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Laurenz Schmitt
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The impact of clinical nutrition on inflammatory skin diseases

Anne Gürtler[1], Laurenz Schmitt[2]
(1) Department for Dermatology and Allergy, University Hospital Munich, LMU, Munich, Germany
(2) Department of Dermatology and Allergology, University Hospital Aachen, Germany

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Prof. Dr. Trautinger, St. Pölten

Summary

The influence of nutrition on the pathophysiology and clinical severity of inflammatory facial dermatoses such as acne, rosacea, seborrheic dermatitis, and perioral dermatitis has been controversially discussed for years. As part of a modern treatment approach, clinicians should provide patients with information on how their choice of diet might impact their dermatologic diagnosis and could potentially enhance therapeutic outcome. Recently, the concept of a gut-skin axis has gained momentum in the understanding of inflammatory dermatoses, with nutrition considered a contributing factor in this context. For example, gastrointestinal symptoms in rosacea patients may indicate a dysbiosis of the gut microbiome, treatment of which may also improve severity of the skin disease. New research efforts were recently made for acne patients addressing the clinical effects of omega-3 fatty acids and probiotics. In contrast, due to the limited data available, no comparable specific dietary recommendations can yet be made for seborrheic or perioral dermatitis. However, there are promising signs that clinical nutrition and dermatology will be more extensively interlinked in the future, both clinically and scientifically.

Introduction

Clinical nutrition is a multidisciplinary field that, like pain medicine, is becoming an integral part of all clinical fields of medicine. It transcends the traditional understanding of nutrition as supplying the human body with macronutrients (carbohydrates, lipids, proteins) and micronutrients (vitamins, trace elements), and considers nutrition an important factor for the prevention and treatment of disease [1].

In internal medicine, evidence based nutritional advice for diseases like obesity, diabetes mellitus, hyperlipidemia, and coronary heart disease (CHD) is already part of the therapeutic gold standard. The impact of nutrition on the development and progression of dermatological diseases, on the other hand, is usually not much considered in clinical practice, and nutritional advice is rarely given. In reality, nutrition may play an important role in many dermatoses. Examples include vitamin deficiencies such as scurvy and pellagra, nowadays only encountered in medical textbooks for those living in industrialized countries, cutaneous manifestations of immune-mediated gastroenterological diseases such as dermatitis herpetiformis Duhring, and acne vulgaris, the most common dermatologic disease of all.

The very first dermatologic textbook by Daniel Turner (1667–1741) actually contained nutritional advice for acne patients [2]. During the last few decades, the impact of nutrition on various dermatoses has been a controversial issue. An epidemiological study by Cordain et al. in 2002 strikingly showed that as compared

with indigenous peoples in Paraguay and Papua New Guinea, inflammatory skin diseases such as acne vulgaris were significantly more common in Western industrialized countries [3]. The authors stated that the paleolithic nutrition of the indigenous peoples, without heavily processed grains and dairy, had a protective effect, while the so-called Western diet was considered acne-promoting.

Nutrition, stress, sleep quality, and climatic changes are nowadays subsumed as "Exposome factors". Exposome factors comprise all non-genetic environmental influences that humans are exposed to over the course of their lives. They also influence the development of dermatological diseases and should not be underestimated by medical practitioners [4, 5].

The following article offers an overview of up-to-date evidence in nutritional medicine for inflammatory dermatoses. Herby, both evidence-based nutritional factors as well as limitations of the current study situation are outlined and advice for everday clinical practice is given (Table S1, online Supporting Information).

The concept of the gut-skin axis

The microbiome is defined as the total of all microorganisms and their genes, with the largest portion represented by bacteria, followed by viruses, fungi, and protozoa. This dynamic system is individually unique, it can adapt to changing environments within a few hours, and is influenced by environmental factors [6]. In the last decade, the microbiome, especially in the gut, has been identified as an immune-regulating system [7]. Nutrition is considered an important regulator of the gut microbiome [8, 9]. A varied, plant-focused diet with a high content of dietary fiber is key for a diverse and balanced gut microbiome [6, 10]. Disorders of the microbial balance may have a significant impact on the host's immune system and thus on the development and progression of diseases [11]. Nutritional recommendations for protective microbial strains in the gut include pulses, seeds, nuts, roots, vegetables, and fruit [12].

A possible connection between the gut microbiome and the skin microbiome was first suggested in 1930 by dermatologists John H. Stokes and Donald M. Pillsbury [13, 14]. They assumed a connection between the psyche, the gut flora, and the development of skin diseases [15]. Nowadays, numerous and complex interactions have been identified between the intestinal and cutaneous flora and vegetative innervation, characterized as the gut-skin axis [16, 17]. However, this complex and multidirectional interaction is not yet fully understood [18]. If the gut barrier is compromised, pathogenic microbiota and their metabolites appear to enter the circulation and alter the skin microbiome. These include phenols, bioactive toxins, and markers for a disrupted gut milieu [19, 20]. *In vitro* studies have shown that phenols impair keratinocyte differentiation by reducing the expression of keratin 10. This may compromise the integrity of the epidermal barrier [21, 22] (Figure 1).

An impaired balance in the composition of the gut and skin microbiome, called dysbiosis, appears to be present in many patients with inflammatory skin diseases [15, 23]. Since antibiotics are frequently used for inflammatory facial dermatoses which may further impair the balance of the gut microbiome, they should be prescribed with restraint [24].

