The editors of JCAD are pleased to present this biannual column as a means to recognize select medical students, PhD candidates, and other young investigators in the field of dermatology for their efforts in scientific writing. We hope that the publication of their work encourages these and other emerging authors to continue their efforts in seeking new and better methods of diagnosis and treatments for patients in dermatology.

ABSTRACT

OBJECTIVE: Rosacea is a common inflammatory cutaneous condition with a complex yet unknown etiopathogenesis. Diet and certain food items are known to trigger or worsen rosacea symptoms, but conflicting and often inconsistent advice is given to patients regarding this link. We provide an up-to-date literature review on the relationship between rosacea and diet. **METHODS:** Using the keywords "alcohol," "diet," "flushing," "food," "inflammation," "rosacea," "skin-gut axis" and "spice" we systemically searched the databases PubMed, MEDLINE and EMBASE for English-language articles in July 2020. **RESULTS:** The most frequently reported triggers implicated in rosacea include alcohol, spicy food, cinnamaldehyde-containing foods (e.g., tomatoes, citrus fruits, chocolate), hot drinks, and histamine-rich foods (e.g., aged cheese, wine, processed meats). Some food items appear to play a protective role, such as omega-3, which appears to protect against ocular rosacea. The relationship between certain food items and the subtype of rosacea is varied, with inconsistent results shown in the few studies that examined this. As an example, alcohol worsens flushing and fatty food triggers both erythematotelangiectatatic and phymatous rosacea in susceptible individuals. **CONCLUSION:** While several food types appear to be associated with exacerbation of rosacea, there are no recommendations that can be applied to all patients. Further studies are needed to examine the exact link between diet and rosacea subtypes.

KEYWORDS: Alcohol, diet, flushing, food, inflammation, rosacea, skin-gut axis, spice

Rosacea and Diet: What is New in 2021?

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Rosacea is a chronic, relapsing, inflammatory cutaneous condition whose clinical features include skin sensitivity, flushing, centrofacial erythema, papules, pustules and hyperplasia of sebaceous glands. Four sub-phenotypes of rosacea have historically been described: erythematotelangiectatic (ETT), papulopustular (PPR), phymatous (PhR), and ocular rosacea. These subtypes often overlap in affected patients.[1] In this review, subtypes will be referred to based on the era of the included studies. However, the inadequacies of subtyping in rosacea must not be overlooked; more recent categorization in terms of phenotypic presentation have been proposed.[1]

Environmental and genetic predisposition play a role in the vascular and inflammatory aspects of the disease.[1] There is a long-standing recognition that certain food types may worsen rosacea. We present the current understanding of the relationship between diet and rosacea.[2]

METHODS

Using the keywords "alcohol," "diet," "flushing," "food," "inflammation," "rosacea," "skin-gut axis" and "spice," we searched databases PubMed, MEDLINE, and EMBASE to find the relevant literature. We excluded any articles that were not in English. Our review was conducted in July 2020, and the time period of evidence was collected from the inception of these databases until July 14, 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 evaluated and listed the evidence based on its strength from level 1 to 5 with systematic reviews and meta analyses considered first, randomized controlled trials second, cascading down to weaker level of evidence, such as case series.

RESULTS

Our search yielded 44 studies, and 32 of these were deemed relevant for review. Our findings are summarized in Table 1.

DISCUSSION

Rosacea and diet. The role of diet as a "trigger" for rosacea is widely accepted. Triggers reported include: spicy food, cinnamaldehyde-containing foods, and alcohol. In a National

