DERMATOLOGY PRACTICAL & CONCEPTUAL

www.derm101.com

Diet and rosacea: the role of dietary change in the management of rosacea

Emma Weiss[1], Rajani Katta[1]

1 Baylor College of Medicine, Houston, TX, USA

Key words: rosacea, diet, gut-skin connection

Citation: Weiss E, Katta R. Diet and rosacea: the role of dietary change in the management of rosacea. Dermatol Pract Concept 2017;7(4):31-37. DOI: https://doi.org/10.5826/dpc.0704a08

Received: June 7, 2017; **Accepted:** August 21, 2017; **Published:** October 31, 2017

Funding: None.

Competing interests: The authors have no conflicts of interest to disclose.

All authors have contributed significantly to this publication.

Corresponding author: Rajani Katta, MD, Katta Dermatology, 6800 West Loop South, Suite 180, Bellaire, TX, 77401, USA. Email: info@kattamd.com

ABSTRACT Dietary change may play a role in the therapy of rosacea. Certain foods and beverages may act as "triggers" for rosacea exacerbations. These may be divided into heat-related, alcohol-related, capsaicin-related, and cinnamaldehyde-related. One potential pathogenic mechanism may be via the activation of transient receptor potential cation channels, which result in neurogenic vasodilatation. Further research is needed on the role of the gut skin connection in rosacea. Epidemiologic studies suggest that patients with rosacea have a higher prevalence of gastrointestinal disease, and one study reported improvement in rosacea following successful treatment of small intestinal bacterial overgrowth. While further research is required in this area, patients may be advised on measures to support a healthy gut microbiome, including the consumption of a fiber-rich (prebiotic) diet.

Introduction

Dermatologists frequently recommend dietary modification to patients with rosacea, with recommendations to avoid "trigger" foods and beverages. Anecdotally, many patients describe rosacea flares with spicy foods or with hot drinks. In this review, we present the possible mechanisms linking these foods and others to rosacea exacerbations. We also highlight the gut-skin connection as it pertains to rosacea, which presents an intriguing avenue for further research.

Background

Rosacea is a chronic inflammatory skin condition that is estimated to affect up to 15% of certain populations, with an increased prevalence in fair-skinned individuals of European descent [1]. It is characterized by recurrent episodes of flushing, along with other skin findings, concentrated to the skin of the central face. In the earlier stages of rosacea, patients may only experience intermittent flushing. In later stages, they may develop persistent erythema and telangiectasias, and/or recurrent papules and pustules. Rosacea is divided into four main subtypes based on these clinical characteristics. These subtypes include erythematotelangiectatic, papulopustular, phymatous, and ocular [2]. Patients may present with symptoms from multiple subtypes concurrently, or with isolated findings that do not fit a specific subtype. These symptoms often fluctuate between intervals of exacerbation and disease-free remission.

For patients not responsive to topical medications, oral anti-inflammatory antibiotics, specifically tetracyclines, are

the mainstay of treatment. However, long-term oral antibiotic therapy is not ideal due to potential side effects as well as the potential for bacterial resistance. Therefore, the role of modifiable lifestyle factors, including diet, has received renewed interest.

It is well known anecdotally that certain foods may act as rosacea triggers. Research has even suggested certain mechanisms whereby other foods may be helpful. As the understanding of the pathogenesis of rosacea continues to evolve, dietary modifications may become an essential component of rosacea therapy.

Pathogenesis

The exact pathogenesis of rosacea is unknown. Given the higher incidence in persons of North European descent, an underlying genetic etiology is hypothesized, although a specific causative gene has not yet been found. At this time, rosacea is thought to result from a combination of immune system dysregulation, abnormal neurological and vascular signaling, and dysbiosis of microorganisms ultimately leading to skin sensitivity and inflammation.

The innate immune system is disrupted in patients with rosacea. This leads to an abnormal inflammatory cytokine release and an anti-microbial peptide (AMP) response. When compared to normal skin, skin affected with rosacea has significantly more cathelicidin expression [3]. Cathelicidin, an AMP expressed by leukocytes and epithelial cells, is an important bacterial defense molecule. Cathelicidin is cleaved into its active form, LL-37, by the serine protease kallikrein 5 (KLK5) [4]. In patients with rosacea, both the LL-37 and KLK5 molecules are different from those in normal skin. These differences cause aberrant downstream effects, including leukocyte chemotaxis, vasodilatation, angiogenesis, and extracellular matrix deposition.

