovascular dysregulation, potentially involving the sympathetic nervous system and vascular changes.
4. Dyslipidemia: Rosacea was associated with dyslipidemia, characterized by elevated levels of total cholesterol (TC), low-density lipoprotein (LDL), and triglycerides (TG). This finding suggests a possible role of chronic inflammation in rosacea, contributing to lipid metabolism abnormalities.

The study also discussed potential mechanisms underlying these associations, such as neurovascular dysfunction in hypertension and chronic inflammation in dyslipidemia. Additionally, it highlighted the need for further research to elucidate the underlying mechanisms and interactions between rosacea and CMD.

However, the study had some limitations, including inherent shortcomings of observational studies, heterogeneity between studies, and potential bias in diagnostic accuracy. Despite these limitations, the findings suggest that screening for CMD indicators among patients with rosacea could aid in early diagnosis and appropriate treatment.

In conclusion, while rosacea may not be directly associated with IHD, stroke, or diabetes, it does show correlations with hypertension and dyslipidemia. Further investigations are warranted to validate these findings and explore underlying mechanisms.

HELICOBACTER PYLORI

Helicobacter pylori (H. pylori) - a Gram-negative, spiral-shaped bacterium that colonizes the gastric mucosa is a significant pathogen responsible for chronic gastritis, peptic ulcer disease, and is strongly associated with gastric cancer and mucosa-associated lymphoid tissue (MALT) lymphoma. (20) It is one of the most common bacterial infections worldwide.

The bacterium's ability to survive in the acidic environment of the stomach is facilitated by its production of urease, which neutralizes stomach acid. It adheres to the gastric epithelial cells using adhesins, causing inflammation and damage to the mucosal lining. (21)

Besides triggering gastric mucosal inflammation, H. pylori infection can interfere with physiological processes such as inflammatory responses, blood vessel dilation, and immune regulation, which have also been observed in skin conditions like rosacea. (22, 23)

While over 70% of those infected with H. pylori remain asymptomatic, some individuals develop symptoms ranging from mild gastritis to severe peptic ulcer disease. (24)

H. pylori infection can be diagnosed using various methods, including non-invasive tests and invasive methods.

The standard treatment for H. pylori involves a combination of antibiotics (commonly clarithromycin, amoxicillin, or metronidazole) and a proton pump inhibitor (PPI) to reduce stomach acid and promote healing. (25)
Preventive measures focus on improving hygiene, access to clean water, and proper food handling practices to reduce transmission. (26)

Ying Gao et al. conducted a systematic review and meta-analysis aimed to elucidate the relationship between rosacea and HP infection. 27 The analysis included 25 datasets from 23 studies, with 51,054 rosacea patients and 4,709,074 controls. The results showed a significantly higher prevalence of HP infection in rosacea patients than controls. Subgroup analysis found increased HP infection prevalence in rosacea studies using one or more tests for HP infection. However, this association was not seen in population-based studies using prescription records for HP eradication drugs. The conclusion is that rosacea is significantly associated with a higher prevalence of HP infection, but high-quality prospective studies are needed to ascertain if Helicobacter Pylori is a risk factor for rosacea.
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The authors have read and agreed with the published version of the manuscript.

Funding Statement: The Study Did Not Receive Special Funding.

Institutional Review Board Statement: Not Applicable.

Informed Consent Statement: Not Applicable.

Data Availability Statement: Not Applicable.

Conflict Of Interest: The authors declare no conflict of interest.

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