Acne

Acne vulgaris, an inflammatory disease of the pilosebaceous follicles, is the most common dermatosis world-wide, with an exceedingly high prevalence in

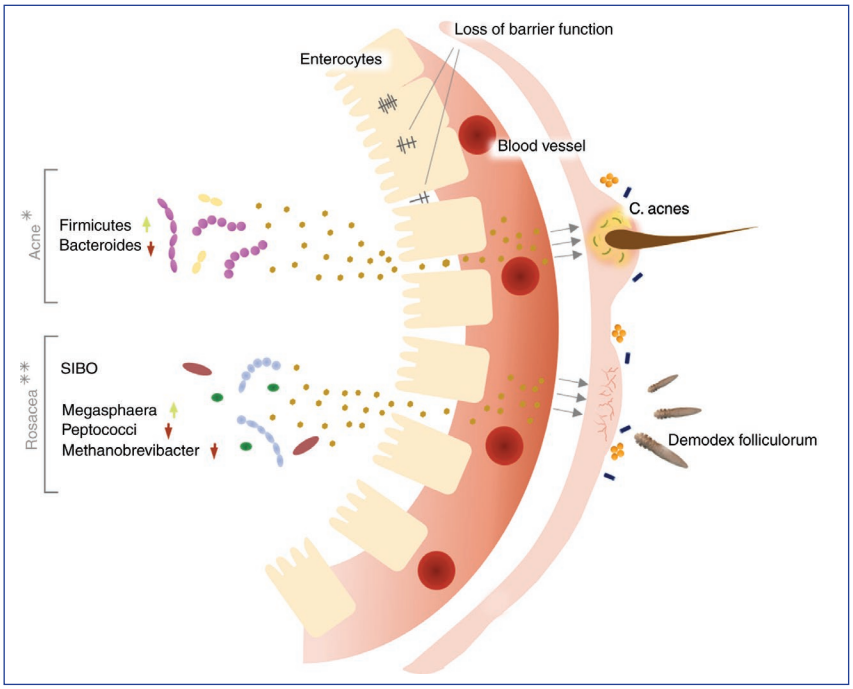

Figure 1 The concept of the gut-skin axis describes the bidirectional interaction between intestinal and cutaneous microbiota. An intestinal dysbiosis (left) may lead to a disturbed intestinal barrier (center), which can contribute to the development and progression of skin diseases such as acne vulgaris and rosacea. Nutrition is considered an important regulator of the gut microbiome in this regard.
Abbr.: C. acnes, Cutibacterium acnes; SIBO, small intestinal bacterial overgrowth
*[20, 121], **[96, 122, 123].

adolescents in the Western industrialized [25]. Acne shows a multifactorial origin with increased androgenic sebaceous gland activity resulting in seborrhea, hyperkeratosis and impaired differentiation of the follicular ostia, release of inflammatory mediators, and hypercolonization of the sebum with *cutibacterium (c.) acnes* [26, 27]. (Figure 2a) As opposed to other inflammatory facial dermatoses, the impact of nutrition on the development and clinical severity of acne has been clearly proven in randomized, controlled interventional studies [28] (Table S1, online Supporting Information).

Today, Melnik et al. consider acne a disease of western civilization, like obesity and coronary heart disease [29]. The abovementioned Western nutrition is thought to play an important role [28, 30]. It is characterized by a high consumption of saccharose (a disaccharide consisting of glucose and fructose), often hidden in industrial foods, as well as consumption of highly processed cereals, large amounts of milk and dairy products, and saturated fats (Figure 3). These components cause significant releases of insulin and insulin like growth factor 1 (IGF-1, somatomedin C) [31]. Insulin like growth factor 1 is produced in the liver and promotes anabolic pathways via membrane-bound IGF receptors. High IGF-1 levels are particularly important for growth during puberty [32].

In the context of acne, increased IGF-1 levels affect expression of the protein kinase mTORC1 (mammalian target of rapamycin complex 1) [33]. The levels of IGF-1 in serum appear to correlate with the clinical severity of the disease [33] (Figure 4).

The influence of IGF-1 on the development of acne can be seen in patients with Laron syndrome. These patients have a genetic disorder of the growth hormone receptor (GHR) with a congenital deficiency of IGF-1. The clinical appearance of Laron syndrome includes growth deficiency, facial malformations, and delayed puberty. Interestingly, these patients have neither acne nor diabetes mellitus. After therapeutic supplementation with IGF-1 to promote growth, patients develop acneiform lesions.

IGF-1 and mTORC1 are considered to be the main nutritional mediators of acne.

