Review paper

The possible role of diet in the pathogenesis of adult female acne

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Abstract

Acne in adults is a chronic, increasingly common disease, especially among women. It differs in pathogenesis and clinical presentation from adolescent acne. Acne in adults is associated with Western diet, defined as high consumption of milk, high glycemic load and high calorie intake. Metabolic signals of this diet result in a significant increase in insulin/insulin growth factor 1 serum level and consequently in the molecular interplay of mammalian target of rapamycin complex 1 kinase (mTORC1)/forkhead box protein 1 (FoxO1) mediated nutrient signaling, leading to increased proliferation of keratinocytes, increased lipogenesis and sebum production and finally to aggravation of acne.

Key words: female acne, diet, insulin growth factor 1, forkhead box protein 1, mammalian target of rapamycin complex 1 kinase.

Introduction

Acne in adults is defined as the presence of acne lesions after the age of 25 years [1]. Acne affects 64% of adults in their 20s and 43% in their 30s [2]. It is affecting an increasing number of adults, especially females and it is observed in up to 54% of women [1, 3]. Acne in adult women, in different age categories, has a significantly higher prevalence than acne in adult men [4]. It is more frequent in African American and Hispanic women than in Continental Indian, Caucasian and Asian ones [5]. The disease is a chronic, relapsing, inflammatory condition and requires long-term treatment [1].

Two main subtypes of adult acne can be identified: persistent adolescent acne (80% of cases) and late-onset acne (20% of cases), with first symptoms appearing well after puberty, usually about the age of 21–25 [6]. Both types are frequently associated with inflammation, hyperpigmentation and scarring [7]. Women are more disturbed by the disease than men [8]. Acne is an important problem because it causes psychological disturbances, in comparison with those among patients with systemic diseases, such as diabetes mellitus, asthma or epilepsy [9]. It leads to negative self-esteem and negative body image. It causes depression symptoms and anxiety. A greater impact on quality of life is associated with older age, female gender and long duration of acne (> 5 years) [9]. The impairment of quality of life can be alleviated by the appropriate acne treatment [9].

Studies suggest that components of Western diet, particularly dairy products may be associated with acne. Acne is absent in populations consuming low glycemic load diet and not consuming refined sugars, grains, milk and dairy products [10]. The beneficial therapeutic effects of low glycemic load diet on the clinical course and intensity of acne and sebum production has been demonstrated in several studies [11–13].

The aim of this review is to highlight that dermatologists treating acne should take into account not only pharmacological treatment, but also dietary interventions, because of the beneficial endocrine effects of low glycemic load diet [14].

Clinical presentation

Clinical features of adult female acne differ from adolescent acne [1], with a predominance of inflammatory lesions such as papules and pustules. Typical features are nodules, usually painful, sometimes indolent, of long duration, which result in residual hyperpigmentation, localized typically on U-zone: cheeks, peri-oral and lower chin

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area [7, 15, 16]. Nodules can be present in the upper face as well and may be present without other inflammatory lesions [3, 7]. The isolated mandibular localization is not the most frequent, affecting only 11.2% of women. This pattern of acne increases with age, after 40 years old [3]. According to last studies most women have both inflammatory and non-inflammatory acne lesions [7]. Comedones may be clinically absent in adults [7]. Involvement of non-facial skin is also very common. The degree of acne severity is similar to that observed in adolescence [17]. The different clinical presentation of acne in women suggests involvement of a different mechanism than that observed in the adolescent group [1].

Pathogenesis of adult acne

Acne is a multifactorial disease which originates in the pilosebaceous unit. The four obvious factors typical of adolescent patients, which contribute to acne physiopathology are: inflammation, colonization with *Propionibacterium acnes*, increased sebum production and hyperkeratosis of the pilosebaceous duct [2, 18]. However, it is very probable that the influence of these factors on the acne course, may be somewhat different in adult female acne than in adolescent acne, and should be considered as a specific problem requiring another approach to treatment [19–21].

Numerous causalities have been proposed to explain post-adolescent acne. It is very probable that acne is an inherited disease. In a multicenter, observational, non-interventional study of 384 women, 56.8% of them reported first-degree family members with acne [3]. Although sebum excretion is influenced by genetic factors, the development of clinical disease is mediated by environmental factors [22]. Additionally, there is a correlation between daily stress and acne severity [3, 23]. Important aggravating factors are sun exposure and smoking [20, 24]. There is a strong correlation between smoking and non-inflammatory adult female acne through an increase in the production of sebum induced by nicotine and a reduction in the production of vitamin E [25]. UV causes inflammation and generates squalene peroxides which are highly comedonic [26]. The role of cosmetics in acne exacerbations remains controversial. Several studies have shown that cosmetics play an aggravating role [16, 17, 20] but in other studies, the cosmetic factor is not shown as an aggravating factor in adult female patients [19]. Probably, some types of cosmetics are more involved in the development of acne lesions, such as sun powders, masks and creams not tested as being non-comedonic [25]. According to Dreno *et al.*, cosmetics can be a factor in adult acne when retentional lesions, mainly closed comedones, are numerous and localized specifically on cheeks and the front head [3]. Some cosmetic ingredients elicit comedones: lanolin, petrolatum and certain vegetable oils [27].

