Received: 18 June 2020 | Revised: 24 June 2020 | Accepted: 26 June 2020

DOI: 10.1111/jocd.13587

REVIEW ARTICLE

JCD Journal of Cosmetic Dermatology WILEY

Rosacea and the cardiovascular system

Tamara Searle BSc[1] | **Firas Al-Niaimi MSc MRCP(Derm) EBDV**[2] | **Faisal R. Ali MA PhD MRCS FRCP**[3,4]

[1]University of Birmingham Medical School, Birmingham, UK

[2]Department of Dermatology, Aalborg University Hospital, Aalborg, Denmark

[3]Vernova Healthcare CIC, Macclesfield, UK

[4]Dermatological Surgery & Laser Unit, Guy's Hospital Cancer Centre, St John's Institute of Dermatology, Guy's and St Thomas' NHS Foundation Trust, London, UK

Correspondence
Faisal R. Ali, Dermatological Surgery & Laser Unit, St John's Institute of Dermatology, Guy's Hospital Cancer Centre, Guy's and St Thomas' NHS Foundation Trust, Great Maze Pond, London SE1 9RS, UK.
Email: f.r.ali.01@cantab.net

Abstract

Rosacea and the cardiometabolic syndrome are both associated with chronic inflammation and a pro-inflammatory phenotype. Emerging clinical evidence supports the relationship between rosacea and cardiometabolic syndrome hypertension and obesity. This article reviews our current findings and understanding in the skin and cardiovascular relationship in rosacea. Rosacea appears to be associated with hypertension, dyslipidemia, and obesity. The role of smoking in rosacea is currently less clear. It remains uncertain whether treatment of these risk factors will aid improvement of rosacea. Greater understanding of rosacea and its association with the cardiovascular system and underlying risk factors could allow for a greater understanding of the body's inflammatory response as well as the formulation of new guidelines for attending clinicians. Dermatologists treating rosacea patients might need to consider enquiring and evaluate their patients' underlying cardiovascular risk factors.

KEYWORDS

flushing, hypertension, metabolic syndrome, obesity, rosacea, smoking

1 | INTRODUCTION

Rosacea is an inflammatory skin condition for which the clinical features are characterized by skin sensitivity, flushing, centrofacial erythema, papules, and pustules. Rosacea has been historically categorized into four subphenotypes: erythematotelangiectatic (ETR), papulopustular (PPR), phymatous (PhR), and ocular subtypes.[1] There is growing interest in the association between the cardiometabolic syndrome and rosacea.[2] We explore this relationship including associations of rosacea with hypertension, obesity, antihypertensive and lipid-lowering drugs, and smoking.

2 | METHODS

Using the keywords "flushing," "hypertension," "metabolic syndrome," "obesity," "rosacea," "drugs", and "smoking," we searched the databases PubMed, MEDLINE, and Embase to find the relevant literature in English language articles only. Our review was conducted in June 2020, and the time period of evidence was collected from the establishment of these databases till June 18, 2020. The level of evidence was evaluated and selected according to the highest level working our way downwards. Using the Oxford Centre of Evidence-Based Medicine 2011 guidance, we analyzed the evidence based on its strength from level one to five with systematic reviews and meta-analyses considered first, randomized controlled trials second, cascading down to weaker level of evidence such as case reports (Table 1).

2.1 | Chronic inflammation

Chronic inflammation is a feature of both rosacea and cardiometabolic disease.[2] Numerous studies support the idea that the metabolic syndrome is a pro-inflammatory state due to raised C-reactive protein (CRP) levels.[3,4] Pro-inflammatory and prothrombotic states are thought to contribute to endothelial dysfunction, commonly present in those with metabolic syndrome.[5]

Patients with severe rosacea (rosacea fulminans) present with indicators of systemic inflammation, such as raised white cell counts,

 © 2020 Wiley Periodicals, LLC

erythrocyte sedimentation rates and CRP.[6-8] All four phenotypes—ETR, PPR, PhR, and ocular—are more likely to be associated with low-grade systemic inflammation, possibly explaining the already established finding that high total cholesterol, low-density lipoprotein, and C-reactive protein are common in all subtypes of rosacea patients.[6,8-10]

