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Research Article

Rosacea and Chronic Systemic Diseases: Case-Control Study in Saudi Arabia

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Abstract

Objective: We sought to examine the association between rosacea and systemic comorbidities in patients attending the dermatology clinic at King Fahd Hospital of the University in Al-Khobar during a 14-month period (February 2016 to May 2017).

Methods: This was a prospective single-center case-control study conducted in the dermatology department of King Fahd Hospital of the University (KFHU) during a 14-month period. Self-administered questionnaires were distributed to rosacea patients and controls. The questionnaires examined demographic data, current comorbidities, family histories, and lifestyles. Study limitations were report and recall biases, which are major limitations of self-reported questionnaires.

Results: A total of 76 patients (38 cases and 38 controls) of Arabic origin were recruited in the study. The mean age was 33.2 years for the cases and 27.4 years for the controls. Positive p values were seen in family histories of rosacea, photosensitivity, and food allergies. Hypertension, cardiovascular, gastrointestinal, respiratory, genitourinary, and dermatological diseases and dyslipidemia were reported as associated comorbidities in rosacea patients.

Limitations: This was a case-control study with moderate sample size and associated medical conditions were self-reported confirmed either by medications use or medical records.

Conclusion: Rosacea is associated with numerous systemic comorbid diseases in our patients attending the dermatology clinic at King Fahd Hospital of the University.

Keywords: *Rosacea; Comorbidities; Inflammation; Papulopustule; Photosensitivity*

Abbreviations

NMSC: Non-Melanoma Skin Cancer; PKKS: Plasma Kallikrein-Kinin System; IBD: Inflammatory Bowel Diseases

Introduction

Rosacea is a chronic inflammatory skin condition that affect the central part of the face. This condition is divided into four clinical subtypes: (1) erythematotelangiectatic; (2) papulopustular; (3) phymatous; and (4) ocular [1]. The exact pathophysiology of rosacea remains unclear. However, genetic factors, dysregulation of innate immunity, microorganisms such as *Demodex folliculorum* and *Staphylococcus epidermidis*, ultraviolet light, and neurogenic dysregulation all seem to be involved in its pathology [2]. Rosacea has recently been found to be associated with multiple comorbidities, including cardiovascular diseases, gastrointestinal disorders, migraines, dementia, Parkinsonism, autoimmune conditions, depression, and malignancies [3]. This is the first study done in our region that was initiated to explore the association between rosacea and systemic comorbidities in Saudi patients attending the dermatology clinic at King Fahd Hospital of the University in Al-Khobar during a 14-month period (February 2016 to May 2017).

Methods

This is a prospective single-center case-control study conducted at the dermatology department of King Fahd Hospital of the University (KFHU) over a 14-month period (February 2016 to May 2017). The study was initiated following approval by the Institutional Review Board (IRB-2016-01-036). All new patients diagnosed with rosacea during the 14-month period at the dermatology clinic of King Fahd Hospital of the University were included in the study. Patients with rosacea were matched by age (within a range of three years) and sex (1:1) to rosacea-free control. With the supervision of the investigating team a self-administered questionnaire adapted from a previously validated questionnaire [3] was distributed to rosacea patients and controls. The study objective was explained to each participant, and an informed consent was obtained. Each participant remained anonymous and data were coded to ensure confidentiality. The questionnaire explored demographic data, current comorbidities, family histories, and lifestyles. Medical conditions were confirmed either by medications use or medical records. The medical conditions included cardiovascular, gastrointestinal, respiratory, metabolic, urogenital, dermatological, and rheumatological diseases and allergies. Cardiovascular diseases included coronary and peripheral artery diseases, cerebrovascular diseases and hypertension. Gastrointestinal diseases included *Helicobacter pylori*, celiac and inflammatory diseases, and irritable bowel syndrome. Respiratory diseases included asthma, chronic obstructive pulmonary disease, chronic bronchitis, and chronic rhinitis. Metabolic disease included diabetes mellitus, dyslipidemia and obesity (BMI > 30 kg). Urogenital disease included chronic or recurrent urinary tract infections and nephritis. Dermatological diseases included atopic dermatitis, contact dermatitis, acne vulgaris, psoriasis and any other dermatological condition not listed in the questionnaire. Inclusion criteria included all established rosacea diagnoses made by a dermatology consultant according to International Classification of Disease (ICD-10) and all patients > 12 years. Exclusion criteria included children < 12 years old and pregnant women. The data was rechecked by the investigator, and no missing data were reported. Coding of the data for all the variables and statistical analysis were done using SPSS (Statistical Package for the Social Sciences V.21). Descriptive analysis of the data was done to determine the frequency of each variable in both cases and controls separately. The distribution of rosacea in continuous variables was tested using the t- and chi-squared tests for categorical variables. Study limitations were recall and report biases, which are major limitations of self-reported questionnaires.