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TABLE 1. Rosacea and diet

STUDY AUTHORS	YEAR	STUDY DESIGN	COUNTRY	PATIENT NUMBER (N)	FOLLOW-UP	DATA COLLECTED	OUTCOMES
Alcohol							
Li et al[4]	2017	Prospective Cohort	USA	4,945 (out of, cohort of 82,737)	14 years	Alcohol intake and incidence of rosacea	• Increased alcohol intake was associated with an increased rosacea incidence (HR at 95% Cis were 1.12; 95% CI 1.05-1.20) for alcohol intake of 1-4 g/day and 1.53 (1.26-1.84) for more than 30g/day. • White wine and spirits were associated with a significantly higher risk of rosacea. These risks were the same regardless of smoking status group.
Caffeine							
Li et al[8]	2018	Prospective Cohort	USA	4,945 (out of cohort of 82737)	14 years	Caffeine intake and incidence of rosacea	• Inverse association between increased caffeine intake and risk of rosacea (hazard ratio [HR] for highest caffeine intake versus lowest, 0.76 95% CI, 0.69-0.84; p<0.001). • Other food containing caffeine such as tea, soda and chocolate was not significantly related to a decreased rosacea risk.
Fatty Foods							
Yuan et al[16]	2019	Retrospective Case-Control	China	2,637	2 years	Severity of rosacea (mild, mild to moderate, moderate and severe)	• High fatty foods intake significantly associated with ETR. (OR = 2.49; 95% CI, 1.26–4.92) and phymatous rosacea (OR = 5.32; 95% CI, 1.42–19.97). • Frequent tea intake was only associated with ETR (OR = 2.73; 95% CI, 1.18–6.32). • Frequent dairy products showed a negative association with ETR (OR = 0.13; 95% CI, 0.03–0.67) and papulopustular rosacea (OR = 0.03; 95% CI, 0.01–0.55) but not with phymatous rosacea. • Sweet food, spicy food and coffee had no associate with any subset of rosacea.
Omega-3 Fatty Acids							
Bhargava et al[36]	2016	Randomized controlled trial	India	130	6 months	Subjective dry eye symptoms and in Meibomian gland score, Schirmer score and tear film break-up time (measures of eye dryness) after groups were randomized to receive either omega-3 fatty acids (capsules containing 180 mg eicosapentaenoic acid and 120 mg docosahexaenoic acid) or placebo twice daily	• There was a significant change in subjective dry eye symptoms and in Meibomian gland score, Schirmer score and tear film break-up time (measures of eye dryness) (p<0.001).
Zinc							
Bamford et al[54]	2012	Randomized double-blind trial	USA	44	90 days	Improvement in rosacea zinc sulphate (220mg, 2 times a day)	• Both groups had an improvement in their rosacea and there was no difference between groups.
Sharquie et al[55]	2006	Double-blind, placebo-controlled study	Iraq	25	6 months	Rosacea severity score after zinc sulphate (100mg, 3 times a day)	• Significant improvements in rosacea severity score (p<0.01)

Rosacea Society (NRS) survey of 1,066 rosacea sufferers, participants reported alcohol (52%, spicy foods (45%), certain fruits (13 %), marinated meats (10%), and certain vegetables (9%) as triggers.[3] Particpants also reported that diet alteration resulted in improvement of rosacea symptoms. While alcohol, spicy food, and cinnamaldehyde have received attention in the literature, few studies have investigated fatty foods and dairy as "triggers" in rosacea.

Alcohol. The most common trigger mentioned in the NRS study included alcohol, namely wine (red wine was reported to be a worse trigger than white wine) and spirits.[3] A large study (n=82,737) by Li et al[4] investigated alcohol intake over 14 years and found that of 4,945 patients with rosacea, increased alcohol intake was associated with an increased rosacea incidence (hazard ratio [HR] at 95%, CIs were 1.12; 95% CI 1.05–1.20) for alcohol intake of 1 to 4 grams per day and 1.53 (1.26-1.84) for more than 30 grams per day. Risks were the same regardless of smoking status.[4] These findings were replicated in a cohort-based survey (n=550) in which alcohol consumption correlated with rosacea; however, there was a weak association between alcohol and rosacea in this study (p=0.01).[5]

Histamine is released as a breakdown product of acetaldehyde and acetone, both alcohol metabolites. Histamine is thought to act on the cutaneous vasomotor system of the dermis causing dysfunction and facial flushing.[6] An additional mechanism for alcohol-induced flushing relates to the opiate-like effects of enkephalin.[7]

The link between alcohol and rosacea was refuted by a study (n=317) by Abram et al,[8] in which alcohol consumption, caffeine intake, and *Helicobacter pylori* status appeared not to be associated with the ability to trigger rosacea. The results of the study may have been weakened by the smaller population size. The most prevalent subtype in this study was PPR.