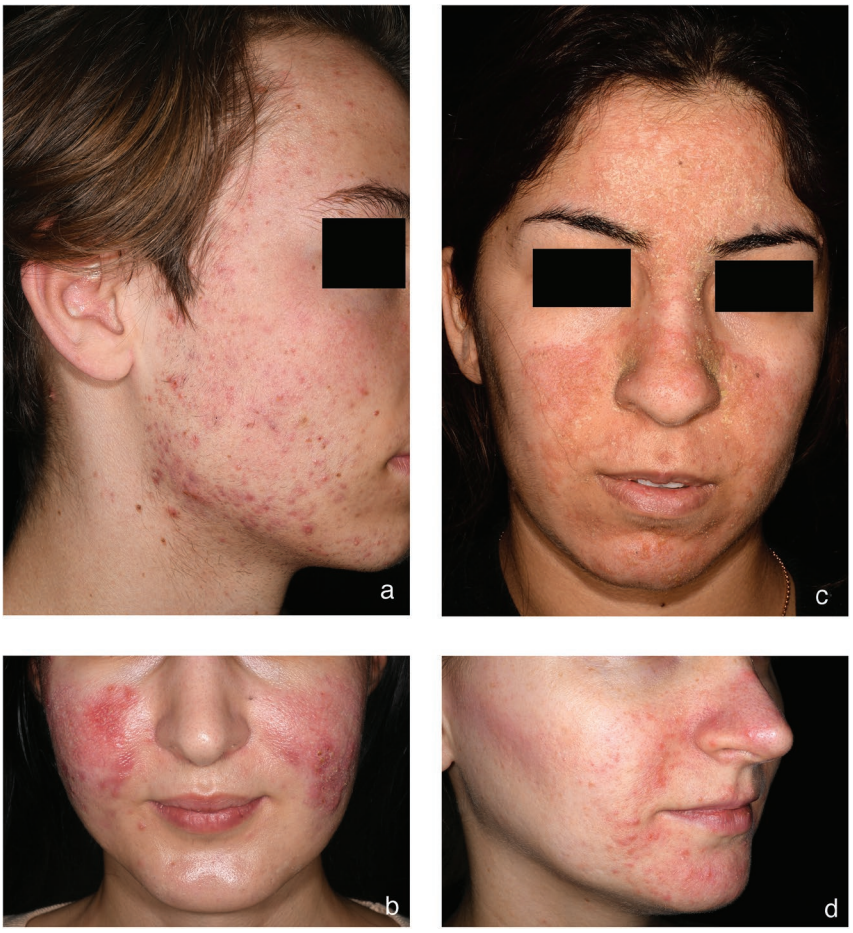

Figure 2 Clinical comparison of inflammatory facial dermatoses: acne vulgaris (a), rosacea (b), seborrheic eczema (c), and perioral dermatitis (d).

Mammalian target of rapamycin complex 1 is a nutrition-sensitive kinase. It is considered to be the main regulator of cell growth in eukaryotic cells and regulates metabolic pathways including lipid biosynthesis. This is accomplished via phosphorylation of the transcription factor SREBP-1 (sterol response element binding protein-1). The regulatory protein SREBP-1 is essential for sebocyte differentiation. Via this mechanism, increased levels of IGF-1 directly increase seborrhea, one of the pathogenetic causes of acne [29].

Apart from direct induction of mTORC1, increased levels of insulin and IGF-1 also increase mTORC1 expression indirectly. Via activation of the phosphoinositol-3 kinase/Akt signal pathway (PI3K/AKT), phosphorylation leads to nuclear export of the transcription factor FoxO1 (forkhead box protein O1) [34, 35]. In the nucleus, Fox proteins bind to DNA sequences from genes that are essential for cell proliferation and differentiation, thus regulating their transcription. Nuclear export of FoxO1 counteracts the inhibiting function of mTORC1 and indirectly activates the protein kinase [36]. As explained above, this increases seborrhea (Figure 4).

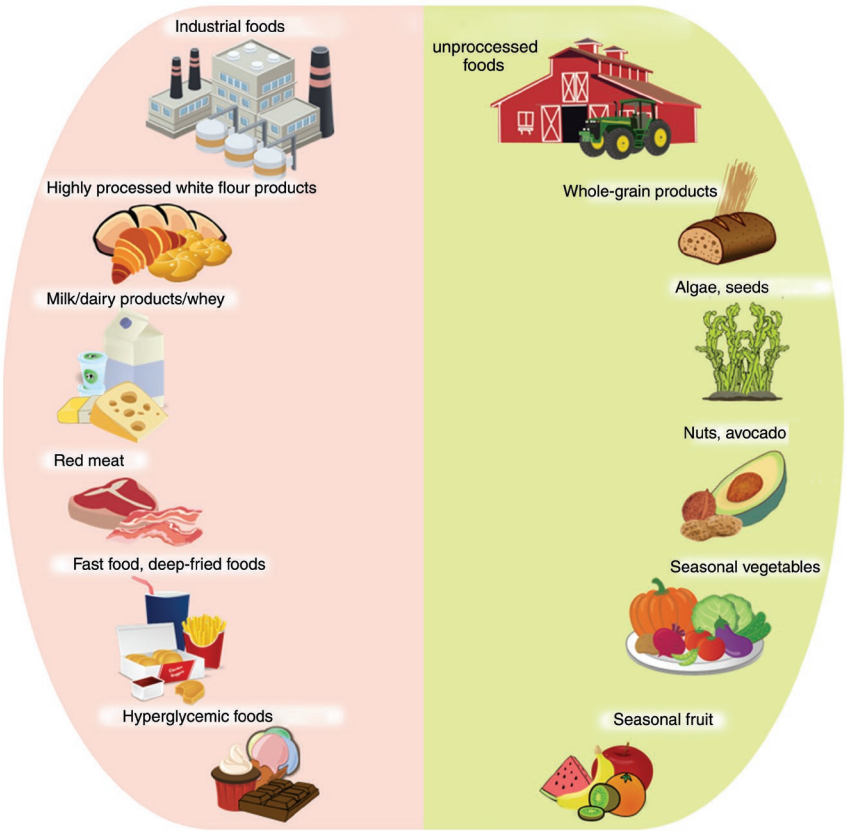

Figure 3 The so-called Western diet, composed of high glycemic, processed foods and dairy products is considered disease promoting for acne (left, red background). Patients should rather focus on unprocessed, seasonal, and plant-derived products (right, green background).

The impact of macronutrients

Carbohydrates

Foods that lead to fast and high increases of blood glucose and insulin have a high glycemic index (GI). These include sweets and soft drinks, but also industrial baked goods made from highly processed flour, and "fast food". These foods have a particularly high glycemic load (GL). A retrospective study with more than 24,000 acne patients showed a striking correlation between clinical severity and consumption of sugary foods and drinks [37]. A dietary change with reduction of the GL, on the other hand, led to clinical improvement of acne and even reduction of pharmacotherapy [38]. In a prospective, randomized, blinded interventional study, Kwon et al. investigated the effect of a ten-week dietary intervention with reduced GL (whole-grain products, vegetables, fruit, fish) and showed clinical improvement of acne with significantly reduced expression of SREBP-1 in biopsies from acne lesions [39]. These effects were confirmed via laboratory chemistry in a randomized, controlled study by Burris et al. They investigated the effect of a low GL diet in adults with moderate to severe acne in comparison with a typical Western diet. After only two weeks, serum concentrations of IGF-1 decreased significantly in the patient group with the low-GL diet [40]. These effects are also seen in clinical practice and correlate with patients' nutrition patterns and clinical appearance.