Trigger factors for rosacea such as ultraviolet radiation and stress alter Toll-like receptor (TLR) signaling, inducing reactive oxygen species and augmenting downstream cytokine and chemokine inflammatory responses.[11] TLR activation is thought to lead to the synthesis of pro-inflammatory cytokines and secretion of antimicrobial peptides such as cathelicidin and chemokines with TLR2 in particular being highly expressed in the skin of rosacea patients.[12]

This is consistent with findings that rosacea patients have increased expression of enzymes responsible for activating cathelicidin, the antimicrobial peptide LL-37. LL-37 promotes leukocyte chemotaxis, angiogenesis, and NF-κB activation, which together can account for the phenotype of rosacea (facial erythema, telangiectasia, papules, and pustules).[13] Neurogenic inflammation occurs in rosacea with release of vasoactive neuropeptides and pro-inflammatory chemokines promoting inflammation.[13,14]

2.2 | Cardiovascular risk factors

The relationship between rosacea and cardiovascular disease is a contentious issue. A recent meta-analysis of 50,442 rosacea patients by Chen and colleagues revealed that rosacea patients had a higher prevalence of dyslipidemia, hypertension, total cholesterol, higher low-density lipoprotein, higher triglycerides, higher systolic and diastolic blood pressure, and higher fasting blood glucose than non-rosacea patients.[15] The authors found no association with ischemic heart disease, stroke, diabetes, or high-density lipoproteins.[15] This review was limited by its lack of rosacea subtype analysis, but provides current insights and supports potential future guidance for cardiovascular screening or assessment among rosacea patients for improving diagnosis and treatment outcomes in premature disease stages.[15]

Overall, current evidence seems to support associations with hypertension, dyslipidemia and rosacea, with less evidence to support rosacea's association with ischemic heart disease.[6,8,15-17] Furthermore, a large Danish study[18] (n = 35,958) found no increased risk of death associated with cardiovascular disease in an assessment of cause-specific mortality of rosacea patients.[18]

2.3 | Hypertension

Three studies have examined the association between rosacea and hypertension.[15,16,19] A Taiwanese case–control study[16] of 33,533 rosacea patients and 67,106 control patients found that patients with rosacea were at increased risk of hypertension (odds ratio [OR] 1.17; 95% confidence interval [CI] 1.12-1.21), dyslipidemia (OR 1.41%; 95% CI 1.36-1.46), and coronary artery disease (OR 1.35; 95% CI 1.29-1.41) after adjusting for cardiovascular risk factors.[16] The small odds ratio and large sample size of this study likely imply that while there may be some statistical association, the association is not likely to be of meaningful clinical significance.

An observational study investigated the risk factors for the reappearance of telangiectasia after successful laser treatment.[20] Patients with facial telangiectasia are slightly more resistant to treatment with a higher relapse rate among male patients with hypertension.[20] Triggers such as alcohol or spicy food can cause neurovascular modifications possibly implicating neurovascular dysfunction as a shared pathophysiology in rosacea and hypertension.[6,15,16,19]

2.4 | Dyslipidemia

Dyslipidemia is significantly associated with rosacea (OR 1.41; 95% CI 1.36-1.46) in a Taiwanese case–control study (n = 33,553).[16] Chronic inflammation associated with dyslipidemia may have systemic implications. Paraoxonase-1 (PON-1) is a high-density lipoprotein-associated antioxidant which is significantly decreased in both rosacea and dyslipidemic patients.[16] It is postulated that chronic inflammation is a shared mechanism.[6,15,16] The small odds ratio and large sample size of this study arguably may bring its clinical significance into question.

2.5 | Carotid intima–media thickness, epicardial fat thickness, and the pro-inflammatory state

Sinikumpu and colleagues support the notion that rosacea is a chronic systemic inflammatory disease with vascular correlation.[2] In their longitudinal study (n = 1,932), 292 rosacea patients were studied with a 63-year follow-up.[2] The mean carotid intima–media thickness (CIMT) was significantly higher in the rosacea group when compared to the control group. The CIMT average 0.61 mm in rosacea group versus 0.59 mm in control ($P < .027$). CIMT is associated with cardiovascular risk factors and could represent premature hidden systemic inflammation.[2] Every 0.1 mm increase in CIMT has been associated with a 10-15% increase in the risk of myocardial infarction and a 13-18% increase in risk of cerebrovascular injury.[21]

In a cross-sectional study[17] of 80 patients, rosacea patients had significantly higher epicardial fat thickness (EFT) (4.46 mm ± 0.65 versus 3.28 mm ± 0.59 in controls) and CIMT (0.72 mm ± 0.19 versus 0.61 mm ± 0.12 in controls) measures compared with controls ($P < .001$). EFT can act in an endocrine fashion, secreting pro-inflammatory cytokines and hormones. While the limitation is the relative small study sample size, nevertheless it might serve as a benchmark for future association studies.