Transient receptor potential (TRP) ion channels are fundamental in the regulation of various physiological and pathophysiological skin conditions. They are important for regulation of the skin barrier, skin cell proliferation, and differentiation and cutaneous immunology.[9] Transient receptor potential vanilloid (TRPV1) receptors are found on sensory nerves and keratinocytes; they are activated by spicy foods, hot drinks, vanilla, cinnamon, caffeine, alcohol, and ultraviolet radiation. These channels release substance P and calcitonin-related-peptide (CGRP) when activated, which results in an inflammatory response, dilating arterioles, flushing, and edema.[10] Substance P and CGRP are elevated in rosacea patients, particularly in those with ETT and sensitive skin.[11–12] The resultant inflammation from these foods causes dysregulation of the epidermal barrier, resulting in increased transepidermal water loss and cutaneous dehydration, both hallmarks characterizing rosacea symptoms.[13]

Niacin might be partially responsible for the "flush" observed in rosacea patients. Niacin, which is found in salmon, peanuts, tuna, liver, and chicken breasts, acts on niacin G-protein-coupled-receptors in Langerhans cells. This causes the release of prostaglandins around capillaries, resulting in erythema, raised cutaneous temperature, pruritus, and stinging.[14–15]

Spicy food and capsaicin. A study by Yuan et al[16] did not show a causal link between spicy food and rosacea, suggesting that it might only aggravate symptoms like flushing, stinging, and burning, rather than accounting for the condition's presence.[16] Spicy food showed no association with rosacea subtype.[16]

In an NRS survey of 400 patients, 78 percent had changed their diet as a measure to control rosacea.[17] Seventy-five percent of patients in this group subsequently had a reduction of rosacea flares. Spices, hot sauce, cayenne, and red pepper were cited as triggers. Regarding the mechanism of these triggers, TRPV1 receptor might be activated by capsaicin found in spicy foods, causing vasodilation and flushing.[8,18–19]

Another NRS survey found that people with rosacea avoided food associated with hot or spicy ingredients (n=516).[20] Of those surveyed, 49 percent avoided Mexican food, 33 percent avoided Indian food, 27 percent avoided Thai food, and 25 percent stopped eating Italian food.

Cinnamaldehyde. Cinnamaldehyde-containing foods, such as tomatoes, citrus fruits, and chocolate were identified as triggers by a separate NRS survey.[17] Transient receptor potential ankyrin receptors-1 (TRPA1) found in sensory nerves in the dermis might be activated by cinnamaldehyde, resulting in vasodilation, and, hence, erythema, and telangiectasia by increasing edema and flushing.[14,21] One case report described a 68-year-old woman with severe exacerbation of rosacea following the consumption of of cinnamon oil, a cinnamaldehyde-containing food, to lower her blood glucose.[22]

Caffeine. In a cohort study that lasted more than 14 years (n=82,737), the caffeine intake of 4,945 patients with rosacea was assessed.[23] A significant inverse relationship between rosacea risk and caffeinated coffee was found, with higher caffeine intake appearing to be associated with a lower rosacea risk (HR for highest caffeine intake versus lowest, 0.76; 95% CI, 0.69-0.84; p<0.001).[23] The same relationship was not observed between decaffeinated coffee and other foods containing caffeine. One possibility is that caffeine induces a significant vasoconstrictory response after intake, reducing rosacea symptoms.[24] Data examining the relationship between rosacea subtype and caffeine intake was lacking in this study.[24]

While a higher caffeine intake could be recommended for patients with rosacea following this study, the described trigger might be due to caffeine, hot temperature of the drink, or other byproducts of the coffee manufacturing process. Another potential explanation for the inverse relationship between rosacea risk and caffeinated coffee that must be considered is that those who have pre-rosacea may avoid caffeinated coffee, as it may lead to exacerbations.

Genome-wide association studies show that polymorphisms in the CYP1A2 gene play a role in the pharmacodynamic and pharmacokinetic response to caffeine.[25] However, authors of this study did not account for CYP1A2 heterogeneity, and it is difficult to extrapolate these findings on all rosacea patients.

There is insufficient data on recommending limiting caffeine intake in patients with rosacea. Furthermore, randomized, controlled trials investigating the effects of coffee and caffeine intake upon skin presentations and the cutaneous micro-environment are also lacking.[26]

It was previously postulated that caffeine can trigger rosacea and worsen symptoms.[27] This was further explored in a study in which water and coffee at 22 °C were found to not cause flushing. While at 60°C, both coffee and hot water led to flushing reactions. Therefore, it was inferred that heat is the agent responsible for flushing, rather than caffeine itself.[28] In an NRS study,[3] 33 percent and 30 percent, respectively, of respondents believed hot coffee and hot tea

to be a rosacea trigger. Hot beverage intake is thought to cause increased vasodilation and sympathetic activation, which results in flushing and telangiectasia.[29]

Histamine. Histamine, released from mast cells, acts in allergic inflammation, promoting vascular hyper-permeability, tissue swelling, increased blood flow, and endothelial barrier dysfunction.[30] Histamine intolerance can be caused by imbalance of ingested histamine with reduced capability for histamine breakdown. Diamine oxidase is the main enzyme responsible for ingested histamine breakdown.[31]