Glycemic index (GI): Relative rise in blood sugar level assigned to a food compared with 100 g glucose.

Glycemic load (GL): GL takes into account the carbohydrate density of a food. (GI x amount of carbohydrates in the specific food, divided by 100). Boiled carrots and baguette bread, for example, have more or less the same GI (≈ 70), but carbohydrate density in carrots (7.1 g per 100 g) is much lower than in a baguette (51.0 g per 100 g). Baguette bread thus has a significantly higher GL than carrots. Eating 100 g boiled carrots will result in a much lower increase in blood sugar levels than eating 100 g of baguette, though both foods have the same GI [41].

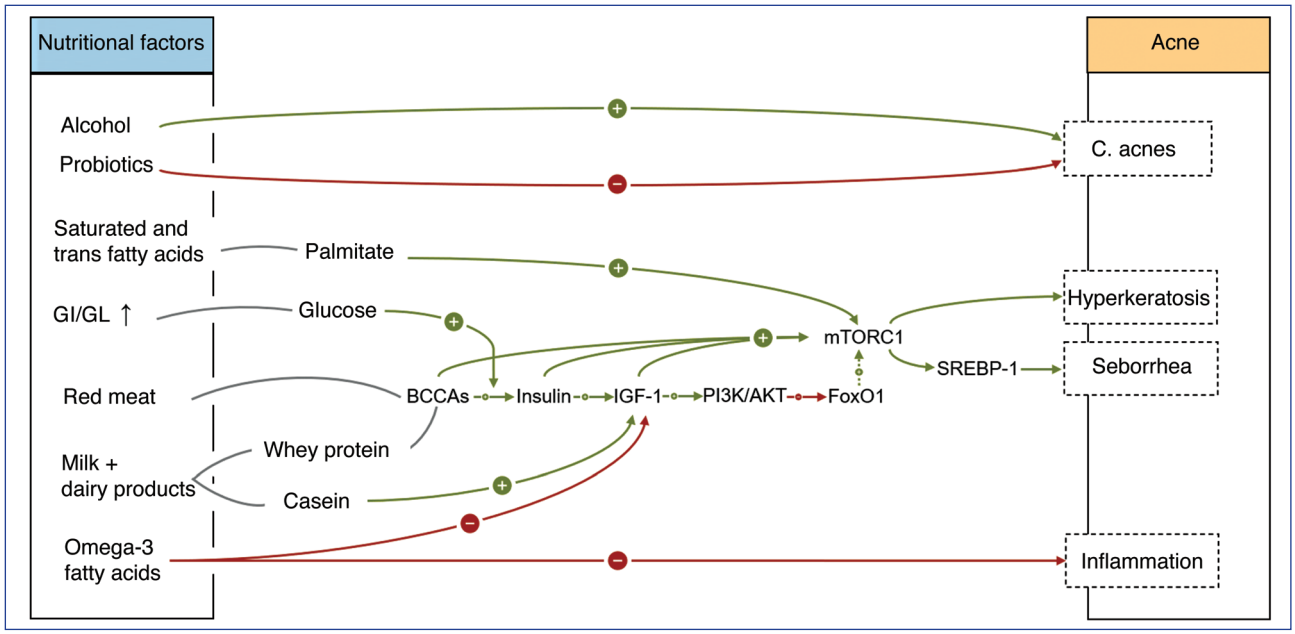

Figure 4 The impact of different foods on the pathogenesis of acne vulgaris.
Abbr.: GI, glycemic index; GL, glycemic load; BCAAs, branched-chain-amino acids; IGF-1, insulin like growth factor 1; PI3K/AKT, phosphoinositol 3-kinase/Akt pathway; FoxO1, forkhead box protein O1; mTORC1, mammalian target of rapamycin complex 1; SREBP-1, sterol response element binding protein-1; C. acnes, Cutibacterium acnes.

Proteins

Cows' milk is used as a base for many dairy products such yoghurt, cream cheese, whipped cream or ice cream. Milk contains lactose (a disaccharide consisting of galactose and glucose), lipids, vitamins, trace elements, and proteins. Especially the protein fraction of cows' milk has pathogenetic relevance for the development of acne since it is strongly insulinotropic [42]. Dairy protein consists mainly of casein as well as some other proteins subsumed as whey. The branched-chain amino acids (BCAA) found in whey, in particular, lead to direct and indirect mTORC1 activation analogous to hyperglycemic foods [43] (Figure 4).

Especially, young male acne patients, frequently consume whey-based protein shakes or BCAA to promote muscle growth when weight training. However, these products not only show an anabolic effect on the muscles but also stimulate the sebocytes [44]. Patients who regularly consume whey protein often display acne on the trunk [45]. Consumption of these food supplements should therefore always be investigated when taking patients' medical history. Alternative protein sources from plants such as peas, rice, or hemp have a different amino acid composition with less BCAA and therefore show less stimulation of the sebaceous glands while still promoting muscle growth [46].

