ROS

REVIEW ARTICLE

Dietary Intervention of Acne Vulgaris: Antiinflammation as the Final Common Pathway

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ABSTRACT | Acne vulgaris (acne for simplicity) is the most common skin disorder with dysregulated inflammation as a prominent underling pathophysiology. While the exact etiologies of acne remain elusive, it has long been suggested that the development of acne is heavily influenced by dietary factors, which in turn provides a basis for dietary intervention of this disease. In this article, we survey recent randomized controlled trials demonstrating an efficacy for multiple dietary modalities in the intervention of acne. These include adoption of low glycemic index/load diets and dietary supplementation with omega-3 fatty acids/fish oil and lactoferrin, as well as a prescription dietary supplement, namely, NicAzel forte tablets. We discuss the potential biological mechanisms underlying the anti-acne efficacy of the above dietary modalities and propose antiinflammation as the final common pathway of dietary intervention of this most common skin disease.

KEYWORDS | Acne; Antiinflammation; Dietary intervention; Dietary risk factors; Inflammation

ABBREVIATIONS | GI/GL, glycemic index/load; IGF-1, insulin-like growth factor-1; IGFBP1, insulin-like growth factor binding protein-1

CONTENTS

1. OVERVIEW

Acne, as the most common skin disease globally, causes tremendous burden in terms of both physiology and psychology, especially in teenagers [1]. Indeed, acne has been identified as a significant risk factor for anxiety and depression in children and young adults. Over the past decades, the increasing global burden of acne has prompted the development of various preventive and therapeutic modalities, including medications and dietary modifications. Due to the adverse effects associated with conventional anti-acne drugs, emphasis has been put on dietary intervention of acne. In this context, recent clinical trials have demonstrated the anti-acne effectiveness for several dietary modifications/modalities. In this mini-review, we survey these clinical studies on various dietary interventional strategies and discuss the potential biological basis behind their anti-acne efficacy. To set a stage for discussing dietary intervention of acne, we begin with a brief introduction to the major dietary risk factors of acne.

2. DIETARY RISK FACTORS OF ACNE

You become what you eat. This fundamental principle also applies to acne. Extensive research over the past decades has uncovered a number of potential dietary risk factors for acne occurrence. The most notable ones include dairy products, foods of high glycemic index and load, and unfortunately, chocolate as well.

2.1. Dairy Products

Acne is caused, at least partly, by hormonal changes. Diet and living habits have great influence on the incidence of acne [2]. Due to the presence of hormones and other growth factors in cow's milk, milk consumption has long been suggested to contribute to the development of acne [3, 4]. Indeed, many observational epidemiological studies showed a close correlation between consumption of dairy products and developing acne [4, 5]. More recently, a meta-analysis of 14 observational studies, involving a total of 71,819 acne patients, found a positive relationship between dairy, total milk, whole milk, low-fat and skim milk consumption and acne occurrence. Compared with the lowest category of dairy intake, the highest category of dairy intake was associated with a 161% increased risk of developing acne. In contrary, no significant association between yogurt/cheese intake and acne development was observed [6]. In another systematic review and meta-analysis of 78,529 children, adolescents, and young adults, Juhl et al. reported that intake of any dairy products, including milk, yogurt, and cheese, was associated with an increased risk for acne in individuals aged 7–30 years. The increased risk for acne associated with dairy intake ranged from 22% to 43% [7]. It remains unknown why the above two reports yielded inconsistent conclusions on the association between intake of yogurt/cheese and acne occurrence. One possibility is the different patient populations, included in the two reports, i.e., the general acne patient population in the former report and children, adolescents and young adults with acne in the latter report. Nevertheless, the current consensus is that consumption of cow's milk is a risk factor for developing acne, especially in children and young adults.

2.2. Foods of High Glycemic Index/Load (GI/GL)

Several early observational epidemiological studies suggested that high GI/GL diet (diet that causes a large increase in blood sugar) might increase the risk of acne [8]. In line with this notion, a recent study in China reported that daily soft drink consumption significantly increased the risk of moderate-to-severe acne in adolescents, especially when the sugar intake from any type of soft drink exceeded 100 grams per day [9]. The above study analyzed survey responses from a total of 8,197 students and found that frequent intake (≥ 7 times per week) of carbonated sodas, sweetened tea drinks, and fruit-flavored drinks was associated with an increased risk of moderate-to-severe acne by 61%, 152%, and 90%, respectively. The intake of sugar from any soft drinks showed a nonlinear association with acne, and sugar intake ≥ 100 g/day was significantly associated with moderate-to-severe acne with an odd ratio of 3.12 [9].