Histamine might accumulate when this enzyme is impaired. This excess histamine can result in the ubiquitous symptoms of hyperreactivity caused by the pathway described above. Symptoms include urticaria, pruritus, and flushing. The role of histamine intolerance in rosacea requires further exploration, since histamine intolerance is found in up to one percent of the United States population.[32] Certain foods high in histamine can act as triggers (e.g., aged cheese, sauerkraut, wine, and processed meat).[33] Chemicals such as sulphites and tyramine are found commonly in the same foods as histamine. Therefore, it might be difficult to distinguish a link between these mediators.[34] It is worth noting that alcohol-related flushing in rosacea can be attributed to histamine resultant from the metabolism of acetone and acetaldehyde.[34]

Omega-3 fatty acids. The efficacy of dietary omega-3 fatty acids in rosacea patients has been reported.[35] Patients with ocular symptoms, particularly dry eyes, were randomized to receive either omega-3 fatty acid capsules (containing 180mg eicosapentaenoic acid and 120mg docosahexaenoic acid) or placebo twice daily for six months (n=130).[36] Researchers found a significant change in subjective dry eye symptoms and measures of eye dryness ($p<0.001$). This led the authors to conclude that omega-3 fatty acids could improve ocular symptoms of rosacea.[36]

Although some dermatologists promote the use of flaxseed oil for ocular rosacea, there are no supporting studies available in the literature for this indication.[37]

Fatty food. A case-control study was conducted across five cities in China (Changde, Wuhan, Fudan, Guangzhou, and Changsha), involving 1,347 patients with rosacea and 1,290 controls over two years.[16] Diets that contained large amounts of fatty food (e.g., fatty meat, fried food, and lard) showed positive correlations with rosacea, possibly due to the role of fatty diets in chronic inflammation.[38] ETT and PhR phenotypes showed particularly positive correlations in this study.[16] A fatty diet might cause an imbalance in the genesis of ceramides and hyaluronic acid and a relative shortage of very low-chain fatty acids in the skin, compromising the epidermal barrier and lengthening epidermal C-fibers.[38] Interestingly, high-fat diets were significantly associated with the ETT and PhR subtypes. This could result in rosacea symptoms, such as pain, burning, and stinging. However, it is difficult to establish the direct effects of dietary fat in the pathology of rosacea, since no other studies to date have investigated a fatty diet and rosacea pathology. Other studies have focused on fat in terms of fatty acid imbalances within the skin in rosacea patients and a rosacea-obesity association.[39]

Dairy. In a study from Yuan et al,[16] diets with a high dairy content showed a negative correlation with rosacea severity, particularly ETT and PPR phenotypes.This study was the first and largest of its kind, and further randomized, controlled trials might alter dietary recommendations for rosacea patients. Dairy products might have anti-inflammatory properties that regulate gut microbiota and reduce intestinal inflammation, both of which are possibly associated with rosacea.[16,40] We based this possible association on studies that use human milk in neonatal guts and bovine milk in a murine study.[41,42] Further research is required to investigate the effect of dairy on rosacea in adults.[16]

Questions arise about the suitability of recommending a dairy-rich diet, given that a large percentage of the Chinese population is lactose intolerant.[43] Other studies have found dairy products to be inflammatory and cause acne vulgaris.[44] Hormones in milk may promote inflammation and acne. In a study of 47,355 women ($p=0.002$), skim-milk ($p=0.003$) was associated with acne vulgaris.[45] Given similarities in the underlying pathophysiology of acne vulgaris and rosacea, it is unclear how dairy could have opposite effects in each condition, and further research is required to replicate these findings.[6,16] Additionally, multiple potential confounding factors, such as social status, affordability, and lactose intolerance, must not be overlooked.

The findings from the study by Yuan et al[16] potentially point towards a diverse course of the disease in different ethnic groups. Since rosacea is more prevalent in Caucasian patients, this could explain the difference in study findings among Western patients.[8] Therefore, findings regarding dairy are inconclusive, with some evidence finding dairy to be a rosacea trigger and others suggesting that dairy could reduce rosacea severity.[3,16]

Miscellaneous. The relationship between rosacea and other food items is less established and seems to be based on case reports or small studies.[46] Other triggers cited in one study include liver, yogurt, cream, cheese, eggplant, spinach, lime, white beans, peas, avocados, bananas, plums, raisins, figs, vanilla, soy sauce, vinegar, and yeast products.[47,48] High blood glucose levels have been found in patients with rosacea, and excess sugary foods might be linked to rosacea, possibly leading to increased inflammation and rosacea exacerbations.[49]

