Review

Glycemic Index, Glycemic Load: New Evidence for a Link with Acne

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In this paper, the link between high glycemic index and load will be reviewed. The data from the literature discussed relate to a short presentation of the physiopathology of acne, including the influence of hyperinsulinemia as a key factor at the beginning of acne.

Key teaching points:

- Definition of glycemic index: The glycemic index (GI) is a numerical system of measuring how much of a rise in circulating blood sugar a carbohydrate triggers.
- Definition of glycemic load: The glycemic load (GL) is a ranking system for carbohydrate content in food portions based on their glycemic index (GI) and the portion size.
- Definition of acne: Acne is the interplay of 4 factors: 1. hyperkeratinization and obstruction of sebaceous follicles; 2/ androgen-stimulated increase in sebum production; and 3. colonization of the follicles by Propionibacterium acnes.
- Definition of IGF-1: Insulin-like growth factor 1 (IGF-1), which was once called somatomedin C, is a polypeptide protein hormone similar in molecular structure to insulin.
- Definition of IGFBP-3: Insulin-like growth factor binding protein 3, also known as IGFBP3, is a protein which in humans is encoded by the IGFBP3 gene, a member of the insulin-like growth factor binding protein (IGFBP) family.

ACNE

Acne is a common but complex skin disease that affects individuals of all ages. In the Western world, acne is estimated to affect 79% to 95% of the adolescent population, 40% to 54% of individuals older than 25 years, and 12% of women and 3% of men of middle age [1]. On the contrary, acne remains rare in non-Westernized societies such as among the Inuit [2], Okinawan Islanders [3], Ache hunter-gatherers, and Kitavan Islanders [1]. Although familial and ethnic factors are implicated in acne prevalence, recent data indicate that the incidence of the disease has increased with the adoption of Western lifestyles [2]. These observations suggest that lifestyle, including diet and in particular its glycemic index (GI) and glycemic load (GL), may be involved in acne pathogenesis [4].

Even if the relationship between GI, GL, and acne is controversial, recent randomized controlled trials showed an improvement in acne after GI and GL were reduced [4–7]. In contrast, Kaymak et al. [8] did not find that dietary GI, GL, and insulin level have a role in the pathogenesis of acne in young patients. The limitation of this last study was that the dietary data were obtained via a dietary questionnaire based on patients' own recollection of intake.

The relationship of acne to foods is certainly not new. Many textbooks of dermatology [9–11] published in the early 1950s contained information regarding specific foods to be avoided to prevent acne. Advice to avoid chocolate, fats, sweets, and carbonated beverages was commonly given to patients as part of acne therapy. However, this dietary advice has been removed from more recent textbooks, and no restriction of specific foods

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Abbreviations: GI = glycemic index, GL = glycemic load, IGF-1 = insulin-like growth factor 1, IGFBP-3 = insulin-like growth factor binding protein 3, RARs = retinoic acid receptors, RXRs = retinoid X receptors, SHBG = sex hormone-binding globulin, PCOS = polycystic ovary syndrome

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has been recommended to patients. It should be noted, however, that it was reported in a recent article [12] that many patients believe that acne is influenced by diet.

Acne is thought to result from the interplay of 3 factors: (1) hyperkeratinization and obstruction of sebaceous follicles caused by abnormal desquamation of the follicular epithelium; (2) androgen-stimulated increase in sebum production; and (3) colonization of the follicle by *Propionibacterium acnes*, which generates inflammation [13,14]. The ultimate mechanisms responsible for factors 1 and 2 are not well understood [14,15]. It is likely that any environmental element underlying the development of acne must operate via modulation of the known proximate or ultimate (genetic) causes.

DIET, HYPERINSULINEMIA, AND ACNE

Although diet is infrequently considered as a causative agent in the development of acne [16], it represents a well-recognized factor in acute [17] and chronic [18,19] hyperinsulinemia. Recent evidence has demonstrated that the hormonal cascade triggered by diet-induced hyperinsulinemia elicits an endocrine response that simultaneously promotes unregulated tissue growth and enhanced androgen synthesis [5,6,8]. Hence, hyperinsulinemic diets may represent a previously unrecognized environmental factor in the development of acne, as is described in the following paragraphs.