Abnormal neurological signaling also plays a role in rosacea pathogenesis. Heat and other factors, including dietary factors, stimulate transient receptor potential cation channels [5]. The stimulation of these channels acts to initiate pro-inflammatory cascades. TRP receptors are expressed by sensory nerves as well as by keratinocytes. They play a role in vasoregulation, pain perception, and inflammation, and are upregulated in patients with rosacea [2].

In addition, microorganisms are thought to be etiopathogens in rosacea, although their role has yet to be clearly defined. A number of studies have documented differences in the skin microbial composition of rosacea patients as compared to those without. Specifically, rosacea patients have higher concentrations of *Demodex folliculorum*, a saprophytic mite that is normally found in sebaceous glands. It is hypothesized that the cell-membrane components of *Demodex* mites activate toll-like receptor 2 (TLR2), which increases KLK5 expression and activity [6]. However, this is not considered the only likely pathogen, as one study found that when *D. folliculorum* colonization was decreased using topical antibiotics, there was no corresponding improvement in symptoms [7]. As antibiotics have been used in the treatment of rosacea, researchers have theorized that bacteria may be a causative factor. *Bacillus oleronius*, a nonmotile, gram-negative bacterium isolated from *Demodex* mites, has been shown to induce antigenic proteins in patients with specific rosacea subtypes [8,9]. When exposed to *B. oleronius*, neutrophils have increased production of matrix metalloproteinase (MMP)-9, tumor necrosis factor, and IL-8, stimulating a robust inflammatory response even in people unaffected by rosacea [2,8,10]. Other studies have looked at the role of *Staphylococcus epidermidis*, a commensal bacterium. In normal skin, *S. epidermidis* produces AMPs that help prevent disease caused by pathogenic bacteria. When placed on skin with rosacea, however, studies have demonstrated that *S. epidermidis* generates specific virulence factors resulting in TLR2 activation and the cathelicidin-KLK5 inflammatory cascade [6].

Triggers

Anecdotally, there are many triggers that may exacerbate rosacea symptoms. These include hot temperatures, sun exposure, spicy foods, alcohol consumption, exercise, and feelings of anger or embarrassment. Some of these triggers, such as hot temperatures, act directly to trigger vasodilatation. Other factors act via different mechanisms, with an ultimate increase in skin inflammation.

Sun exposure is one of the most commonly cited triggers for flushing and worsening of rosacea symptoms. Exacerbations from ultraviolet (UV) radiation are thought to be the result of three processes. First, vitamin D induces keratinocyte cathelicidin overexpression, which then initiates a pro-inflammatory cascade. Secondly, UVB light increases skin vasculature proliferation via fibroblast growth factor 2 (FGF2) and vascular endothelial growth factor 2 (VEGF2) [11]. Lastly, skin exposed to excess UV radiation has more reactive oxygen species (ROS), further propagating the KLK5-cathelicidin inflammatory cascade [10]. These proposed mechanisms may help guide dietary recommendations to ameliorate these changes.

Dietary triggers are also frequently cited by patients, although there is a lack of research in this area. In one survey by the National Rosacea Society of over 400 patients, 78% had altered their diet due to rosacea. Of this group, 95% reported a subsequent reduction in flares [12].

The triggers reported in this group may be broken down into heat-related, alcohol-related, capsaicin-related, and cinnamaldehyde-related. Specifically, hot beverages acted as

a trigger, including hot coffee (33% described it as a trigger) and hot tea (30%). Alcohol was another frequent trigger, including wine (52%) and hard liquor (42%). Capsaicin is found in certain spices and peppers. Respondents frequently reported spices as a trigger (75%), as well as hot sauce (54%), cayenne pepper (47%), and red pepper (37%). Finally, cinnamaldehyde is found in several seemingly unrelated foods, including tomatoes, citrus, cinnamon, and chocolate [13]. In this survey, cinnamaldehyde-containing foods were also described as frequent triggers, including tomatoes (30%), chocolate (23%), and citrus (22%).