Both CIMT and EFT are thought to be indicators of a pro-inflammatory state and predictors of cardiovascular disease.[19] In rosacea, the pro-inflammatory response has been associated with cathelicidin peptides and endoplasmic reticulum stress.[4] Other

TABLE 1 Rosacea and the cardiovascular system

Study authors	Study Type	Patient number (n)	Outcome	Level of evidence
Cardiovascular risk factors				
Egeberg A, Fowler JF, Gislason GH, Thyssen JP[18]	Cohort	35,958	No increased risk of death associated with cardiovascular disease	4
Hypertension				
Hua TC, Chung PI, Chen YJ, *et al*[16]	Case–control	33,533	Rosacea patients were at increased risk of hypertension (odds ratio [OR] 1.17; 95% confidence interval [CI] 1.12-1.21), dyslipidemia (OR 1.41%; 95% CI 1.36-1.46), and coronary artery disease (OR 1.35; 95% CI 1.29-1.41)	4
Dyslipidemia				
Hua TC, Chung PI, Chen YJ, *et al*[16]	Case–control	33,533	Dyslipidemia is significantly associated with rosacea (OR 1.41, 95% CI 1.36-1.46]	4
Carotid intima–media thickness, epicardial fat thickness, and the pro-inflammatory state				
Sinikumpu SP, Jokelainen J, Auvinen J, *et al*[2]	Nested case–control	1932	Mean carotid intima–media thickness (CIMT) was significantly higher in the rosacea group when compared to the control group	4
Belli AA, Altun I, Altun I[17]	Cross-sectional	80	Rosacea patients had significantly higher epicardial fat thickness (4.46 mm ± 0.65 versus 3.28 mm ± 0.59 in controls) and CIMT (0.72 mm ± 0.19 versus 0.61 mm ± 0.12 in controls) measures compared with controls ($P < .001$)	2
Insulin resistance				
Belli AA, Gok SO, Akbaba G, Etgu F, Dogan G[25]	Case–control	47	Increased rates of insulin resistance found in the rosacea group but no difference in the rate of metabolic syndrome as compared to a control group. Fasting blood glucose, total cholesterol, systolic and diastolic blood pressure levels, as well as mean low-density lipoprotein, triglyceride, total cholesterol and CRP were significantly higher than in the control group	4
Obesity				
Li S, Cho E, Drucker AM, Qureshi AA, Li WQ[26]	Longitudinal cohort	5249	Risk of rosacea was greater in those with larger body mass indexes (BMI), compared with those with lower BMI ($P < .0001$) (HR 1.48 for rosacea 95% CI 1.33-1.64 for BMI greater than 35)	4
Aksoy B, Ekiz Ö, Unal E, *et al*[27]	Multicentric retrospective observational	1816	Rosacea patients were significantly more likely to suffer from metabolic comorbidities, particularly obesity and hypertension	2
Medications				
Spoendlin J, Voegel JJ, Jick SS, Meier CR[30]	Matched case–control	107,854	Across 107,854 cases and controls, there was no increased risk associated with CCBs and rosacea. Beta-blockers were associated with a slightly decreased risk of rosacea, in particular the ETR subtype. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers did not affect rosacea risk	4
Smoking				
Spoendlin J, Voegel JJ, Jick SS, Meier CR[37]	Observational	120,084	Past smokers had an increased risk of rosacea and current smokers had reduced risk of rosacea when compared to never smokers	2

(Continues)

TABLE 1 (Continued)

Study authors	Study Type	Patient number (n)	Outcome	Level of evidence
Li S, Cho E, Drucker AM, Qureshi AA, Li WQ[38]	Cohort	95,908	Compared with never smoking, there was an increased risk of rosacea with past smoking was found but a decreased risk associated with current smoking	4
Kucukunal A, Altunay I, Arici JE, Cerman AA[45]	Case–control	400	Increased risk of rosacea in current smokers	4

pro-inflammatory cytokines such as IL-8, IL-1β, and TNF-α are reported to be overexpressed in patients with rosacea.[22,23]