Hyperinsulinemia and Free IGF-1 and IGFBP-3

Chronic and acute hyperinsulinemia initiate a hormonal cascade that favors unregulated tissue growth by simultaneously elevating the levels of free insulin-like growth factor 1 (IGF-1) and reducing the levels of insulin-like growth factor binding protein 3 (IGFBP-3) [20–23]. Because free IGF-1 is a potent mitogen [24], elevated concentrations of free growth factor have the potential for stimulating growth in tissues, including the follicle.

It is well known that IGF-1 in humans is required for keratinocyte proliferation [25], and that in transgenic mice, overexpression of IGF-1 results in hyperkeratosis and epidermal hyperplasia [26]. These data support the possible idea that insulin-trigged elevation in free IGF-1 levels may promote acne via skin hyperkeratinization. Furthermore, women with post-adolescent acne maintain elevated serum concentrations of IGF-1 [27] and are mildly insulin resistant [28].

The reductions in IGFBP-3 levels stimulated by elevated serum insulin [20,21] or by acute ingestion of high glycemic load carbohydrates [29] also may contribute to unregulated cell proliferation in the follicle. In fact, in murine knockout cells lacking the IGF receptor, IGFBP-3 acts as a growth inhibitory factor [30]. IGFBP-3 inhibits growth by preventing IGF-1 from binding to its receptor. Moreover hyperinsulinemia induces production of transforming growth factor beta-1 [31]. Increased concentrations of this and other cytokines depress localized keratinocyte synthesis of IGFBP-3, thereby increasing the availability of free IGF-1 to its keratinocyte receptors [31], which, in turn, promotes keratinocyte proliferation. Consequently, hyperkeratinization of sebaceous follicles may result synergistically from elevations in free IGF-1 levels and/or reductions in concentrations of IGFBP-3.

IGFBP-3 and Retinoid Receptors

Insulin-mediated reductions in IGFBP-3 levels may further promote unregulated follicular growth by affecting the nuclear retinoid signaling pathway. Retinoids are natural and synthetic analogues of vitamin A that inhibit cell proliferation and promote apoptosis [32]. The natural retinoids (*trans* retinoic acid and 9-*cis*-retinoic acid) of the body act by binding 2 families of nuclear receptors: retinoic acid receptors (RARs) and retinoid X receptors (RXRs). Retinoid receptors, in turn, activate gene transcription by binding as RAR-RXR heterodimers or RXR-RXR homodimers to retinoic acid response elements located in the promoter regions of target genes, whose function is to limit growth in many cell types [33].

IGFBP-3 is also a ligand for the RXR alpha nuclear receptor and enhances RXR-RXR homodimer mediated signaling [34]. As has been shown in knockout rodents, the RXR alpha gene is required for actions of the 2 endogenous retinoic acid ligands [35,36]. RXR alpha is the major RXR receptor in the skin [37], and together with IGFBP-3, is growth inhibitory in many cell lines [38]. Additionally, low plasma levels of IGFBP-3 induced by hyperinsulinemia may reduce the effectiveness of the natural retinoids of the body to activate genes that normally would limit follicular cell proliferation.

Hyperinsulinemia, IGF-1, Androgenesis, and Sebum Production

Sebum production is stimulated by androgens [13,14], also as a consequence of the well-established androgenic effect of hyperinsulinemia. In fact, insulin and IGF-1 stimulate the synthesis of androgens in ovarian [39,40] and testicular [41,42] tissues. Moreover, insulin and IGF-1 inhibit the hepatic synthesis of sex hormone binding globulin (SHBG) [43,44]. Cross-sectional studies demonstrate inverse relationships between serum SHBG, insulin [45], and IGF-1 [46–48]. Direct injections of recombinant IGF-1 in humans elicit androgenesis and acne [49]. Higher serum androgen [50], insulin [27], and IGF-1 [28] concentrations in women are associated with the presence of acne. Taken together, these data suggest that the endocrine cascade induced by hyperinsulinemia enhances sebum synthesis and acne development.