As discussed in the preceding section, transient receptor potential (TRP) channels are one possible pathogenic mechanism in rosacea. Various stimuli can activate TRP channels and cause increased skin blood flow via neurogenic vasodilatation leading to symptoms of flushing and burning [14]. Sulk et al. found that several of the vanilloid channels (TRPV1-6) are active in patients with rosacea [5]. Located in keratinocytes, neuronal, endothelial, and immune cells [15], vanilloid receptors are activated by increased temperatures and capsaicin [16], which results in vasodilation and inflammation-induced hyperalgesia [14,17]. Similarly, TRPA1 is an ankyrin receptor located primarily in sensory neurons. Activated by mustard oil and cinnamaldehyde, TRPA1 regulates vasodilation and may be responsible for flushing episodes [18,19].

The Gut-Skin Connection

Increased Risk of GI Disease in Rosacea Patients

Research indicates the possible role of a gut-skin connection in rosacea. In a population-based cohort study of close to 50,000 Danish patients with rosacea, the prevalence of celiac disease, Crohn's disease, ulcerative colitis, *Helicobacter pylori* infection (HPI), small intestinal bacterial overgrowth (SIBO), and irritable bowel syndrome were all higher among patients with rosacea as compared with control subjects [20].

Others have looked at this connection as well, with conflicting results noted in different populations and for different conditions.

In the case of HPI, several studies have reported a higher frequency in patients with rosacea [21-25]. *H. pylori* are gram-negative bacteria that may cause chronic gastritis, gastric and duodenal ulcers, and gastric adenocarcinoma. Numerous studies have indicated improvement of rosacea symptoms following *H. pylori* eradication [2,23,26-29]. However, the pathogenic link is difficult to establish, as antibiotics are helpful in the treatment of each disease [2,29].

In the case of SIBO, two separate studies found an increased association of SIBO in patients with rosacea, although a prospective study by Gravina et al. did not confirm these results [23,27-30].

The association between inflammatory bowel disease (IBD) and rosacea is another topic of interest. A Taiwanese nationwide cohort study of over 89,000 patients with rosacea found an independent association with IBD incidence, as compared to matched controls [31]. This association has been replicated by Egeberg et al.'s Danish study and Li et al.'s prospective study in American women [30,32]. Moreover, both IBD and rosacea share possible genetic overlap on the histocompatibility complex class II gene HLA DRB1*03:01 [33,34].

From a clinical standpoint, rosacea patients reporting gastrointestinal (GI) symptoms warrant referral to a specialist for further evaluation. Both *H. pylori* and SIBO can be diagnosed with non-invasive laboratory tests including urine, fecal and breath tests. Specifically, SIBO can be detected using a lactulose and glucose H2/CH4 breath test [27,35,36], although reports indicate a wide range of sensitivity and specificity [37]. Similarly, *H. pylori* can be diagnosed with noninvasive urea breath tests, stool antigen test, and serum/urine antibody tests [38]. The urea breath test, in particular, has a high reported sensitivity and specificity [39].

While studies on GI interventions as therapies for rosacea are limited, given the evidence for a gut-skin connection, such interventions provide a promising avenue for further research. These findings also suggest that dietary measures to decrease the risk of GI comorbidities may become standard recommendations in the future.

The GI System as a Therapeutic Target

The association between GI disease and rosacea is intriguing, as it suggests avenues for therapeutic intervention. In one study, researchers found that patients with rosacea were 13 times more likely to have SIBO. They theorized that circulating cytokines, particularly TNF-α, may have played a role in the increased prevalence of rosacea. Treatment of the SIBO with antibiotics in 40 patients led to remission of rosacea in all cases. Even more remarkable was the finding that the remission persisted in the majority at the three-year follow-up [40].

In addition, SIBO has been linked to decreased gut motility. In one case report, a reduction of gut transit time via a high-fiber intervention resulted in improvement of rosacea [41], suggesting another promising area of investigation.