While further studies are undertaken, it would be prudent to regard rosacea as being indicative of a pro-inflammatory state and to consider monitoring for cardiometabolic risk factors, where appropriate.[16,17,20-23] Dosal and colleagues endorse testing rosacea patients for cardiovascular risk factors and addressing any if found.[6] They also suggest that rosacea is independently a risk factor for cardiovascular disease and that rosacea treatment could be targeted to both cutaneous and systemic disease. The authors propose possible benefits with trials of aspirin (81 mg) and low-dose tetracycline for primary prevention targeting both vascular and cutaneous disease.[6]

Low-dose tetracycline has previously been used to reduce incidence of acute myocardial infarction through possible matrix metalloproteinase inhibition. Therefore, its role in reducing inflammation could have cutaneous and cardiovascular benefits.[24]

2.6 | Insulin resistance

A further study (n = 47) reported increased rates of insulin resistance in the rosacea group but no difference in the rate of metabolic syndrome as compared to a control group.[25] Fasting blood glucose, total cholesterol, systolic and diastolic blood pressure levels, as well as mean low-density lipoprotein, triglyceride, total cholesterol, and CRP were significantly higher than in the control group. These findings support the relationship between rosacea, insulin resistance, and some cardiovascular risk factors.[25]

2.7 | Obesity

A possible link between obesity and rosacea has been proposed.[19] A longitudinal cohort study by Li and colleagues,[26] involving 5249 cases of rosacea over 14 years found that the risk of rosacea was greater in those with larger body mass indexes (BMI), compared to those with lower BMI ($P < .0001$) (HR 1.48 for rosacea; 95% CI 1.33-1.64 for BMI greater than 35). Patients who had gained weight after 18 years of age also had a greater incidence of rosacea (HR 1.04; 95% CI 1.03-1.05) per 10 pounds of weight gain. Those with a higher waist and hip circumference independent of BMI had a significantly higher risk of rosacea ($P < .0001$).[26] This study was limited by the lack of information on rosacea subtypes.[26]

This was supported by another study,[27] (n = 1816) which found that rosacea patients were significantly more likely ($P < .001$) to suffer from metabolic comorbidities, particularly obesity (8.8% of rosacea group versus 3.7% in control group) as well as hypertension (11.5% in rosacea group versus 8.9% in control group).[27] Emerging evidence is supporting a relationship between obesity and rosacea and weight-loss management in rosacea treatment could be a future treatment option advocated by dermatologists.[28]

2.8 | Medications

The association between rosacea and cardiometabolic risk factors has generated interest in whether medications used to treat the underlying risk factors impact upon the rosacea. Historically, calcium channel blockers (CCBs) were thought to exacerbate rosacea with increase in erythema and telangiectasia reported.[29] However, a large matched case–control study of antihypertensive drugs and incident of rosacea was conducted over a 14-year period.[30] Across 107,854 cases and controls, there was no increased risk associated with CCBs and rosacea. This large case–control study refutes previous suggestion supporting the association between CCBs and rosacea. The authors of this study suggest that previous findings were based on a weak body of evidence linking flushing reactions to CCBs with a lack of diagnostic criteria.[30] Reports suggest that a diagnosis of flushing or the ill-defined "pre-rosacea" do not always result in rosacea itself.[31]

Beta-blockers were associated with a slightly decreased risk of rosacea, in particular the ETR subtype.[30] This may be related- to the therapeutic benefits on reduction of flushing with the use of beta-blockers. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers did not affect rosacea risk in this study.[30]

The use of HMG-CoA reductase inhibitors (statins) and fibrates have shown a significant association with rosacea.[32] This must be interpreted with caution, since dyslipidemia patients are significantly more likely to have rosacea.[32] In addition, in one study, those without dyslipidemia who were given statins were less likely to be diagnosed with rosacea compared with those with dyslipidemia.[32] This might be due to the anti-inflammatory properties of statins and their ability to upregulate antioxidant enzymes and reduce systemic inflammation.[33,34]

Statins are also thought to have a role in angiogenesis in epidermal endothelial cells with higher doses inhibiting the production of vascular endothelial growth factor.[35] Statins also inhibit matrix

metalloproteinases, involved in the pathogenesis of rosacea.[36] Large randomized controlled trials are required to investigate the role of statins in rosacea.