The role of insulin is also supported by the high prevalence of acne in women with polycystic ovary syndrome (PCOS), a

condition associated with insulin resistance, hyperinsulinemia, and hyperandrogenism [51]. Insulin resistance may be correlated with the underlying disturbance in PCOS, where elevated IGF-I concentrations and low SHBG levels are found [52]. Recently, based on this view, the treatments for PCOS now include oral hypoglycemic agents [53].

DIETARY INTERVENTION STUDIES

In spite of the above-mentioned evidence, few well-controlled dietary studies have examined the effects of diet on acne. Fulton et al. [54], in a crossover, single-blind study, found no effect of chocolate on acne when compared with a placebo bar. However, later examination of the ingredients in the placebo indicated that its composition was virtually identical to that of the chocolate [55]. Anderson examined the effects of daily consumption of chocolate, milk, or nuts and found no effects [56]. However, this study has been criticized for its small sample size, short follow-up, and lack of control [57]. Chiu et al. [58] showed an association between worsening diet quality and exacerbation of acne during a preexamination period. However, stress was found to be the main contributing factor, and the diet was assessed with the use of nonscientific methods. Recently, a retrospective evaluation of dietary intake showed a positive association between milk consumption and severe acne [59].

Cordain et al. [1] postulated that high glycemic load diets may be a significant contributor to the high prevalence of acne seen in Western countries. The authors suggest that frequent consumption of high GI carbohydrates may repeatedly expose adolescents to acute hyperinsulinemia. Therefore, a low glycemic load diet may have a therapeutic effect on acne related to the beneficial endocrine consequences of these diets. This hypothesis was based on the fact that high glycemic load diets may influence 1 or more of the 4 underlying causes of acne mentioned above [29]. A different conclusion was reached by Kaymak et al. [8], who found that glycemic index, glycemic load, and insulin levels in younger patients do not have a role in the pathogenesis of acne. However, again the evaluation of the diet was made on the basis of a voluntary self-completed questionnaire. In a more recent study [6], the effects of a low glycemic load diet on acne and the fatty acid composition of skin surface triglycerides were evaluated. Total acne lesions and inflammation were dramatically decreased in the treated subjects. The new finding was noted after the fatty acid of the skin surface triglyceride was analyzed. In fact, the subject of the low glycemic load diet group demonstrated an increase in the ratio of saturated fatty acids (in particular, palmitic acid) versus monounsaturated fatty acids (in particular, C16:1), thereby suggesting a decrease in the enzymatic desaturation of C16:0 in the treated group. Worthy of note, the enzyme delta-6 desaturase, which is responsible for converting palmitic acid into the monounsaturated sapienic fatty acid (16:1), is unique and characteristic of human sebaceous glands. Taken together, the data presented by Smith et al. [6] suggest a possible role of desaturase enzymes in sebaceous lipogenesis and the clinical manifestation of acne. However, further work is needed to clarify the underlying role of diet, and in particular of the low glycemic index and low glycemic load diet, in sebum gland physiology.

CONCLUSION

To our knowledge, the studies of Smith et al. [4,7] published in 2007 are the first studies to show a therapeutic effect of dietary intervention on acne. After 12 weeks, the low glycemic load diet was shown to significantly reduce lesion counts and improve insulin sensitivity when compared with a high glycemic load diet. Although the authors could not isolate the effects of the low glycemic load diet from those of weight loss, their findings are consistent with earlier suggestions of the association between hyperinsulinemia and acne, as were already mentioned. Moreover, Smith et al. [5,6] supported these findings in 2 articles published in 2008. In these papers, a new hypothesis was proposed: that diet may influence the skin surface triglyceride, which in turn may be related to acne pathogenesis. However, these observations remain to be substantiated and the underlying mechanisms determined in larger scale studies.

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