There is no difference in microbiology in adult acne in comparison to adolescent acne. The density of *P. acnes* and level of sebum secretion does not appear to contribute to the different characteristics of late onset acne [15]. However, the failure to respond to many oral antibiotic courses, suggests that antibiotic resistance of *P. acnes* is a part of adult acne [19]. Resistant strains of. *P acnes* may induce chronic stimulation of the innate immunity in adult acne, exacerbating inflammatory acne lesions [7].

Role of hormones

Acne has a multifactorial pathogenesis but the androgenic stimulation of sebaceous glands is always important [1]. No clear pattern of endocrine abnormalities has been demonstrated in post adolescent acne [15]. The underlying endocrine disorder is rare in female with adult-onset acne. Systemic signs of hyperandrogenemia, such as irregular menstrual cycles or hirsutism, may indicate the presence of endocrine condition and need further diagnosis [7, 28]. It is probable that acne is a result of exacerbated response of the pilosebaceous unit to the normal circulating androgens [29]. According to different studies, 39–85% of women have worsening of acne in the days before menstruation, especially women aged over 30 years, in comparison to younger adults (53% vs. 39%, respectively) [30]. The premenstrual flare of acne is caused by an increase in the testosterone to estrogen ratio in the luteal phase [31]. Even in women with normal androgen levels, oral contraceptives and antiandrogen medications are effective treatment for acne. Other hormones influencing the sebum production are: estrogens, growth hormone, insulin, insulin-like growth factor 1 (IGF1), glucocorticosteroids, adrenocorticotropic hormone and melanocortins [32]. The androgenic hormones present in dairy products, as well as others that are circulating naturally, can have their natural effect on androgen-sensitive cell's androgen receptor, thus stimulating an increase in sebum production [33].

Relationship between acne and insulin-like growth factor 1

The involvement of IGF1 in pathogenesis of acne was proved by clinical observations that the puberty period, characterized by a peaking level of androgens, growth hormone, insulin and IGF1, is also the time of maximum sebum production and the peak in the incidence of acne [34]. Moreover, studies report a correlation between IGF1 level and acne lesion counts in adult women together with a significantly higher level of IGF1 in women with acne than in controls [35]. Insulin-like growth factor 1 stimulates lipogenesis in sebaceous glands by the induction of sterol response element-binding protein-1 (SREBP1) [32, 36, 37]. Overstimulated SREBP1 increases the total amount of sebum and enhances the relative

amount of monounsaturated fatty acids in sebum, thus influencing *P. acnes* colonization and biofilm formation [38]. Recently, polymorphism in the promoter of the IGF1 gene has been reported and a functional relationship between IGF1 polymorphism and circulating IGF1 levels and acne severity. This polymorphism consists of a highly polymorphic microsatellite composed of variable cytosine adenosine (CA) repeats. The number of CA repeats ranges between 10 and 24. In Caucasian population, the most common allele contains 19 repeats. The carriers of the 192 bp allele and/or 194 bp allele of the IGF1 promoter have higher circulating IGF-1 levels. Allele 192–194 was significantly higher in the acne group than in controls, with predominance of 194 allele. In addition, high 192–194 frequency was observed in patients with severe acne [39].

Effect of Western diet on adult acne

The link between acne and Western diet, defined as high consumption of cow's milk and dairy products, high calorie intake high glycemic load and high fat and meat intake, have been demonstrated in several studies [10, 40–42]. Studies of diverse populations show that individuals with acne commonly attribute the condition or its exacerbation to diet [43–47]. In Mahmood and Bowe's opinion, current knowledge on this topic is sufficient to encourage patients with acne to avoid high glycemic index food and substitute it for fresh fruits, vegetables, lean meats, fish and seafood [48, 49].