2.9 | Smoking

The relationship between smoking and rosacea is less clear. Four studies found an increased risk of rosacea in past-smokers[37-40] and two studies found a decreased risk of rosacea in current smokers.[37,38]

In a large case–control study of 5462 rosacea patients, 65% were never smokers, 28% were past smokers, and 6.3% were current smokers.[37] Past smokers had an increased risk of rosacea and current smokers had reduced risk of rosacea when compared to never smokers (OR 0.64; 95%CI 0.62-0.67; n = 120,084).[37] This is possibly due to vasoconstriction associated with smoking and hence reduced flushing.[37]

In a separate large cohort study (n = 95,908),[38] found that compared with never smoking, an increased risk of rosacea with past smoking was found but a decreased risk associated with current smoking.[38] Increased pack-years were associated with greater risk of rosacea in past smokers and with a decreased risk in present smokers.[38] Rosacea risk significantly increased following three to nine years of smoking cessation and even after 30 years, there still appeared to be an increased risk of rosacea for past smokers.[38] A smaller study found that people with rosacea smoked less than the rest of the general public.[41]

A separate study found that rosacea was of higher prevalence in previous smokers as compared to nonsmokers or present smokers.[39] Another study also found that smoking cessation was associated with increased odds ratio for rosacea as compared to non- or current smokers.[40]

Smoking might result in microvascular vasoconstriction, decreasing vasodilatory symptoms associated with rosacea such as flushing.[37,42] Immunosuppression caused by smoking might also reduce inflammation associated with rosacea.[43] In previous smokers, it was hypothesized that rebound vasodilation upon stopping smoking and nicotine withdrawal could result in greater rosacea risk.[37,42] In addition, hormonal mechanisms triggered by smoking-related changes could be associated with rosacea, such as falling estrogen levels.[44] The long latency period between stopping smoking and developing rosacea in many studies (up to 30 years) cannot be overlooked as a potential for other confounding factors and future research must deal with this.[38] The current studies are limited by their lack of investigation of rosacea subtypes and given the vasodilatory effects found in this smoking association there is likely to be a vascular component of rosacea. This might be relevant for patients who only have inflammatory rosacea in which the risk and associations might be different.

Two other studies did not replicate these findings.[45,46] A case–control study found (n = 400) an increased risk of rosacea in current smokers,[45] while another cohort study (n = 550) found a positive correlation between number of pack-years and rosacea.[46]

Future research is required to resolve the inconsistencies in these findings and to gain a better understanding as to the association between previous smokers and rosacea.

3 | CONCLUSION

Recent evidence continues to reveal an association between the cardiovascular system and rosacea. Both rosacea and the cardiometabolic syndrome are indicative of an underlying pro-inflammatory state. Rosacea appears to be correlated with hypertension, dyslipidemia, and obesity; however, it remains unclear at present whether treatment of these risk factors will facilitate improvement of rosacea. Clinicians treating rosacea patients should consider whether there are underlying cardiovascular risk factors and investigate and treat these accordingly for the patients' holistic health. The role of smoking in rosacea pathogenesis remains unclear; tentatively, ex-smokers may be at increased risk of rosacea while current smokers appear to be protected. When counseling patients about reduction of smoking, attention may also be given to prophylactically addressing any impending rosacea.

Future large randomized clinical trials should investigate whether treatment of cardiovascular risk factors can facilitate clearance of rosacea and conversely whether worsening of these cardiovascular factors worsen clinical symptoms of particular subgroups of rosacea.[15]

CONFLICTS OF INTEREST

None declared.

ETHICAL APPROVAL

Consent for publication: All authors have approved this final submitted version of the manuscript and consent to its submission for consideration of publication.

ORCID

Tamara Searle https://orcid.org/0000-0001-5303-6881
Firas Al-Niaimi https://orcid.org/0000-0002-0684-4322
Faisal R. Ali https://orcid.org/0000-0002-8588-791X

REFERENCES

1. Tan J, Almeida LM, Bewley A, et al. Updating the diagnosis, classification and assessment of rosacea: recommendations from the global ROSacea COnsensus (ROSCO) panel. *Br J Dermatol*. 2017;176(2):431-438.
2. Sinikumpu S, Jokelainen J, Auvinen J, et al. Increased risk of cardiovascular diseases in female rosacea patients: a nested case-control study. *Acta dermatol*. 2019;99(7–8):705-706.
3. Sharma P. Inflammation and the metabolic syndrome. *Indian J Clin Biochem*. 2011;26(4):317-318.
4. Esposito K, Giugliano D. The metabolic syndrome and inflammation: association or causation? *Nutr Metab Cardiovasc Dis*. 2004;14:228-232.
5. Pro-Inflammatory SG, Factors P, Syndrome M. *EJIFCC*. 2007;18(1):39-46.