Prebiotics, Probiotics, and the Role of the Microbiome

Given the evidence for an increased risk of GI disease in rosacea, further research into the role of the microbiome in rosacea is warranted. The role of the gut microbiome is an area of research of multiple inflammatory skin diseases. Synbiotics are a combination of prebiotics and probiotics, substances

that support a healthy gut microbiome. In a meta-analysis of published randomized controlled trials (RCTs) in atopic dermatitis (AD), it was found that the use of synbiotics for at least eight weeks had a significant effect on a measure of AD severity [42]. Research is underway into the use of synbiotics in other inflammatory skin diseases.

The Microbiome

There has been much research into the gut microbial community, known as the microbiota, along with its component genes, known as the microbiome [43]. The human microbiome shows marked variation among individuals, and can be impacted by multiple factors, including diet. Research is underway to explore the role of the microbiome as an important regulator in human immunity and as an instigator of disease.

The human microbiome is comprised of multifaceted microbial communities that colonize the human body. The implication of the microbiome in human disease has been an increasing topic of research. The Human Microbiome Project, established in 2008, seeks to characterize the human microbiome and its role in human health and disease [44,45]. In the GI tract, the microbiome is made up of trillions of microbes including bacteria and other microbes such as fungi and archaea [46]. The skin is also colonized by an equally complex microbiome that varies with host genetic and environmental influences. Emerging research suggests that the collection of microbial communities that populate the skin and GI tract, rather than single microorganisms alone, is responsible for disease [47].

The gut microbiome plays an important role in training both the innate and adaptive immune systems. In a mouse model, it was found that specific strains of gut microbiota regulated the expression of genes that impacted intestinal barrier function and immunity, among other effects [48]. Given these effects, the gut microbiome has the potential to affect many organ systems, including the skin.

The composition of intestinal bacteria has been postulated to play a role in the pathogenesis of rosacea. In one theory, dysbiosis of intestinal bacteria results in activation of plasma kallikrein-kinin pathways, leading to downstream neurogenic inflammation [41]. Some authors have suggested that this may, in part, explain the effectiveness of antibiotics in rosacea therapy [31]. While the microbiome represents an important therapeutic target, it is important to recognize the marked variation of human intestinal microbiome among individuals. Factors that may account for these differences include genetics, diet, environmental exposures, hygiene, and other variables. Notable geographical variations have been seen in gut microbiome composition, warranting further research of gut composition in global communities [49].

Dietary Measures to Promote a Healthy Gut Microbiome

Prebiotics and Dietary Fiber

Recommendations to promote a healthy gut microbiome include the consumption of a fiber-rich diet. Many dietary plant fibers act as prebiotics. Prebiotics have been defined as non-digestible food ingredients that selectively stimulate the growth and/or activity of beneficial GI microbes [50]. Research indicates that consuming a wide variety of dietary fibers, in sufficient quantity, will encourage the growth of a diverse and a healthy gut microbiome [46,51].

Studies indicate that dietary effects on the microbiome may occur rapidly [43]. A lack of dietary fiber has been linked to deleterious effects on the gut flora and the gut itself. In one study, mice fed a diet lacking in fiber experienced a proliferation of pathogenic bacteria. These bacteria then began to digest the protective gut mucus layer [52]. In contrast, a diet rich in plant fibers supports the growth of beneficial microbes. These beneficial microbes have been shown to support gut health and skin health in multiple ways.

Probiotics

The growth of beneficial microbes in the GI tract may be encouraged by diet. Such microbes may also be consumed in the form of probiotics. The Food and Agriculture Organization of the United Nations (FAO) and World Health Organization (WHO) define probiotics as "live microorganisms which when administered in adequate amounts confer a health benefit on the host" [53].

Probiotic foods and supplements are worth further study, although at this time clinical trials in rosacea are lacking. Probiotic foods include fermented foods in which live active microbial communities are a key component. This includes such foods as yogurt, kefir, miso, kimchi, and sauerkraut. A number of retail probiotic food products have been developed in which live microbes are added to food products, although studies suggest that many contain a lower number and diversity of microbes [54]. A number of probiotic supplements are sold as well, with marked differences in variety and type of microbes, as well as dosages.