A meta-analysis of studies with more than 78,000 children, adolescents, and young adults showed an impressive correlation between milk consumption and manifestation of acne [42]. Consumption of one glass of milk per day resulted in a significantly higher odds ratio for developing acne compared with one glass of milk per week. Consumption of whole milk showed a lower risk of acne compared with low-fat milk. A meta-analysis performed by Dai et al. also confirms a stronger association between consumption of low-fat milk and acne as compared with

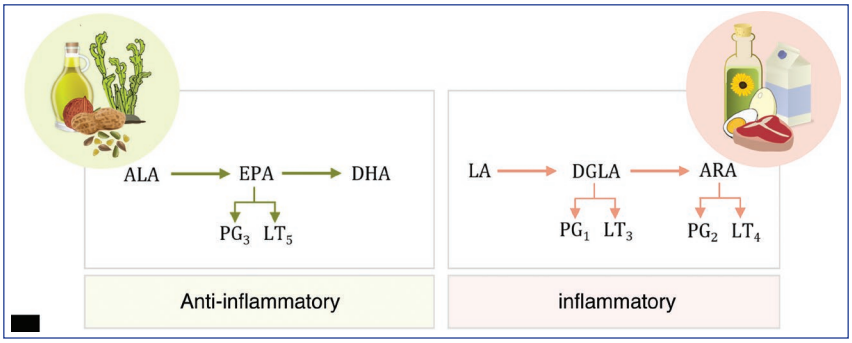

Figure 5 The Western diet is characterized by an imbalance of omega-6 fatty acids in ratio to omega-3 fatty acids. (20 : 1 on average vs. < 5 : 1 as an optimal ratio). *Abbr.*: ALA, alpha-linolenic acid; EPA, eicosapentaenoic acid; DHA, do cosahexaenoic acid; PG, prostaglandins; LT, leukotriene; LA, linoleic acid; DGLA, dihomogammalinolenic acid; ARA, arachidonic acid.

whole milk [43]. As a possible explanation, it was hypothesized that the amount of milk consumed may have been higher with low-fat milk than with whole milk. However, this has not been conclusively proven.

Fat

Apart from the foods described above which aggravate acne, diet changes with potentially preventive and therapeutic effects are being investigated as a complementary measure for pharmacotherapy. Omega-3 fatty acids (ω-3 FA) appear most promising due to their anti-inflammatory effects. The ω-3 FAs eicosapentaenic acid (EPA) and docosahexaenic acid (DHA) belong to the polyunsaturated fatty acids. They constitute substrates for the synthesis of anti-inflammatory group 5 leukotrienes and group 3 prostaglandins and decrease IGF-1 [47]. ω-3 FA are contained in linseed oil, canola oil, walnuts, algae, and seeds – particularly chia seeds, hemp seeds, and coarsely ground linseeds. The ω-3 FA contained in algae are also transferred to marine fish through the food chain (Figure 5).

Three interventional studies have evaluated the clinical severity of acne after ω-3 FA supplementation [48–50]. Jung et al. conducted the highest-quality study. In a randomized, controlled interventional design, 45 acne patients received 1 g/d EPA and 1 g/d DHA from fish oil over a period of ten weeks. Inflammatory skin lesions reduced according to subjective and objective methondology. Skin biopsies also showed reduced amounts of inflammation mediators [48]. Further interventional studies with longer follow-up periods and investigation of ω-3 FA levels are, however, necessary to fully assess the potential role of ω-3 FA in acne treatment. Previous studies have shown that patients with comparable pre-treatment levels of ω-3 FA and identical supplementation doses achieve different serum levels [51, 52].

Probiotics and prebiotics

Probiotics and prebiotics are also discussed as potential adjunctive options for the prevention and treatment of acne, due to their regulating effects on the gut and skin microbiota [53]. Probiotics are defined as living microorganisms with a beneficial health effect for the host [54]. These include, for example, lactobacillus strains

and bifidus bacteria [55]. Fermented foods such as sauerkraut, kimchi, miso, kombucha, or yoghurt contain probiotic microorganisms. Prebiotics are food components that cannot be broken down by endogenous enzymes but can promote the growth and activity of protective bacterial species in the colon [54]. These include starch in potatoes and grains, pectin in fruit, and oligosaccharides such as inulin in vegetables. *In vitro* studies have also shown that probiotics have an inhibiting effect on the proliferation of *c. acnes* [56]. In a randomized, placebo-controlled pilot study conducted by Fabbrocini et al., 20 acne patients received supplements with *lactobacillus rhamnosus*. After twelve weeks, clinical appearance of the skin had improved, and skin biopsies showed reduced IGF-1 gene expression and increased FoxO1 gene expression [56, 57]. Larger and more detailed studies, including analysis and sequencing of stool samples, are necessary before a clear recommendation for supplementation can be given [15].

The impact of micronutrients and supplements

Vitamins and trace elements

Intake of dietary supplements with vitamins and trace elements is widely used and intended to promote general health. Dietary supplements are, however, not indicated if the individual has no proven deficiency [58]. Vitamin B6 and B12 can actually trigger acne lesions, and existing acne may be exacerbated [59, 60]. Changes of the skin microbiome are discussed as a possible pathogenetic explanation for these clinical exacerbations [61–63].

Dietary supplements without a proven deficiency are not indicated.

Existing vitamin and trace element deficiencies however, should be treated. Studies have shown that acne patients may have a significant deficiency of vitamin D and zinc as compared with controls who have healthy skin [64]. A meta-analysis showed an interesting inverse correlation between patients' vitamin D levels and clinical severity of their acne. Vitamin D treatment of sebocytes in vitro showed anti-inflammatory properties with reduced expression of interleukin-6 and matrix-metalloproteinase 9 which might explain a possible pathomechanism [65, 66]. Yee et al. showed that oral zinc supplementation in acne patients led to a reduced appearance of inflammatory eruptions as compared with a cohort without zinc, concluding that zinc may constitute a safe and cost-effective addition to pharmacotherapy [67, 68]. Zinc is an essential trace element found in the catalytic center of many proteins; it is thought to have antioxidant properties [69]. Large-scale interventional studies are needed here as well in order to recommend nutritional intervention.

Parallels with acne inversa

A pilot study by Brocard et al. investigated the clinical effects of zinc supplementation in patients with acne inversa, a chronic recurrent inflammatory skin disease affecting the intertriginous regions. Patients with treatment-refractory Hurley stages I and II received zinc monotherapy with 90 mg once a day over a period of four months. This resulted in complete clinical remission (26 % of patients) or partial clinical remission of the inflammatory skin lesions (63 % of patients). The supplement also reduced the cutaneous expression of interleukin 6 and tumor necrosis factor TNFα in both lesional and non-lesional skin, with a significantly more pronounced downregulation in lesional versus non-lesional samples [70].