6. Dosal J, Keri J. Rosacea and cardiovascular disease: Is there an association? *J Am Acad Dermatol*. 2015;73(2):308-309.
7. Haber R, El Gemayel M. Comorbidities in rosacea: a systematic review and update. ? *J Am Acad Dermatol*. 2018;78(4):786-792.
8. Duman N, Ersoy Evans S, Atakan N. Rosacea and cardiovascular risk factors: a case control study. *J Eur Acad Dermatol Venereol*. 2014;28(9):1165-1169.
9. Vera N, Patel NU, Seminario-Vidal L. Rosacea comorbidities. *Dermatol Clin*. 2018;36(2):115-122.
10. van Zuuren EJ. Rosacea. *N Engl J Med*. 2017;377:1754-1764.
11. Gerber PA, Buhren BA, Steinhoff M, Homey B. Rosacea: the cytokine and chemokine network. *J Investig Dermatol Symp Proc*. 2011;15(1):40-47.
12. Yamasaki K, Gallo RL. Rosacea as a disease of cathelicidins and skin innate immunity. *J Investig Dermatol Symp Proc*. 2011;15:12-15.
13. Yamasaki K, Di Nardo A, Bardan A, et al. Increased serine protease activity and cathelicidin promotes skin inflammation in rosacea. *Nat Med*. 2007;13:975-980.
14. Rainer BM, Kang S, Chien AL. Rosacea: Epidemiology, pathogenesis, and treatment. *Dermatoendocrinol*. 2017;9(1):e1361574.
15. Chen QI, Shi X, Tang Y, et al. Association between rosacea and cardiometabolic disease: a systematic review and meta-analysis. *J Am Acad Dermatol*. 2020. https://doi.org/10.1016/j.jaad.2020.04.113
16. Hua T-C, Chung P-I, Chen Y-J, et al. Cardiovascular comorbidities in patients with rosacea: a nationwide case-control study from Taiwan. *J Am Acad Dermatol*. 2015;73(2):249-254.
17. Belli AA, Altun I, Altun I. Thickness of carotid intima and epicardial fat in rosacea: a cross-sectional study. *An Bras Dermatol*. 2017;92(6):820-825.
18. Egeberg A, Fowler JF, Gislason GH, Thyssen JP. Nationwide assessment of cause-specific mortality in patients with rosacea: A cohort study in Denmark. *Am J Clin Dermatol*. 2016;17(6):673-679.
19. Stefanadi EC, Dimitrakakis G, Antoniou C-K, et al. Metabolic syndrome and the skin: a more than superficial association. Reviewing the association between skin diseases and metabolic syndrome and a clinical decision algorithm for high risk patients. *Diabetol Metab Syndr*. 2018;10(1):9.
20. Guida S, Galimberti MG, Bencini M, Pellacani G, Bencini PL. Telangiectasia of the face: risk factors for reappearance in patients treated with dye laser. *J Eur Acad Dermatol Venereol*. 2017;31(8):1355-1359.
21. Darabian S, Hormuz M, Latif MA, Pahlevan S, Budoff MJ. The role of carotid intimal thickness testing and risk prediction in the development of coronary atherosclerosis. *Curr Atheroscler Rep*. 2013;15(3):306.
22. Casas C, Paul C, Lahfa M, et al. Quantification of Demodex folliculorum by PCR in rosacea and its relationship to skin innate immune activation. *Exp Dermatol*. 2012;21:906-910.
23. Melnik BC. Endoplasmic reticulum stress: key promoter of rosacea pathogenesis. *Exp Dermatol*. 2014;23:868-873.
24. Meier CR, Derby LE, Jick SS, Vasilakis C, Jick H. Antibiotics and risk of subsequent first-time acute myocardial infarction. *JAMA*. 1999;281(5):427-431.
25. Belli AA, Gok SO, Akbaba G, Etgu F, Dogan G. The relationship between rosacea and insulin resistance and metabolic syndrome. *Eur J Dermatol*. 2016;26(3):260-264.
26. Li S, Cho E, Drucker AM, Qureshi AA, Li WQ. Obesity and risk for incident rosacea in US women. *J Am Acad Dermatol*. 2017;77(6):1083-1087.