Results

A total of 76 patients (38 cases and 38 controls) of Arabic origin were recruited in the study. The mean age was 33.2 years for the cases and 27.4 years for the controls. The majority of the cases and controls were females 79% (30); 21% (8) were males in both groups. Positive p values were seen in family histories of rosacea, photosensitivity and food allergy. Rosacea duration varied between patients with 31.6% (12) cases diagnosed within one year and 68.4% (17) cases diagnosed for more than two years. Eleven (29.8%) of rosacea patients had hypertension compared to one (2.6%) of the controls. Four (10.5%) of rosacea patients had cardiovascular diseases, while there was none in the control group. Fifteen (39.5%) of rosacea patients had gastrointestinal diseases compared to 5 (13.2%) of the control group. Dyslipidemia was found in 10 (26.3%) of rosacea patients compared to 2 (5.3%) of the controls. Four (10.5%) rosacea patients had dia-

betes mellitus compared to 4 (10.5%) of the controls. Obesity was not reported in both groups. Thirteen (34.2%) rosacea patients had respiratory diseases compared to 6 (15.8%) in the control group. Five (13.2%) rosacea patients had genitourinary diseases, while there were none in the control group. Two (5.2%) rosacea patients had rheumatological diseases compared to 1 (2.6%) of the controls, and 13 (34.2%) of rosacea patients had joint pain compared to 7 (18.4%) in the control group. Thirteen (34.2%) rosacea cases had dermatological diseases including atopic dermatitis, contact dermatitis, acne vulgaris and psoriasis compared to 4 (36.8%) of the controls. Eleven (29.8%) rosacea cases had chronic headaches compared to 7 (18.4%) subjects in the control group (Table 1).

Comorbid disease	Cases= n = 38 No. (%)	Control n = 38 No. (%)
Hypertension	11 (29.8%)	1 (2.6%)
Diabetes mellitus	4 (10.5%)	4 (10.5%)
Dyslipidemia	10 (26.3%)	2 (5.3%)
Cardiovascular disease	4 (10.5%)	0
Respiratory disease	13 (34.2%)	6 (15.8%)
Gastrointestinal	15 (39.5%)	5 (13.2%)
Genitourinary	5 (13.2%)	0
Rheumatology	2 (5.2%)	1 (2.6%)
Joint pain	13 (34.2%)	7 (18.4%)
Dermatological diseases	13 (34.2%)	4 (36.8%)
Headache	11 (29.8%)	7 (18.4%)

Table 1: *Distribution of comorbidities in rosacea cases and controls (n = 76).*

Discussion

Rosacea is a chronic, inflammatory skin condition that affects the face. The prevalence of rosacea in many studies varies from 0.09% to 22.41% in the general population and 5.46% to 23.14% in dermatology patients. The highest prevalence has been found among adults of 30 years of Northern European heritage with fair skin [4-6]. Unfortunately, in our area the incidence is unknown. However, in our rosacea study patients we found a mean age of 33.2 years with female predominance. Family histories of rosacea, photosensitivity, and food allergies were significant findings in our patients.

Many recent studies have uncovered associations between rosacea and an increase in the risk for a variety of systemic disorders, many with potentially serious outcomes [7-22]. These comorbidities include a range of systemic diseases:

1. **Cardiovascular diseases:** Different studies have shown an increase in the incidence of hypertension, coronary artery disease, myocardial infarction, ischemic and hemorrhagic strokes and cardiovascular deaths [3,7-9,18,19]. In our patients, there was higher percentage of hypertension and ischemic heart disease compared to the controls.

2. **Gastrointestinal diseases:** Studies have found a higher prevalence of gastrointestinal disorders in rosacea patients, including celiac and Crohn's diseases, irritable bowel syndrome, and ulcerative colitis in addition to a significantly increased risk for death due to gastrointestinal diseases [12,13]. Our patients reported a higher percentage of gastrointestinal disorders, including Crohn's disease, irritable bowel syndrome, and ulcerative colitis.

