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The relationship of diet and acne
A review

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Abbreviations: AAD, american academy of dermatology; αLA, alpha-linolenic acid; RA, retinoic acid; PPAR, peroxisome proliferator-activated receptors; SHBG, sex hormone binding globulin; IGF-I, insulin-like growth factor-I; AD, Alzheimer disease

Nutrition and diet are affecting overall health; that statement needs no particular citation as every nutritional textbook advocates for this. But can diet affect acne? Acne is one of the most common dermatological conditions, affecting millions of young adult worldwide.[1] It is generally accepted that excess sebum, hormones, bacteria and hyper proliferation of follicular cells are the major etiologic factors for acne.[2]

The current status of the relationship of diet and acne is not clear and under debate. On the one hand, the American Academy of Dermatology published recommendations[3] in 2007 suggesting that caloric restriction has no benefit in the treatment of acne and that there is insufficient evidence to link the consumption of certain "food enemies" to acne.[4] On the other hand, recent studies have suggested a rather close relationship between diet and acne.[5,6]

But let's start from the very beginning and precisely from the founder of modern medicine, Hippocrates. One pillar of his teachings was "Let food be your medicine and let medicine be your food." This statement was cited in another, very recent, review on the subject of diet and acne.[7] Since that review was published in 2004, many articles and commentaries have been published on the debate.[8-13] Before continuing with the review of the publications of the last five years, it is appropriate to quote the conclusions of that review, as in my opinion there is no better way to express agreement and appreciation:

"We did not realize how daunting it would be to write an article dedicated to making sense of the relationship of acne to foods.

It turns out that there are no meta-analyses, randomized controlled clinical studies, or well-designed scientific trials that follow evidence-based guidelines for providing solid proof in dealing with this issue.

We emerged from our search disappointed and confess at the outset that what we present in this article will not settle this controversial issue and that the reader will not get a clear-cut message from us; such is the nature of the beast.

We reviewed the updated arguments, facts, and relevant data on this ancient debate, but we warn the truth-seekers among you that the jury is still out."

Indeed at that time there were no better words to describe "the nature of the beast."

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Can Nutrients Affect Acne?

However it is very obvious that Hippocrates' ancient but very wise statement should hold some truth when applied to acne, given that the most efficacious current therapies for acne are retinoids. Oral administration of isotretinoin (13-cis-retinoic acid/Accutane) or topical application of its isomer and natural retinoid, tretinoin, are used as anti acne therapies[14,15] 13-cis-retinoic acid (RA) is the only drug that targets all four pathogenic factors of acne and is the most efficient in sebum suppression.[16] 13-cis-RA is a retinoid that could derive from the metabolism of Vitamin A. Although several websites proclaim that it is found in small quantities naturally in the body without citing a reference,[17] we know that at least the natural isomers of retinoic acid also affect the disease. With that in mind, we can certainly predict an association between diet and acne.

Vitamin A plays an essential role in skin's health. Vitamin A deficiency causes abnormal visual adaptation to darkness but also dramatically affects the cutaneous biology as dry skin, dry hair and broken fingernails are among the first manifestations of vitamin A deficiency.[18] This nutrient, which is stored in the liver, is found also in the skin, particularly in the sebaceous glands, known to express retinoid receptors.[19,20] Let's also not forget that most dermatologists are influenced by nutritional studies to recommend ingestion of isotretinoin with fatty foods. Retinol (Vitamin A), carotenoids (provitamin A) and retinoids (Vitamin A metabolites) are absorbed better with parallel intake of vegetable oils.[21-26]

Therefore how could we ever rule out the possibility that diet has no effect on acne? Especially when diet influences the absorption of a nutrient or a drug that affects the mitigation of that disease? May be we cannot treat acne with nutrition but we can certainly influence it. Perhaps no single food does causes acne or effectively treats its symptoms, but certainly we can advocate that it could ameliorate or worsen its severity.