Association with a Western diet appears to be a further parallel with acne vulgaris [71]. Patients with Acne inversa are significantly more frequently obese, so

lifestyle changes with nutritional interventions to lose weight are therapeutically recommended [72, 73]. High glycemic foods, dairy products, and saturated fats should be markedly reduced to improve clinical symptoms [74]. Monfrecola et al. showed an increased expression of mTORC-1 in lesional and non-lesional skin of affected patients. The level of expression showed a direct correlation with the clinical severity of the Acne inversa [75].

Acne inversa, but not acne vulgaris, is associated with inflammatory bowel disease (IBD) such as Crohn's disease and ulcerative colitis. A meta-analysis conducted in 2016 showed that 12.8 % of patients with Acne inversa had irritable bowel syndrome (IBS) [76], eight times the prevalence in the general population of Europe [77]. This might indicate an altered gut microbiome and consecutively disordered immune milieu, similar to rosacea patients.

Rosacea

Evidence on the impact of nutrition in rosacea patients is very limited as compared with acne.

Rosacea is an important differential diagnosis of centrofacial dermatoses. Its clinical spectrum is broad, with persisting or recurrent erythema, teleangiectasia, papules and pustules up to phymatous changes. The pathophysiology is complex, with a combination of genetic factors, dysregulation of the innate and adaptive immune response, vascular and neuronal malformation, and dysbiosis of the skin microbiome [78–81] (Figure 2b).

In spite of ongoing research efforts, evidence on the impact of nutrition in rosacea patients is limited, especially as compared with acne. There are however some interesting new findings and nutritional approaches above and beyond avoidance of nutritional triggers which have been known for decades.

Coffee, spicy foods, and alcohol – anecdotal evidence or clinical recommendation

According to current findings, coffee does not appear to be associated with an increased incidence of rosacea [82–84]. Spicy, hot foods and alcohol, on the other hand, may contribute to clinical exacerbation with increased erythema and inflammatory eruptions. The food components act via transient receptor potential channels (TRP), cationic cellular channels that can be further differentiated into subgroups. Sulk et al. reported that especially *transient receptor potential vanilloid* (TRPV) 1 to 6 and *transient receptor potential ankyrin* (TRPA) 1 are active in rosacea patients [85]. They are expressed by keratinocytes and perivascular sensor neurons in the dermis and possess a binding site for the burning ingredients in pepper and chilies, piperin and capsaicin. Release of substance P and the neuropeptide *calcitonin gene-related peptide* (CGRP) induces vasodilation and excessive inflammatory reaction (Figure 6).

According to an epidemiological study by Li et al. with more than 82,000 patients, alcohol appears to be a dose-dependent predictor for an increased prevalence of rosacea [86]. Lately, alcohol-induced changes of the gut microbiome have been proposed as a possible causal connection [87].

Association with gastrointestinal diseases

It is now common practice to screen patients with rosacea for ocular involvement. Gastroenterological problems, however, are often not actively assessed or connected to the cutaneous symptoms. Yet rosacea should be considered a systemic disease

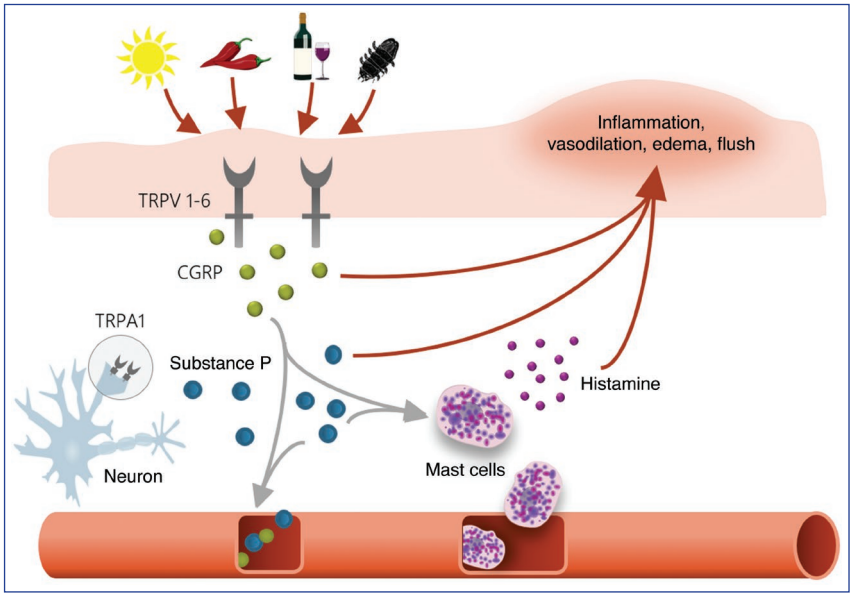

Figure 6 The influence of exposome factors, including nutrition, on the pathogenesis of rosacea.
Abbr.: TRPV, transient receptor potential vanilloid; TRPA, transient receptor potential ankyrin; CGRP, Calcitonin Gene-related peptide.

with its pathogenesis determined by the gut-skin axis [88, 89]. This is confirmed by a cohort study with nearly 50,000 rosacea patients. The prevalence of celiac disease, IBD, *Helicobacter (H.) pylori* infection, and small intestinal bacterial overgrowth (SIBO) was significantly higher in rosacea patients than in a control group with healthy skin [90, 91]. From a clinical point of view, rosacea patients who report gastrointestinal symptoms should be investigated further [92].