Does the positive association between sugar intake and acne risk make any biological sense? It is known that high sugar diets increase insulin secretion and cause inflammation [10], which may thus provoke acne, especially in susceptible individuals. Indeed, as discussed next, multiple randomized controlled trials demonstrated a causal relationship between sugar intake and acne occurrence by showing that reducing

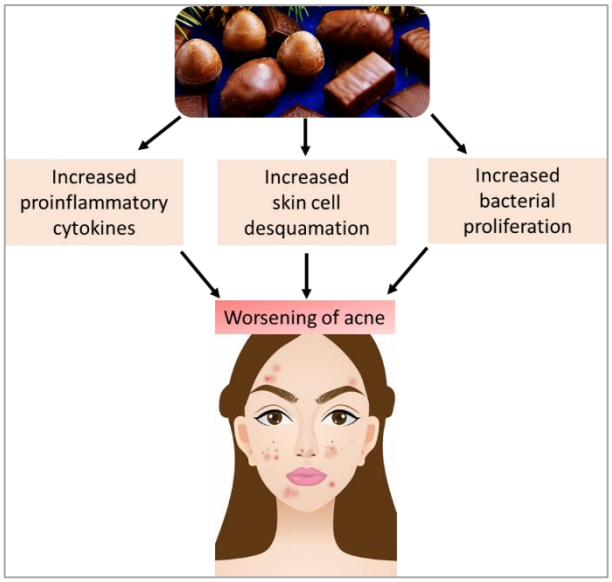

FIGURE 1. Potential biological mechanisms by which chocolate consumption worsens acne. See text (Section 2.3) for detailed description.

sugar intake improved the clinical conditions of patients with acne.

2.3. Chocolate

For so many years, it was thought that eating chocolate had no role in worsening acne [11]. Recently, several small-scale interventional studies in persons with mild-to-moderate acne, however, showed that chocolate, when consumed in normal amounts, can in fact exacerbate acne lesions [12–14]. In one study involving 54 college students with acne, the number of acne lesions was shown to be more than doubled two days following intake of a 1.55 oz (43 g) Hershey's milk chocolate bar. In contrast, the number of acne lesions remained unchanged after taking 15 Jelly Belly jellybeans which provided the same glycemic load [12]. The pro-acne effect of chocolate was unlikely due to milk or sugar in the Hershey's milk chocolate bar, as consumption of 99% dark chocolate still worsened acne lesions [13, 14]. A more recent survey of 10,502 adolescents and young adults in seven European countries reported that consumption of chocolate is associated with a 27.6% increase in the risk of developing acne. Notably, in this large population study, chocolate consumption was identified as the second major risk factor of acne, secondary only to heredity [15].

How does chocolate consumption worsen acne? Some researchers suggested that certain phenolic compounds naturally present in coca may be able to stimulate inflammatory cells to release proinflammatory cytokines [16]. However, natural polyphenols, such as resveratrol and tea catechins, are generally considered anti-inflammatory compounds that may in fact protect against acne development [17]. It is possible that the polyphenols in chocolate are converted into proinflammatory molecules (e.g., quinones) during the process of making cocoa powder from the roasted cacao beans. While how chocolate-derived phenolic compounds stimulate proinflammatory cytokine production remains elusive, studies showed that chocolate consumption also could enhance corneocyte desquamation and promote skin bacterial colonization [18], both of which might contribute to acne exacerbation associated with chocolate consumption (**Figure 1**).

3. DIETARY MODIFICATIONS AND MODALITIES FOR ACNE INTERVENTION

Identification of dietary risk factors in acne development makes it possible to devise dietary-based strategies to reduce the risk of developing acne and to improve the clinical conditions of those who already have had acne. Among the effective dietary strategies are adoption of a low GI/GL diet and intake of dietary supplements with anti-inflammatory properties.