In addition let's also consider that the lipophilic vitamins A and D have an important impact on keratinocyte biology, which can also be crucial to their proliferation in acne. The susceptibility of keratinocytes to the antiproliferative effects of vitamins A and D has been reported.[27] It was documented that the observed inhibition of proliferation of mouse and human keratinocytes in vitro by retinoic acid is mediated by independent mechanisms to Peroxisome proliferator-activated receptors (PPAR) receptors an inconsistent notion that RA potentiates cell proliferation by activating PPARβ/Δ.[28] Another report demonstrated that all-transRA, an isoform of RA, increased aquaporin 3 expression and enhanced its biological activity in human skin.[29] Vitamins A and D are the first group of nutrients that has been reported to exhibit properties of skin hormones.[30] In that property they control metabolism, activation, inactivation, and elimination of specialized skin cell. Many retinoids are also hormones since they bind to and activate specific nuclear receptors, affect their function, and are subsequently inactivated. Vitamin A and its natural metabolites have been approved for the topical and systemic treatment of mild, moderate and severe, recalcitrant acne, as well as photoaging, biologic skin aging, acute promyelocytic leukaemia and Kaposi's sarcoma.[30] Vitamin D's critical importance for the skin and consequently for the human body's endocrine system is demonstrated by the fact that the skin is both the site of synthesis of vitamin D active metabolites, as $1,25(OH)_2D_3$. In keratinocytes, $1,25(OH)_2D_3$ regulates growth and differentiation; for that reason vitamin D analogues have been developed for the treatment of psoriasis which is characterized as an aggressive hyperproliferative skin disease. In addition Vitamin D analogues are reported to affect the immune system and to offer protection against cancer and other diseases, including autoimmune and infectious diseases, in various organs and tissues.[30]

All the above examples are cited to reiterate the fact that these nutrients and their metabolites can influence skin hydration, hyperproliferation and metabolism. Besides the lipophilic vitamins A and D, reports have proven that vitamin E, the other major lipophilic vitamin, is delivered onto the skin via the activity of the sebaceous gland.[31,32] That sebaceous delivery could make a difference in inflammatory acne where lipid oxidation could further the inflammation status of the disease. Antinflammatory compounds such as zileuton, which targets certain enzymes of the lipid oxidation pathways, are in clinical studies.[33,34] These pathways involve metabolites of polyunsaturated fatty acids. As in the case of vitamins there are also two fatty acids in our body that cannot be synthesized by human cells: linoleic (18:2, Δ9,12) and α-linolenic acid (18:2, Δ9,12,15) (αLA). These are important nutrients that need to be obtained by the diet and are therefore referred to as essential fatty acids. These two essential nutrients are precursors to the omega-6 and omega-3 fatty acid families, respectively, a family of metabolites that are involved in numerous important physiological processes, including inflammation. Therefore we could safely assume that absence of these important nutrients from our diet could have important implications for both acne and our overall health.

Numerous studies have revealed that clinical imbalances of specific essential fatty acids are associated with a variety of skin problems. Hence dry, itchy, scaly skin is a hallmark sign of fatty acid deficiency.[35] More relevant to this review is a publication which suggested that the sebum of acne patients is relatively deficient in linoleic acid.[36]

The exact fate of these essential nutrients in human sebaceous cells is not yet fully elucidated. An experimental study[37] unveiled a unique metabolic fate of linoleic acid in sebaceous cells, which is preferentially beta-oxidized in contrast to the other predominant fatty acids, which are incorporated to the most prevalent sebaceous lipids. That rapid oxidation and degradation in sebaceous cells allows palmitic acid to be available as the sole substrate to the delta 6 desaturase of sebaceous cells, the predominant desaturase of human sebaceous cells.[38] That enzyme normally catalyzes the synthesis of more omega-6 derivatives from linoleic acid, since it is the enzyme's preferred substrate. There is also substantial evidence that linoleic acid is an essential structural component of skin ceramides, important for barrier function.

Sebum analysis demonstrates that these essential fatty acids and their derivatives constitute small amounts of surface lipids.[39] However, two intriguing studies,[40,41] revealed a tight association of these two fatty acids and skin. When guinea pigs were dosed with radioactively-labeled linoleic and αLA acids, skin and fur lipids were predominantly labeled. Especially in the case of the ^{14}C-labeled αLA administered, 46% of the radioactivity was associated with the skin and fur lipids; and about 39% of the label was not recovered in the body lipids and was assumed to be expired as CO_2 or unabsorbed. These data identify a new route of metabolism of αLA in this species and presumably through the sebaceous glands onto fur lipids and skin. Of course, in humans the distribution could be different but at least the above study revealed that these essential nutrients could enter from the diet, survive the digestive tract and reach the skin's surface unaltered. A very recent nutritional study[42] in two groups of women who were given flaxseed or borage oil for 12 weeks revealed that the daily ingestion of 2.2 g αLA and linoleic acid or 2.2 g linoleic and γ-linolenic acid, respectively, demonstrated some skin benefits. Skin irritation, changes in skin reddening and blood flow were diminished in both groups, compared to the placebo group, providing evidence that skin properties can be modulated by intervention with dietary lipids.