Szlachic et al. found *H. pylori* colonization in 88 % of rosacea patients studied [93]. These gram-negative bacteria can cause gastric ulcers and are considered risk factors for gastric cancer. If *H. pylori* is detected, eradication with antibiotics is indicated, and this has been shown in studies to contribute to a marked improvement of cutaneous rosacea symptoms [93–95]. SIBO, defined as bacterial overgrowth of the small intestine with a microbial concentration of > 10^5 colony-forming units per ml in an anaerobic endoscopic jejunal aspirate culture, may cause various gastrointestinal complaints [96]. Drago et al. studied rosacea patients with SIBO. After oral antibiotic treatment with rifamixin, remission of the cutaneous symptoms was achieved and remained stable over a follow-up period of three years in most patients [97].

Future studies should investigate the role of nutritional intervention for rosacea. Omega-3 fatty acids may be a topic of interest, especially for inflammatory dominated cases. However, it is yet unknown whether rosacea patients actually have ω-3 FA deficiency. In a randomized, controlled study in patients with ocular involvement, six months of supplementation with von 325 mg EPA and 175 mg DHA twice a day resulted in objective improvement of ocular symptoms [98].

Seborrheic eczema

Seborrheic eczema is a common and chronic inflammatory skin disease with its main predilection sites on the scalp, the hairline, and the periorbital area [99] (Figure 2c). Apart from a genetic predisposition, risk factors include male sex,

immunosuppression, increased seborrhea, Fitzpatrick skin types I–III, the cold season, and increased cutaneous colonization with malassezia yeast [100]. Treatment includes topical or systemic antifungals as well as topical corticosteroids and calcineurin inhibitors. Since these usually offer no more than temporary relief, it is especially important to identify modifiable lifestyle factors that may influence the course of this inflammatory facial dermatosis [101].

A cross-sectional study by Sanders et al. included 4379 volunteers of whom 636 (14.5 %) had seborrheic eczema. The participants' nutritional patterns were specified, and foods with a correlation to seborrheic eczema were highlighted [101]. Four groups were characterized: Group 1 ate mainly vegetables. Group 2 showed a "Western diet", group 3 ate mainly fruit, and group 4 had a high calorie intake from saturated fats. Interestingly, group 3 (mainly fruit) showed an up to 25 % decreased risk of seborrheic eczema, while group 2 (Western diet) showed a 47 % increase in the risk for this dermatosis [101]. Fruit, with a multitude of vitamins and plant secondary compounds such as flavonoids, may have reduced the risk of seborrheic dermatosis significantly. Similar effects have already been reported for neurologic diseases [102, 103].

Another hypothesis on how fruit may have a positive influence on skin health involves psoralen. This aromatic hydrocarbon increases sensitization of the skin to UV radiation [104]. Psoralen is found in many plants such as citrus fruit. This might promote a positive course of the disease and is in accordance with the observation that seborrheic dermatitis is less common in the warm season [100, 105].

As opposed to acne vulgaris, seborrheic eczema does not show any direct correlation to increased insulin and IGF-1 levels in the serum although sebum production is also increased [106].

Studies on vitamin B7 (biotin) deficiency and seborrheic eczema are inconsistent. Biotin is a water-soluble vitamin which is involved in many enzymatic reactions as a prosthetic group. It is contained in yeast, nuts, soybeans, rice, and grains. Patients with hair loss often show biotin deficiency. A cross-sectional study with 541 participants showed that 35 % of a cohort with telogen effluvium and reduced plasma levels of biotin also had seborrheic eczema [107]. However, a double-blind, placebo-controlled study in small children showed that daily oral supplementation with 5 mg biotin over a period of two weeks did not lead to any significant improvement of seborrheic eczema [108]. This lack of effect may, however, be explained by the short treatment duration which might have prevented a sufficient effect, and also by the fact that biotin deficiency was not verified before the study.

Probiotics may also modify the clinical course in seborrheic eczema. Mahmoudi et al. investigated the effect of kombucha ethyl acetate from fermented tea *in vitro* against malassezia species isolated from 19 patients with seborrheic dermatitis. The ethyl acetate fraction showed dose-dependent antifungal activity against malassezia species *in vitro*, in some cases with a higher antifungal potential than topical ketoconazole [109]. It is as yet unclear if this potential can be used *in vivo*, since there are currently no clinical studies on supplementation of probiotics in patients with seborrheic eczema.

Perioral dermatitis

Perioral dermatitis (POD) can present as erythema with papules, pustules, and fine lamellar scaling with characteristic sparing of the perioral region. It is usually a self-limiting disorder (Figure 2d). The etiology of POD is not completely clear, but irritation of the facial skin through excessive skin care, including too-intense cleansing or extensive use of cosmetics, appears to contribute significantly to its

development [110, 111]. For this reason, "zero therapy", meaning discontinuation of all external products, is recommended. If the skin feels very taut, calcineurin inhibitors and additional applications of black tea dressings can be recommended.

The available database also indicates that supplementation of zinc (in cases of proven deficiency) may effectively reduce the symptoms of POD [112–114]. In cases of chronically recurring or treatment-refractory POD, zinc deficiency should be considered as a differential diagnosis [115].

The herbs oregano and thyme contain carvacrol, thymol, and monoterpenes with possible allergenic potential. According to one study, this may have a negative effect on the course of POD [116]. Propyl gallate, a food additive coded as E310 and found in various foods such as oils, processed potato products such as crisps, spices, cake mixes, or chewing gum, may also lead to contact sensitization and maintainance of POD [117].

Apart from these aspects, there are currently no concrete evidence-based nutritional recommendations for POD.

Nutritional recommendations in clinical practice

Any nutritional recommendations indicated for the respective disease should be given as a complement to pharmacotherapy. Trying to cure severe facial dermatoses solely via nutritional measures, however, constitutes malpractice. Many patients will address the topic of "skin and nutrition" by themselves. There is a lot of disinformation and misunderstanding, so evidence-based recommendations are usually appreciated.