3.1. Restriction of High GI/GL Diets

Multiple randomized controlled trials over the past several years consistently showed that as compared with regular high GI/GL diets, adoption of low GI/GL diets resulted in clinical improvements (decreased numbers of acne lesions and severity of inflammation) in acne patients [19–21]. Mechanistically, intervention with low GI/GL diets was shown to improve sebaceous lipogenesis [22] and decrease insulin-like growth factor-1 (IGF-1) [23, 24], a well-established factor in the pathogenesis of acne. Moreover, adoption of low GI/GL diets was found to improve the biochemical alterations under-

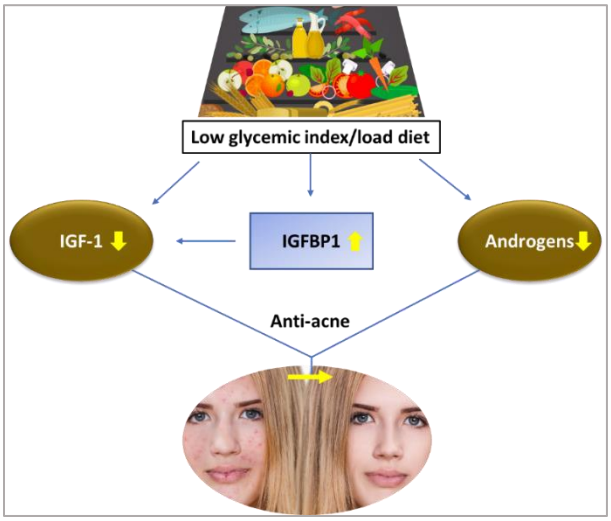

FIGURE 2. Potential biological mechanisms underlying the anti-acne effectiveness of adoption of low GI/GL diets. See text (Section 3.1) for detailed description.

lying acne, including decreased androgens and increased insulin-like growth factor binding protein-1 (IGFBP1) [24, 25]. In this context, androgens are known to have an important impact on the pathogenesis of acne [26]. On the other hand, IGFBP1 functions to decrease free IGF-1 levels and was shown to protect against vascular inflammation [27]. In summary, multiple randomized controlled trials with biochemical and histopathological evidence support the benefit of adopting a low GI/GL diet in acne patients. Low GI/GL diets improve acne likely via decreasing IGF-1, androgens, and sebum, all of which are proinflammatory (**Figure 2**).

3.2. Omega-3 Fatty Acids and Fish Oil

Omega-3 (ω-3) fatty acids constitute a series of essential unsaturated fatty acids that have a final carbon-carbon double bond in the n-3 position (also known as the ω position), that is, the third bond from the methyl end of the fatty acid. As such, they are also called n-3 fatty acids. These fatty acids constitute the major bioactive component of fish oil. Patients with acne were found to have decreased omega-3 fatty acids [28], suggesting a potential protective role for these anti-inflammatory fatty acids in acne. Indeed, dietary supplementation with fish oil or enriched omega-3-fatty acids was shown to ameliorate inflammatory and non-inflammatory acne lesions, particularly in patients with moderate-to-severe acne [29, 30]. The omega-3 fatty acids present in fish oil or dietary supplements were shown to suppress *P. acnes* bacterial growth [31], in addition to their well-known anti-inflammatory activity [32]. The above dual beneficial effects may largely account for the anti-acne efficacy of omega-3 fatty acids and fish oil.

3.3. Other Dietary Supplements

Two other dietary supplements were reported to also possess anti-acne properties. They are lactoferrin and a formulated dietary supplement, called NicAzel forte. NicAzel forte has been promoted as a prescription dietary supplement for treating inflammatory skin conditions, including acne.

3.3.1. Lactoferrin

Lactoferrin is a glycoprotein present in milk. Studies demonstrated that this glycoprotein exerted protective effects, including antimicrobial and anti-inflammatory activities [33]. Several randomized controlled trials showed an efficacy for dietary supplementation with lactoferrin in treating acne. For example, in a 12-week, double-blind, placebo-controlled study, 36 acne patients were randomly assigned to ingest fermented milk with 200 mg of lactoferrin daily (lactoferrin group) or fermented milk only (placebo group). Patients in the lactoferrin group showed marked improvements as evidenced by significant decreases in inflammatory lesion count (by 38.6%), total lesion counts (by 23.1%), and acne grade (by 20.3%) compared with the placebo group at 12 weeks. Furthermore, sebum content in the lactoferrin group was decreased by 31.1% compared with the placebo group. Notably, in the above study, the amount of skin triacylglycerols was decreased in the lactoferrin group, but not in the placebo group. Moreover, the decreased amount of triacylglycerols in the lactoferrin group was significantly correlated with decreases in the sebum content, acne lesion counts, and acne grade. The study concluded that dietary supplementation with lactoferrin-enriched fermented milk ameliorated acne with a selective decrease of triacylglycerols in skin surface lipids

[34]. The benefit of lactoferrin in acne was further confirmed by a subsequent trial [35].