3. **Neurological and autoimmune diseases:** In a large retrospective study in Denmark, rosacea patients were found to be at significantly greater risk of Parkinson's disease [15,16], while other studies found a slightly elevated risk for dementia and Alzheimer's disease [16], multiple sclerosis, and migraines [17,20]. However, in our study chronic headache was the only reported condition.

4. **Cancer:** In Denmark, a population-based cohort study concluded that rosacea led to an increase in the risk of non-melanoma skin cancer (NMSC) and breast and hepatic cancers [23]. These findings are consistent with another more recent study conducted in the United States in which it was found that a personal history of rosacea was associated with an increased risk of thyroid cancer and non-melanoma skin carcinoma [21]. Fortunately, no cancers were reported in our patients.

5. **Metabolic/endocrine disorders:** In a Turkish case-control study, high cholesterol, low density lipoprotein, and C-reactive protein levels were more common in patients with rosacea [8]. In our study, only dyslipidemia was reported at a higher percentage among rosacea patients.

Respiratory diseases were believed to have no significant association with rosacea [24], but respiratory problems in addition to chronic headaches and joint pain were reported by our rosacea patients.

Although all studies have established associations between rosacea and chronic systemic diseases, the pathophysiological connections are complex and remain unclear. Rosacea is thought to be due to an inflammatory process that results from the complex interplay of an aberrant immune system, neurovascular changes, ultraviolet radiation, epidermal barrier dysfunction, and abnormal skin flora. The innate and adaptive immune systems are activated in rosacea with coordinated activity of multiple cell types, including keratinocytes, macrophages, mast cells, fibroblasts, neutrophils, TH1 and 17 and B cells, and vascular endothelium [25-27]. These cells produce primary effector molecules, such as cathelicidin-related antimicrobial peptides, reactive oxygen species (ROS), matrix metalloproteinases and cytokines, including interleukin (IL)-1b and -17, tumor necrosis factor, and interferon-gamma, all of which drive rosacea inflammation [25-29] and are similarly involved in the comorbid conditions. The potential explanation for the link between NMSC and rosacea may be that the skin barrier dysfunction in rosacea patients results in reduced endogenous transurocanic acid, leading to an increase in ultraviolet radiation-induced DNA damage and phototumorigenesis [30].

Limitation of the Study

Limitations of case-control studies should be taken into account. These limitations include recall and response biases in self-reported checklists and moderate sample sizes that impact researchers' ability to analyze low prevalence conditions. Needless to say, rosacea has been shown to have high predictive value for the development of serious hidden systemic disorders, and its presence might provide a valuable early warning for these disorders. Additional in-depth clinical, genetic, biomarker, and microbiological studies are needed to delineate the temporal relationship between rosacea and comorbidity onsets to achieve a deeper understanding of rosacea and its non-cutaneous implications. Although rosacea is not a life-threatening condition, the awareness of possible systemic comorbidity associations and early identification may prove to be life-extending.

Conclusion

In conclusion, this is the first study done in Saudi Arabia that has explored rosacea and its associated comorbidities, which in turn supported other studies done previously in different parts of the world confirming the link between rosacea and systemic comorbidities. Physicians should be aware of these associations to provide comprehensive care to patients with rosacea, especially to those presenting with more severe disease. Future multicenter study with larger sample size is highly recommended.

Bibliography

1. Wilkin J., *et al*. "Standard classification of rosacea: report of the National Rosacea Society Expert Committee on the Classification and Staging of Rosacea". *Journal of the American Academy of Dermatology* 46.4 (2002): 584-587.

2. Two AM., *et al*. "Rosacea: part I. Introduction, categorization, histology, pathogenesis, and risk factors". *Journal of the American Academy of Dermatology* 72.5 (2015): 749-758.

3. Rainer B., *et al*. "Rosacea is associated with chronic systemic diseases in a skin severity dependent manner: Results of a case-control study". *Journal of the American Academy of Dermatology* 73.4 (2015): 604-608.

4. Gether L., *et al*. "Incidence and prevalence of rosacea: a systematic review and meta-analysis". *British Journal of Dermatology* 179.2 (2018): 282-289.

5. Parisi R and Yiu ZZ. "The worldwide epidemiology of rosacea". *British Journal of Dermatology* 179.2 (2018): 239.

6. Spoendlin J., *et al*. "A study on the epidemiology of rosacea in the U.K". *British Journal of Dermatology* 167.3 (2012): 598-605.

7. Hua TC., *et al*. "Cardiovascular comorbidities in patients with rosacea: a nationwide case-control study from Taiwan". *Journal of the American Academy of Dermatology* 73.2 (2015): 249-254.