Further research is necessary to determine optimal dosages and strains of microbes, as well as to determine viability of ingested microbes. Despite some promising results in other inflammatory skin diseases, clinical trials in rosacea are lacking. However, research has suggested potential mechanisms whereby probiotics may be helpful in rosacea therapy. First, they shift the composition of gut bacteria and help to counter pathogenic bacteria. An imbalance of gut microbiota has been linked to IBD, as well as other chronic diseases [55]. Studies have demonstrated anti-inflammatory effects, as in the alleviation of T-cell mediated skin inflammation in mice

following use of oral probiotic bacteria [56]. In addition, in vitro incubation of metabolites from a particular probiotic strain prevented both unprompted and stress-induced ROS formation [57]. Finally, probiotic bacteria may impact the skin barrier. In one RCT, use of an oral probiotic resulted in improvement in skin barrier function and reduced skin sensitivity in human subjects [58].

Given these demonstrated cutaneous effects of probiotics, as well as their suggested efficacy in other inflammatory skin diseases, further research into their clinical use is warranted.

Specific Dietary Nutrients

At this time, there is no convincing evidence that specific nutrients act to alleviate rosacea symptoms. However, promising results from a few studies support the utility of further research into the effects of omega-3 fatty acids and zinc.

Omega-3 fatty acids are polyunsaturated fatty acids and include eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and alpha linolenic acid (ALA). As EPA and DHA are substrates for anti-inflammatory prostaglandins that competitively inhibit pro-inflammatory pathways, they have been studied in multiple diseases [59]. Limited research is available for their use in rosacea, although one RCT found a statistically significant improvement in subjects with dry eye symptoms, some of whom had rosacea, with the use of 325 mg of EPA and 175 mg of DHA two times daily for three months [60].

Limited trials have evaluated the use of zinc in rosacea [61]. Zinc is fundamental for development of the cell-mediated innate immune system and acts as an antioxidant and anti-inflammatory molecule. Studies on zinc supplementation in rosacea have produced conflicting results. While one trial noted significant improvement with 100 mg of zinc sulfate three times a day [62], another found no difference in improvement after 90 days of 220 mg of zinc sulfate twice a day [63].

Other Comorbidities

While the association of cardiovascular disease (CVD) and chronic inflammatory diseases, such as rheumatoid arthritis and psoriasis, is well established, the risk of CVD in rosacea is not clear. In psoriasis, dietary modification to decrease the risk of comorbidities is now considered an important aspect of therapy, given the increased risk of CVD as well as metabolic diseases such as diabetes and hypertension [1,3].

A number of studies have examined this risk in rosacea patients. In one case-control study, patients with rosacea had an increased risk of CVD [3]. The authors hypothesized that cathelicidin peptides and serine proteases acted as common etiopathogens for both rosacea and atherosclerosis. However, a Danish case-control study of close to 5,000 patients with rosacea found no increased risk of adverse cardiovascular events [64]. Given these findings, more research is required into the risk of CVD in rosacea patients. If confirmed, then dietary modifications to reduce this risk would be warranted.

Conclusion

Dietary triggers are frequently cited by patients as playing a role in rosacea exacerbations. At this time, patient-reported triggers fall into four categories: heat-related, alcohol-related, capsaicin-related, and cinnamaldehyde-related. One suggested mechanism of action is via activation of TRP channels, which result in neurogenic vasodilation. Diet may also impact rosacea via a gut-skin connection. While epidemiologic research supports this connection, research is underway to determine the pathophysiologic mechanisms. At this time, patients may be advised on measures to promote a healthy gut microbiome, including the importance of a fiber-rich (prebiotic) diet.