27. Aksoy B, Ekiz Ö, Unal E, et al. Systemic comorbidities associated with rosacea: a multicentric retrospective observational study. *Int J Dermatol*. 2019;58(6):722-728.
28. Rainer BM, Fischer AH, Da Silva DL, Kang S, Chien AL. Rosacea is associated with chronic systemic diseases in a skin severity–dependent manner: results of a case-control study. *J Am Acad Dermatol*. 2015;73(4):604-608.
29. Natale F, Cirillo C, Granato C, et al. Worsening of rosacea in patients treated with dihydropyridine calcium channel blockers: a clinical observation. *Hypertens Res*. 2011;34(6):790-791.
30. Spoendlin J, Voegel JJ, Jick SS, Meier CR. Antihypertensive drugs and the risk of incident rosacea. *Br J Dermatol*. 2014;171(1):130-136.
31. Powell FC. What's going on in rosacea? *J Eur Acad Dermatol Venereol*. 2000;14:351-352.
32. Son JH, Chung BY, Jung MJ, Choi YW, Kim HO, Park CW. The risk of rosacea according to chronic diseases and medications: a 5-year retrospective. Multi-institutional case-control study. *Ann Dermatol*. 2018;30(6):676-687.
33. Diamantis E, Kyriakos G, Quiles-Sanchez LV, Farmaki P, Troupis T. The anti-inflammatory effects of statins on coronary artery disease: an updated review of the literature. *Curr Cardiol Rev*. 2017;13(3):209-216.
34. Jowkar F, Namazi MR. Statins in dermatology. *Int J Dermatol*. 2010;49:1235-1243.
35. Katsumoto M, Shingu T, Kuwashima R, Nakata A, Nomura S, Chayama K. Biphasic effect of HMG-CoA reductase inhibitor, pitavastatin, on vascular endothelial cells and angiogenesis. *Circ J*. 2005;69:1547-1555.
36. Luan Z, Chase AJ, Newby AC. Statins inhibit secretion of metalloproteinases-1,-2,-3, and -9 from vascular smooth muscle cells and macrophages. *Arterioscler Thromb Vasc Biol*. 2003;23:769-775.
37. Spoendlin J, Voegel JJ, Jick SS, Meier CR. A study on the epidemiology of rosacea in the UK. *Br J Dermatol*. 2012;167(3):598-605.
38. Li S, Cho E, Drucker AM, Qureshi AA, Li WQ. Cigarette smoking and risk of incident rosacea in women. *Am J Epidemiol*. 2017;186(1):38-45.
39. ABRAM K, Silm H, Maaroos HI, Oona M. Risk factors associated with rosacea. *J Eur Acad Dermatol Venereol*. 2010;24(5):565-571. https://doi.org/10.1111/j.1468-3083.2009.03472.x
40. Breton AL, Truchetet F, Véran Y, et al. Prevalence analysis of smoking in rosacea. *J Eur Acad Dermatol Venereol*. 2011;25(9):1112-1113.
41. Mills CM, Marks R. Environmental factors influencing rosacea. *Clin Exp Dermatol*. 1996;21(2):172-173.
42. Edvinsson ML, Andersson SE, Xu CB, Edvinsson L. Cigarette smoking leads to reduced relaxant responses of the cutaneous microcirculation. *Vasc Health Risk Manag*. 2008;4(3):699-704.
43. Mills CM, Hill SA, Marks R. Transdermal nicotine suppresses cutaneous inflammation. *Arch Dermatol*. 1997;133(7):823-825.
44. Meirowitz N. Flushing and papules in a middle-aged woman. *Obstet Gynecol*. 2005;105(6):1482.
45. Kucukunal A, Altunay I, Arici JE, Cerman AA. Is the effect of smoking on rosacea still somewhat of a mystery. *Cutan Ocul Toxicol*. 2016;35(2):110-114.
46. Aldrich N, Gerstenblith M, Fu P, et al. Genetic vs environmental factors that correlate with rosacea: a cohort-based survey of twins. *JAMA Dermatol*. 2015;151(11):1213-1219.

How to cite this article: Searle T, Al-Niaimi F, Ali FR. Rosacea and the cardiovascular system. *J Cosmet Dermatol*. 2020;00:1–6. https://doi.org/10.1111/jocd.13587