8. Duman N., *et al*. "Rosacea and cardiovascular risk factors: a case control study". *Journal of the European Academy of Dermatology and Venereology* 28.9 (2014): 1165-1169.

9. Egeberg A., *et al*. "Assessment of the risk of cardiovascular disease in patients with rosacea". *Journal of the American Academy of Dermatology* 75.2 (2016): 336-339.

10. Egeberg A., *et al*. "Rosacea and gastrointestinal disorders: a population-based cohort study". *British Journal of Dermatology* 176.1 (2017): 100-106.

11. Egeberg A., *et al*. "Nationwide assessment of cause-specific mortality in patients with rosacea: a cohort study in Denmark". *American Journal of Clinical Dermatology* 17.6 (2016): 673-679.

12. Spoendlin J., *et al*. "Rosacea in patients with ulcerative colitis and Crohn's disease: a population-based case control study". *Inflammatory Bowel Disease* 22.3 (2015): 680-687.

13. Kim M., *et al*. "Inflammatory bowel disease is associated with an increased risk of inflammatory skin diseases: a population-based cross-sectional study". *Journal of the American Academy of Dermatology* 76.1 (2017): 40-48.

14. Egeberg A., *et al*. "Exploring the association between rosacea and Parkinson disease: a Danish nationwide cohort study". *JAMA Neurology* 73.5 (2016): 529-534.

15. Lyon S., *et al*. "LB766 Parkinson's disease association with rosacea: a large, single center, retrospective study". *Journal of Investigative Dermatology* 136.8 (2016): B3.

16. Egeberg MD., *et al*. "Patients with rosacea have increased risk of dementia". *Annals of Neurology* 79.6 (2016): 921-928.

17. Egeberg A., *et al*. "Clustering of autoimmune diseases in patients with rosacea". *Journal of the American Academy of Dermatology* 74.4 (2016): 667-672.

18. Akin Belli A., *et al*. "The relationship between rosacea and insulin resistance and metabolic syndrome". *European Journal of Dermatology* 26.3 (2016): 260-264.

19. Aldrich N., *et al*. "Genetic vs environmental factors that correlate with rosacea: a cohort-based survey of twins". *JAMA Dermatology* 151.11 (2015): 1213-1219.

20. Egeberg A., *et al*. "Prevalence and risk of migraine in patients with rosacea: a population-based cohort study". *Journal of the American Academy of Dermatology* 76.3 (2017): 454-458.

21. Li WQ., *et al*. "Personal history of rosacea and risk of incident cancer among women in the US". *British Journal of Cancer* 113.3 (2015): 520-523.

22. Egeberg A., *et al*. "Association of rosacea with risk for glioma in a Danish nationwide cohort study". *JAMA Dermatology* 152.5 (2016): 541-545.

23. Egeberg A., *et al*. "Rosacea and risk of cancer in Denmark". *Cancer Epidemiology* 47 (2017): 76-80.

24. Aksoy B., *et al*. "Systemic comorbidities associated with rosacea: a multicentric retrospective observational study". *International Journal of Dermatology* 58.6 (2018): 722-728.

25. Schwab VD., *et al*. "Neurovascular and neuroimmune aspects in the pathophysiology of rosacea". *Journal of Investigative Dermatology Symposium Proceedings* 15.1 (2011): 53-62.

26. Steinhoff M., *et al*. "Clinical, cellular, and molecular aspects in the pathophysiology of rosacea". *Journal of Investigative Dermatology Symposium Proceedings* 15.1 (2011): 2-11.

27. Buhl T., *et al*. "Molecular and morphological characterization of inflammatory infiltrate in rosacea reveals activation of Th1/Th17 pathways". *Journal of Investigative Dermatology* 135.9 (2015): 2198-2208.

28. Yamasaki K., *et al*. "Increased serine protease activity and cathelicidin promotes skin inflammation in rosacea". *Nature Medicine* 13.8 (2007): 975-980.

29. Yamasaki K., *et al*. "TLR2 expression is increased in rosacea and stimulates enhanced serine protease production by keratinocytes". *Journal of Investigative Dermatology* 131.3 (2011): 688-697.

30. Barresi C., *et al*. "Increased sensitivity of histidinemic mice to UVB radiation suggests a crucial role of endogenous urocanic acid in photoprotection". *Journal of Investigative Dermatology* 131.1 (2011): 188-194.

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