References

1. Rainer BM, Fischer AH, Luz Felipe Da Silva D, 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.
2. Two AM, Wu W, Gallo RL, Hata TR. Rosacea: Part I. Introduction, categorization, histology, pathogenesis, and risk factors. *J Am Acad Dermatol.* 2015;72(5):749-758.
3. 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.
4. Yamasaki K, Di Nardo A, Bardan A, et al. Increased serine protease activity and cathelicidin promotes skin inflammation in rosacea. *Nat Med.* 2007;13(8):975-980.
5. Sulk M, Seeliger S, Aubert J, et al. Distribution and expression of non-neuronal transient receptor potential (TRPV) ion channels in rosacea. *J Invest Dermatol.* 2012;132(4):1253-1262.
6. Ferrer L, Ravera I, Silbermayr K. Immunology and pathogenesis of canine demodicosis. *Vet Dermatol.* 2014;25(5):427-e65.
7. Koçak M, Yağli S, Vahapoğlu G, Ekşioğlu M. Permethrin 5% cream versus metronidazole 0.75% gel for the treatment of papulopustular rosacea: a randomized double-blind placebo-controlled study. *Dermatology.* 2002;205(2-3):265-270.
8. O'Reilly N, Menezes N, Kavanagh K. Positive correlation between serum immunoreactivity to Demodex-associated Bacillus proteins and erythematotelangiectatic rosacea. *Br J Dermatol.* 2012;167(5):1032-1036.
9. Li J, O'Reilly N, Sheha H, et al. Correlation between ocular Demodex infestation and serum immunoreactivity to bacillus proteins in patients with facial rosacea. *Ophthalmology.* 2010;117(5):870-877.e1.
10. Yamasaki K, Gallo RL, Li G, et al. The molecular pathology of rosacea. *J Dermatol Sci.* 2009;55(2):77-81.
11. Bielenberg DR, Bucana CD, Sanchez R, et al. Molecular regulation of UVB-induced cutaneous angiogenesis. *J Invest Dermatol.* 1998;111(5):864-872.