Nutritional counseling starts with a detailed medical history, including current medications and use of supplements. The physician must actively ask about patient's dietary habits and about known triggers depending on the dermatosis. A food diary may offer additional information. In the physical examination, height, weight and BMI (body mass index) should be noted in addition to the skin findings. Furthermore, laboratory parameters might offer further insights (IGF-1, HbA1c, fructosamine, albumin, vitamin B12, biotin, zinc). Additional instrumental diagnostics such as bioelectric impedance analysis (BIA) to determine body fat percentage may be performed as indicated.

As a basic principle, nutritional recommendations should not focus on single foods nor "superfoods", but rather promote a long-term and sustainable life-style change incorporating plant-derived, unproccessed and seasonal nutrients.

Nutrition that promotes skin health should be based on fresh, seasonal and un-processed, plant-focused foods [118] (Figure 3). In particular, the diversity of fruit, vegetables, pulses, seeds, and nuts appears to be decisive in disease protection for both the gut and the skin microbiome [12]. Several hours of fasting between meals are recommended, and snacks should be reduced, to decrease insulin and IGF-1 levels [119]. Supplementation of vitamins and trace elements should only be recommended in cases of deficiency.

Outlook

An up-to-date approach for prevention and treatment of dermatological disease involves not only pharmacotherapy but also evidence-based recommendations on lifestyle including nutrition.

While Hippocrates' quote *let food be thy medicine and medicine be thy food* is still doubted by some, the impact of nutrition on the development and progression of dermatological diseases is nowadays undisputed. Modern treatment approaches should therefore address not only one symptom but all exposome factors influencing the human body.

Future clinical studies in the area of dermatology and clinical nutrition are needed to provide further evidence-based insights into nutritional recommendations for patients. The main challenge remains to plan and conduct high-quality interventional studies with randomization, blinded design, and appropriate follow-up [120].

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Correspondence to

Dr. med. Anne Gürtler
Department and Clinic for Dermatology and Allergology
University Hospital Munich, LMU

Frauenlobstraße 9–11
80337 München, Germany

E-mail: a.guertler@med.uni-muenchen.de

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CME Questions/Lernerfolgskontrolle

1. Welcher Ernährungsstil wurde in epidemiologischen Studien von Cordain et al. mit einer niedrigeren Inzidenz einer Akne im Vergleich zu einer westlichen Ernährung herausgestellt?

a) FODMAP-Diät
b) Low-Carb-Diät
c) Paläolithische Diät
d) HCG-Diät
e) Formula-Diät

2. Was wird nicht zu den sogenannten Exposom-Faktoren gezählt?

a) Noxen (beispielsweise Rauchen)
b) Ernährung
c) UV-Strahlung
d) Umweltverschmutzung
e) Körpergröße

3. Mit welcher entzündlichen Dermatose ist eine DünndarmfehlBesiedleung (SIBO, *small intestinal bacterial overgrowth)* assoziiert?

a) Akne vulgaris
b) Seborrhoisches Ekzem
c) Periorale Dermatitis
d) Rosazea
e) Akne inversa

4. Welche Aussage zum pathophysiologischen Hintergrund zum Thema Akne und Ernährung ist nicht richtig?

a) IGF-1 ist ein Wachstumsfaktor, der in der Leber gebildet wird und anabole Signalwege fördert.
b) Der Transkriptionsfaktor FoxO1 hat eine inhibierende Funktion auf mTORC-1 und wird durch erhöhte IGF-1-Spiegel inaktiviert.
c) Erhöhte IGF-1-Spiegel führen zu einer verminderten mTORC-1-Aktivierung
d) SREBP-1 wird über eine Phosphorylierung durch mTORC-1 aktiviert.
e) IGF-1 und mTORC-1 gelten als zentrale nahrungsbedingte Mediatoren einer Akne.

5. Welches Nahrungsmittel verschlechtert eine Rosazea gemäß aktueller Evidenz?

a) Kaffee
b) Alkohol
c) Tee
d) Apfelsaft
e) Schokolade

6. Für welche Substanz konnte *in vitro* gezeigt werden, dass sie dosisabhängig ähnliches antimykotisches Potenzial gegen Malassezia-Stämme aufweist wie Ketoconazol und sich dadurch günstig auf die seborrhoische Dermatitis auswirken könnte?

a) Kombucha-Ethylacetat
b) Ceylon Zimt
c) Piperin
d) Capsaicin
e) Kurkuma

7. Bei welcher Dermatose spielen die diätetisch beeinflussbaren Vanilloid-Rezeptoren (TRPV) und der Ankyrinrezeptor (TRPA) eine pathogenetische Rolle?

a) Seborrhoisches Ekzem
b) Rosazea
c) Akne vulgaris
d) Akne inversa
e) Periorale Dermatitis

8. Welches Nahrungsmittel zählt nicht zu den Ernährungsempfehlungen für ein vielfältiges Darmmikrobiom?

a) Saccharose
b) Linsen
c) Flohsamen
d) Walnüsse
e) Leinsamen

9. Welches Spurenelement konnte nach Supplementation in klinischen Studien bei Patienten mit Akne inversa zu einer klinischen Verbesserung des Hautbefundes beitragen?

a) Fluor
b) Zink
c) Selen
d) Eisen
e) Kupfer

10. Welches Nahrungsmittel enthält einen besonders hohen Anteil an Omega-3-Fettsäuren und kann diätetisch empfohlen werden?

a) Pommes Frites
b) Chips
c) Sonnenblumenkernöl
d) Leinöl
e) Kokosöl

Liebe Leserinnen und Leser,
der Einsendeschluss an die DDA für diese Ausgabe ist der 30. April 2022. Die richtige Lösung zum Thema „Arzneimittelexantheme unter modernen zielgerichteten Therapien – ein Update zu Immuncheckpoint- und EGFR-Inhibitoren“ in Heft 11 (November 2021) ist: 1e, 2d, 3c, 4e, 5a, 6e, 7e, 8e, 9e, 10c.

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