More recently, a double-blind, randomized, placebo-controlled trial was carried out to determine the efficacy and safety of lactoferrin with vitamin E and zinc as an oral therapy for mild to moderate acne. A total of 168 acne patients aged 13–40 years old were randomly assigned to take either a capsule formulation containing lactoferrin (100 mg) with vitamin E (11 units) and zinc (5 mg) or placebo, twice a day for 3 months. A total of 164 subjects completed the study. The treatment group showed a significant 14.5% reduction in total acne lesions as early as 2 weeks with the maximum reduction (28.5%) occurring at week 10 compared to the placebo group. Maximum reduction in comedones (by 32.5%) and inflammatory lesions (by 44%) was also seen at week 10 compared with the placebo. Although to a less extend, the sebum level was significantly reduced by 6.2% compared with the placebo. Notably, no adverse events were observed during the trial. The study thus concluded that a twice daily regimen of lactoferrin with vitamin E and zinc significantly reduced acne lesions in people with mild-to-moderate acne [36].

3.3.2. NicAzel Forte: A Prescription Dietary Supplement

The NicAzel forte tablet is a uniquely formulated dietary supplement for oral administration. Each green-colored, oval-shaped tablet is imprinted on one side with "EL510" and contains Azerizin®, a proprietary blend of natural ingredients with anti-inflammatory and antimicrobial properties, along with inhibiting effects on sebum production. Each NicAzel forte tablet provides the following: Azerizin®, 700 mg; zinc (zinc oxide), 12 mg; pyridoxine (vitamin B6), 8 mg; copper (cupric oxide), 2 mg; and folic acid, 0.5 mg. ®Azerizin is a blend of nicotinamide, azelaic acid, quercetin and curcumin. Nicotinamide and azelaic acid are well recognized to possess anti-acne activities [37]. Quercetin and curcumin are plant-derived polyphenols with anti-inflammatory and antioxidant properties [17].

The effects of adding NicAzel forte, 1 to 4 tablets daily, to their current acne treatment regimen were evaluated in a multicenter, open-label, 8-week, prospective study involving 235 patients with inflammatory acne [38]. At week 8, 88% of the patients experienced a visible reduction in inflammatory lesions, and 81% of the patients rated their appearance as much or moderately better compared with baseline. More than three-fourth of the patients thought NicAzel forte was at least as effective as previous treatment with oral antibiotics. The study concluded that patients with inflammatory acne showed significant improvement in acne severity and overall appearance when NicAzel forte was added to their existing treatment regimen [38].

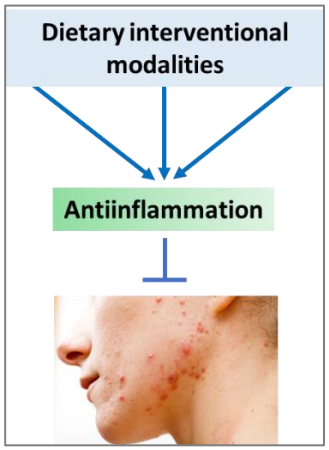

FIGURE 3. Antiinflammation as the final common pathway of dietary intervention of acne. Various dietary interventional modalities (e.g., lower GI/GL diets, fish oil, Lactoferrin, and NicAzel forte) share a final common mechanism—antiinflammation in protecting against acne.

4. CONCLUSION AND PERSPECTIVES

The saying "you are what you eat" has a major health implication, that is, replacing what is bad for your body with what is beneficial for your health in your daily diet. This is particularly reverent to persons with acne. On the one hand, you need to avoid the pro-acne diets, such as foods with high GI/GL load, dairy products, and chocolate. On the other hand, you should adopt a healthy dietary pattern, such as the Kitavan diet that constitutes mainly low GI/GL foods, fruits, and fish, and is devoid of dairy products and processed foods [37]. This is especially important if you are an acne-prone person (e.g., with a family history of inflammatory acne).

It can't be overemphasized that the well-known healthy dietary patterns, including the Kitavan diet mentioned above as well as the Mediterranean diet (which also emphasizes eating primarily plant-based foods, such as fruits and vegetables, whole grains, and fish) are not only good for your skin health, but also beneficial for your cardiovascular system. Adoption of such dietary patterns, thus, helps you maintain both a healthy heart and naturally beautiful skin. The question then is why the healthy diets and dietary supplements (e.g., fish oil) are beneficial for both the skin and the heart? This is because they are anti-inflammatory diets. Such anti-inflammatory diets are also effective in controlling other disorders, including diabetes, cancer, and neurodegenerative diseases, all of which share a common pathophysiology, that is, chronic inflammation. Hence, anti-inflammation is the final common pathway of dietary intervention of acne as well as many other diseases (**Figure 3**).

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