Vitamin B. Tulipan[50] first suggested that rosacea could be the result of a vitamin B-complex deficiency. Riboflavin (vitamin B2) deficiency might also be associated with rosacea and potentially be a key factor in B-complex deficiencies.[51] In a study by Wozniacka et al[52] topical 1-methylnicotinamide (0.25% gel) was used for the treatment of rosacea (n=34) twice daily for four weeks. Improvement was noted in 26 patients (i.e., good or moderate). One patient suffered from skin irritation and withdrew from the study. To date, systemic nicotinamide has not been tested, perhaps due to the associated risk of flushing.[52]

Zinc. Studies using zinc in rosacea treatment have produced contradictory results.[53] In a randomized double-blind trial (n=44), there was no significant difference in improvement in rosacea between those given oral zinc sulphate 220mg twice daily and those given placebo for 90 days.[54]

This was not replicated in a study of 25 patients over six months.[55] Here, zinc sulphate 100mg three times daily was found to be a good treatment for rosacea with significant improvements in rosacea severity score ($p<0.01$).[55] Zinc sulphate is water-soluble, meaning it is not absorbed well by the body.[56] To increase zinc levels, nutritionists use zinc picolinate, the form the body absorbs best. This could explain the result in the former trial (3

months) versus the latter (6 months).[56]

Probiotics. Many reports support probiotic use in treatment of chronic inflammatory conditions, such as rosacea, with limited side-effects.[57,58] The evidence for the skin-gut axis could support probiotic use as adjunctive treatment in rosacea patients.[59]

Robust randomized, controlled trials supporting probiotic use are lacking. It has been suggested that probiotics may alter the gut microbiome, counteracting opportunistic bacteria that cause microbiome imbalances.[60] Probiotics might have an anti-inflammatory role as well as improving skin barrier efficacy by enhancing barrier recovery after damage.[61] Probiotics might attenuate vasodilation, edema, mast cell breakdown, and TNF-α release.[60]

Most studies have found that the initial beneficial effect of probiotics cannot be sustained upon discontinuation and that probiotics do not necessarily allow for recolonization of beneficial gut microorganisms.[57] More research is needed to assess the effect of different strains of probiotics for different conditions. For example, a randomized, controlled trial found *Lactobacillius reuteri* to be an efficacious adjunct to triple therapy for *H. pylori*, improving the eradication rate by more than eight percent and reducing side effects when compared to placebo.[61]

Bacillus subtilis-3 has been shown to be efficacious in the treatment of *H. pylori*. It is thought to enable passage across the gastric barrier, allowing spore colonization in the gastrointestinal tract and subsequent alteration of the microbiome.[62]

Clinical implications. When counselling patients, it is important to emphasize triggers that affect one patient may not affect another. This is why there is a need for a personalized approach once patients have established what their particular dietary triggers are. In a 2018 survey, 73 percent of patients reported that changing their diet did reduce rosacea exacerbation frequency.[19] Most frequently, alcohol, spicy food, cinnamaldehyde-containing foods (e.g., tomatoes, citrus fruits, chocolate), hot drinks, and histamine-rich foods (e.g., aged cheese, wine, processed meats) can act as triggers. Some evidence exists supporting the use of supplementary omega-3-fatty acids in ocular rosacea.[36]

Initial evidence exists that fatty foods might exacerbate rosacea and dairy-based foods may protect from rosacea. Similarly, there is a rationale for the use of fermented foods, such as kefir, but these items are not supported by large trials.[62]

Limitations. This review has several limitations. The vast majority of the referenced studies are based on a questionnaire design, which is inevitably subject to the recall and diagnosis biases. The nutritional association with diseases and nutritional intervention in treatment require further quantitative analysis to elucidate the dose-response effect and to reduce the risk of biological speculation. Furthermore, in many of the studies, the sample sizes were small, the composition of the patient groups were different, and the results were sometimes contradictory; future research should control for these possible confounding factors.

CONCLUSION

Recent evidence continues to shed light on the role of diet in rosacea treatment. While there are many reported dietary triggers, many healthy patients never develop rosacea symptoms. There remains a need for an individualized approach, with patients avoiding those triggers that they identify as exacerbating their own disease. Dermatologists can assist by highlighting likely dietary triggers and referring to dietary guidelines and nutritionists as part of their holistic care of patients.

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