12. Drake L. Hot sauce, wine and tomatoes cause flare-ups, survey finds Rosacea.org. https://www.rosacea.org/rr/2005/fall/article_3.php. Accessed June 7, 2017.
13. Scheman A, Rakowski EM, Chou V, Chhatriwala A, Ross J, Jacob SE. Balsam of Peru: past and future. *Dermatitis*. 2013;24(4):153-160.
14. Aubdool AA, Brain SD. Neurovascular aspects of skin neurogenic inflammation. *J Investig Dermatol Symp Proc*. 2011;15(1):33-39.
15. Pecze L, Szabó K, Széll M, et al. Human keratinocytes are vanilloid resistant. *PLoS ONE*. 2008;3(10):e3419.
16. Caterina MJ, Schumacher MA, Tominaga M, Rosen TA, Levine JD, Julius D. The capsaicin receptor: a heat-activated ion channel in the pain pathway. *Nature*. 1997;389(6653):816-824.
17. Earley S. Vanilloid and melastatin transient receptor potential channels in vascular smooth muscle. *Microcirculation*. 2010;17(4):237-249.
18. Campbell TM, Neems R, Moore J. Severe exacerbation of rosacea induced by cinnamon supplements. *J Drugs Dermatol*. 2008;7(6):8-10.
19. Pozsgai G, Bodkin J V, Graepel R, Bevan S, Andersson DA, Brain SD. Evidence for the pathophysiological relevance of TRPA1 receptors in the cardiovascular system in vivo. *Cardiovasc Res*. 2010;87(4):760-768.
20. Egeberg A, Weinstock LB, Thyssen EP, Gislason GH, Thyssen JP. Rosacea and gastrointestinal disorders: a population-based cohort study. *Br J Dermatol*. 2017;176(1):100-106.
21. Argenziano G, Donnarumma G, Iovene MR, Arnese P, Baldassarre MA, Baroni A. Incidence of anti-Helicobacter pylori and anti-CagA antibodies in rosacea patients. *Int J Dermatol*. 2003;42(8):601-604.
22. Diaz C, O'Callaghan CJ, Khan A, Ilchyshyn A. Rosacea: a cutaneous marker of Helicobacter pylori infection? Results of a pilot study. *Acta Derm Venereol*. 2003;83(4):282-286.
23. Gravina A, Federico A, Ruocco E, et al. Helicobacter pylori infection but not small intestinal bacterial overgrowth may play a pathogenic role in rosacea. *United Eur Gastroenterol J*. 2015;3(1):17-24.
24. Gürer MA, Erel A, Erbaş D, Çağlar K, Atahan Ç. The seroprevalence of Helicobacter pylori and nitric oxide in acne rosacea. *Int J Dermatol*. 2002;41(11):768-770.
25. Zandi S, Shamsadini S, Zahedi MJ, Hyatbaksh M. Helicobacter pylori and rosacea. *East Mediterr Health J*. 2003; 9(1-2):167-171.
26. Boixeda de Miquel D, Vázquez Romero M, Vázquez Sequeiros E, et al. Effect of Helicobacter pylori eradication therapy in rosacea patients. *Rev Esp Enferm Dig*. 2006;98(7):501-509.
27. Parodi A, Paolino S, Greco A, et al. Small intestinal bacterial overgrowth in rosacea: clinical effectiveness of its eradication. *Clin Gastroenterol Hepatol*. 2008;6(7):759-764.
28. Szlachcic A. The link between Helicobacter pylori infection and rosacea. *J Eur Acad Dermatol Venereol*. 2002;16(4):328-333.
29. Tüzün Y, Keskin S, Kote E. The role of helicobacter pylori infection in skin diseases: Facts and controversies. *Clin Dermatol*. 2010;28(5):478-482.
30. Egeberg A, Weinstock LB, Thyssen EP, Gislason GH, Thyssen JP. Rosacea and gastrointestinal disorders— a population-based cohort study. *Br J Dermatol*. 2016:1-7.
31. Wu C-Y, Chang Y-T, Juan C-K, et al. Risk of inflammatory bowel disease in patients with rosacea: Results from a nationwide cohort study in Taiwan. *J Am Acad Dermatol*. 2017;(155):1-7.
32. Li WQ, Cho E, Khalili H, Wu S, Chan AT, Qureshi AA. Rosacea, use of tetracycline, and risk of incident inflammatory bowel disease in women. *Clin Gastroenterol Hepatol*. 2016;14(2):220-225.e3.
33. Chang ALS, Raber I, Xu J, et al. Assessment of the genetic basis of rosacea by genome-wide association study. *J Invest Dermatol*. 2015;135(6):1548-1555.
34. Goyette P, Boucher G, Mallon D, et al. High-density mapping of the MHC identifies a shared role for HLA-DRB1*01:03 in inflammatory bowel diseases and heterozygous advantage in ulcerative colitis. *Nat Genet*. 2015;47(2):172-179.
35. Riordan SM, McIver CJ, Walker BM, Duncombe VM, Bolin TD, Thomas MC. The lactulose breath hydrogen test and small intestinal bacterial overgrowth. *Am J Gastroenterol*. 1996;91(9):1795-1803.
36. Rezaie A, Buresi M, Lembo A, et al. Hydrogen and methane-based breath testing in gastrointestinal disorders: the North American consensus. *Am J Gastroenterol*. 2017;112(5):775-784.
37. Khoshini R, Dai S-C, Lezcano S, Pimentel M. A systematic review of diagnostic tests for small intestinal bacterial overgrowth. *Dig Dis Sci*. 2008;53(6):1443-1454.
38. Gong Y, Li Q, Yuan Y. Accuracy of testing for anti-Helicobacter pylori IgG in urine for H. pylori infection diagnosis: a systematic review and meta-analysis. *BMJ Open*. 2017;7(4):e013248.
39. Zhou Q, Li L, Ai Y, Pan Z, Guo M, Han J. Diagnostic accuracy of the 14C-urea breath test in Helicobacter pylori infections: a meta-analysis. *Wien Klin Wochenschr*. 2017;129(1-2):38-45.
40. Drago F, De Col E, Agnoletti AF, et al. The role of small intestinal bacterial overgrowth in rosacea: a 3-year follow-up. *J Am Acad Dermatol*. 2016;75(3):e113-e115.
41. Kendall SN. Remission of rosacea induced by reduction of gut transit time. *Clin Exp Dermatol*. 2004;29(3):297-299.
42. Chang Y-S, Trivedi MK, Jha A, Lin Y-F, Dimaano L, García-Romero MT. Synbiotics for prevention and treatment of atopic dermatitis. *JAMA Pediatr*. 2016;170(3):236.
43. Turnbaugh PJ, Ridaura VK, Faith JJ, Rey FE, Knight R, Gordon JI. The effect of diet on the human gut microbiome: a metagenomic analysis in humanized gnotobiotic mice. *Sci Transl Med*. 2009;1(6):6ra14-6ra14.
44. Turnbaugh PJ, Ley RE, Hamady M, Fraser-Liggett CM, Knight R, Gordon JI. The human microbiome project. *Nature*. 2007;449(Oct):804-810.
45. Arumugam M, Raes J, Pelletier E, et al. Enterotypes of the human gut microbiome. *Nature*. 2011;473(7346):174-180.
46. Holscher HD. Dietary fiber and prebiotics and the gastrointestinal microbiota. *Gut Microbes*. 2017;8(2):172-184.
47. Picardo M, Ottaviani M. Skin microbiome and skin disease the example of rosacea. *J Clin Gastroenterol*. 2014;48:S85-86.
48. Hemarajata P, Versalovic J. Effects of probiotics on gut microbiota: mechanisms of intestinal immunomodulation and neuromodulation. *Therap Adv Gastroenterol*. 2013;6(1):39-51.
49. Gupta VK, Paul S, Dutta C. Geography, ethnicity or subsistence-specific variations in human microbiome composition and diversity. *Front Microbiol*. 2017;23;8:162.
50. Gibson GR, Scott KP, Rastall RA, et al. Dietary prebiotics: current status and new definition. *Food Sci Technol Bull Funct Foods*. 2010;7(1):1-19.
51. El Kaoutari A, Armougom F, Gordon JI, Raoult D, Henrissat B. The abundance and variety of carbohydrate-active enzymes in the human gut microbiota. *Nat Rev Microbiol*. 2013;11(7):497-504.
52. Desai MS, Seekatz AM, Koropatkin NM, et al. A dietary fiber-deprived gut microbiota degrades the colonic mucus barrier and