Food with a high glycemic index is rapidly absorbed, increases serum glucose levels and stimulates increased glucose-dependent insulin signaling. Milk proteins, naturally containing growth hormones and anabolic steroids, significantly contribute to high IGF1 signaling [11, 42]. Although milk has a low glycemic index, it aggravates acne by increasing the level of IGF1 [50], a potent mitogen which, after binding to its receptors, induces cell proliferation and inhibits apoptosis of keratinocytes and sebocytes and stimulates sebum production [30, 51]. Insulin and IGF1 augment sebum production, stimulate adrenal androgen synthesis, and increase androgen bioavailability, all of which play a role in the pathogenesis of acne. Findings of the studies by Smith have illustrated the various interactions between high glycemic load diet, insulin sensitivity, hormonal mediators, and acne [12, 52]. Regular consumption of foods with a high glycemic index elevates serum insulin concentration, which suppresses sex hormone-binding globulin (SHBG) concentration, raises androgen concentration and contributes to acne [32]. Conversely, low-glycemic-index foods have been shown to increase SHBG and reduce androgen levels. Higher SHBG levels have been associated with lower acne [41]. Histopathological and immunohistochemical evidence that a low glycemic load diet reduces the size of sebaceous glands, inflammation, and diminishes the expression of pro-inflammatory interleukin-8 and sterol regulatory element binding protein-1 (SREBP-1), a key transcription factor of lipid biosynthesis [40]. Cordain published his first article on diet and acne, in which he correlated the Western diet with the disorder [13]. He demonstrated that acne is absent in populations consuming diets without refined sugar, grains, milk and dairy products [14]. Also, Kwon *et al.* confirmed that glycemic load plays a substantial role in the pathogenesis of adult acne [40]. Grossi *et al.* found a close association between moderate to severe acne and high intake of milk, dairy and sweets also with obesity and low intake of fish. The intake of fish (1 day/week or more), vegetables and body mass index (BMI) lower than 18.5 kg/m^2 were all associated with limited or no acne [53].

Western diet-derived metabolic signals are sensed by the FoxO1 and mTORC1

Acne aggravation is a result of upstream activation of insulin-/IGF1 signaling (IIS) on metabolic regulations mediated by forkhead box protein O1 (FoxO1) and mTORC1 (nutrient-sensitive mammalian target of rapamycin complex 1 kinase) [10, 54–56].

FoxO1 is localized on the nucleus, and it is expressed in all mammalian tissues including sebaceous glands. In the natural resting state of an androgen-responsive cell, the androgen receptor is repressed by the presence of FoxO1. If one wishes to open up the androgen receptor so that it can be stimulated by androgens, one needs to remove FoxO1 from the nucleus [33, 54]. This can be done by phosphorylating the FoxO1 molecules, which renders them soluble and capable of leaving the nucleus, leaving behind a de-repressed (and therefore active and receptive) androgen receptor. Phosphorylation is accomplished by a two-step process that is induced by elevated levels of insulin or IGF1 and is mediated by two enzymes, phosphoinositol-3-kinase and Akt kinase, so ultimately androgen sensitivity is enhanced by elevated IGF1 and insulin [54, 56]. The reduction of FoxO1 levels in the nucleus, sensitizes the androgen receptor to endogenous androgens, and to the exogenous androgens and androgen precursors in dairy products [33, 54]. Anything that sensitizes the androgen receptor and then stimulates that androgen receptor will turn on acne [55]. Insulin-like growth factor 1 suppresses lipid metabolism, by regulation the key transcription factor of lipid synthesis SREBP-1c. Insulin-like growth factor 1 induced SREBP-1 expression and enhanced lipogenesis in SEB-1 sebocytes via activation of the PI3K/Akt pathway, whereas FoxO1 antagonized the expression of SREBP-1c. Thus, reduced expression of SREBP-1 should be expected on a low glycemic load diet associated with attenuated IIS [56].

mTORC1 is a nutrient-sensing kinase that regulates growth and metabolism in all eukaryotic cells. mTORC1 signaling stimulates gene transcription, translation, ribosome biogenesis, protein synthesis, cell growth, cell pro-

liferation and lipid synthesis [54]. mTORC1, integrates signals of cellular energy, growth factors (insulin, IGF1) and protein-derived signals, predominantly leucine, provided in high amounts by milk proteins and meat. mTORC1 activates SREBP, the transcription factor of lipogenesis. Consequently, leucine stimulates mTORC1-SREBP signaling and leucine is directly converted by sebocytes into fatty acids and sterols for sebaceous lipid synthesis [42]. High glycemic diet overactivates mTORC1, by increased activation of its substrates [38] and thus leads to increased proliferation of keratinocytes, hyperplasia of sebaceous glands and increased lipogenesis responsible for seborrhea [54]. Over-activated mTORC1 increases androgen hormone secretion and most likely amplifies androgen-driven mTORC1 signaling of sebaceous follicles.

Conclusions

Further research is needed to fully elucidate the role of low glycemic diet in adult acne, but dietary interventions should be taken to account in treatment because of the beneficial endocrine effects of this diet. The treatment of acne in adult females should embrace a number of aspects, including appropriate medical therapy and changes in dietary habits, such as reducing the calorie intake, restrict total diary consumption, higher consumption of fruits and vegetables and green tea, containing natural plant-derived mTORC inhibitors, and increased consumption of fish as a source of anti-inflammatory ω-3 fatty acids.

Conflict of interest

The authors declare no conflict of interest.

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