enhances pathogen susceptibility. *Cell.* 2016;167(5):1339-1353.e21.
53. Hill C, Guarner F, Reid G, et al. Expert consensus document: The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. *Nat Rev Gastroenterol Hepatol.* 2014;11(8):506-514.
54. Scourboutakos MJ, Franco-Arellano B, Murphy SA, Norsen S, Comelli EM, L'Abbé MR. Mismatch between probiotic benefits in trials versus food products. *Nutrients.* 2017;9(4):400.
55. Kober M, Bowe WP. The effect of probiotics on immune regulation, acne, and photoaging. *Int J Womens Dermatol.* 2015;1(2):85-89.
56. Hacini-Rachinel F, Gheit H, Le Luduec JB, Dif F, Nancey S, Kaiserlian D. Oral probiotic control skin inflammation by acting on both effector and regulatory T cells. *PLoS One.* 2009;4(3):e4903.
57. Benson KF, Redman KA, Carter SG, et al. Probiotic metabolites from Bacillus coagulans GanedenBC30TM support maturation of antigen-presenting cells in vitro. *World J Gastroenterol.* 2012;18(16):1875-1883.
58. Gueniche A, Benyacoub J, Philippe D, et al. Lactobacillus paracasei CNCM I-2116 (ST11) inhibits substance P-induced skin inflammation and accelerates skin barrier function recovery in vitro. *Eur J Dermatol.* 2010;20(6):731-737.
59. Maroon JC, Bost JW. Omega-3 fatty acids (fish oil) as an anti-inflammatory: An alternative to nonsteroidal anti-inflammatory drugs for discogenic pain. *Surg Neurol.* 2006;65(4):326-331.
60. Bhargava R, Kumar P, Kumar M, Mehra N, Mishra A. A randomized controlled trial of omega-3 fatty acids in dry eye syndrome. *Int J Ophthalmol.* 2013;6(6):811-816.
61. Prasad AS. Zinc: role in immunity, oxidative stress and chronic inflammation. *Curr Opin Clin Nutr Metab Care.* 2009;12(6):646-652.
62. Sharquie KE, Najim RA, Al-Salman HN. Oral zinc sulfate in the treatment of rosacea: a double-blind, placebo-controlled study. *Int J Dermatol.* 2006;45(7):857-861.
63. Bamford JTM, Gessert CE, Haller IV, Kruger K, Johnson BP. Randomized, double-blind trial of 220 mg zinc sulfate twice daily in the treatment of rosacea. *Int J Dermatol.* 2012;51(4):459-462.
64. Egeberg A, Hansen PR, Gislason GH, Thyssen JP. Assessment of the risk of cardiovascular disease in patients with rosacea. *J Am Acad Dermatol.* 2016;75(2):336-339.