Another class of nutrients that derives from the diet includes minerals such as zinc, copper and iron, known to influence anti-inflammatory and pro-inflammatory enzymes, for example desaturases or lipoxygenases. Could a diet rich in zinc bring a benefit to acne? Could a diet rich in iron deteriorate it? We simply do not know, since the proper clinical studies have not been done.

Could Diet Affect Acne?

The fact that Western diets are often deficient in the longer chain omega-3s and their precursor αLA, raises an additional issue for this discussion. It is known that the ratio of omega-6 to omega-3 fatty acids in a typical Western diet can be 10:1–20:1,[43,44] versus

a 3:1–2:1 in a non-Western diet[44] or primitive, non-industrialized populations.[45]

These findings were the basis for population-studies that revealed that non-Western diets correlated with the absence of acne.[45] Several studies have suggested that inflammatory markers correlate with an increase of the omega-6/omega-3 ratio.[43] The Omega-6 fatty acids are thought to induce more pro-inflammatory mediators and have been associated with the development of inflammatory acne.[46,47] On the other hand, intake of high levels of omega-3 fatty acids is associated with decreases in inflammatory factors.[48] In addition there are epidemiological studies that demonstrate that increasing the intake of omega-3 fatty acids through a diet rich in fish and seafood results in lower rates of inflammatory disease.[43,49] There are also studies claiming that sebum production is increased by the consumption of dietary fat or carbohydrate[50] and that variations in carbohydrates could also affect sebum composition.[51,52]

In general our Western diet is not only deprived of omega-3s but is also a diet rich in refined carbohydrates. It has been reported that people living in the Kitavan Islands (off the coast of Papua New Guinea) and the Aché hunter-gathers of Paraguay do not suffer from acne and this is associated with their low-glycemic diet, consisting mainly of fresh fruits, vegetables, and lean proteins.[45] This conclusion is in agreement with recent studies[5,6] on low-glycemic diets that will be discussed at a later paragraph. In brief, one prospective cohort study[53] found an association between high-glycemic-index foods and longer acne duration, whereas two randomized controlled trials[5,6] associated low-glycemic-index diet with reduced acne risk.

In addition, to these reports two previous studies[54,55] had reported on how caloric restriction can change sebum composition. However we do not know if this could relate to the pathological condition of acne.

Current Status and Studies

As noted above, a comprehensive review of the literature in 2004 concluded that there was no conclusive evidence on the effects of diet on acne.[7] Has there been any progress since that time? Another review in 2005,[10] restated that, within the dermatology community, a consensus had emerged that diet was unrelated to the etiology of acne. That review summarized the few poorly designed studies, more than 30 years old, which contain very little objective data. In general, those studies were inconclusive due to methodological limitations: small sample size, lack of appropriate controls, potential recall bias, incomplete reported results or failure to clearly define the changes in acne.[56,57]

Interestingly, that review mentioned that there should be a link between diet and acne as many dietary factors influence a variety of hormones and growth factors that influence sebaceous gland biology and production of sebum. At the end of the article there was a statement that there have not been any recent studies to explore the relationship of diet and acne.

That same year, a study[58] was published which linked acne to the consumption of milk. The investigators raised also the point that the majority of the milk and dairy products consumed in the United States come from pregnant cows. Could these products be responsible for acne since milk exposes us to the hormones that cows produce when they are pregnant? Given also the fact that hormones clearly play a role in acne; as sebum production may be influenced by androgens and hormonal mediators, such as sex hormone binding globulin (SHBG) and insulin-like growth factor-I (IGF-I), all of which may be influenced by dietary factors. The study was based on a questionnaire given to a group of 47,355 women who were asked to remember what they ate in high school, years prior to the study. Another later study asked teenage boys to recall what they ate and to self-determine the severity of their acne.[59]

Researchers concluded that there was an association between drinking milk and acne. However these studies had limitations because the questionnaire required self-assessment of acne and was based on memory of food intake. This can be difficult and subjective since recalling what one ate days ago can be difficult. Also an association between drinking milk and acne means that more validated and well-designed studies are needed to prove if there is an association or a cause.

Factors such as heredity were ignored and the data revealed a very low prevalence rate of acne. For example, the group that consumed 2–3 glasses of milk per day had 1,344 responders that reported acne, only 7.7% of the total of 17,272 (therefore over 15,800 individuals did not report acne). Similarly, the self-reported prevalence of acne in the group of 6,280 individuals who had less than one serving of milk per week was only 6.5%. Therefore, there was a 20% increase in the prevalence of acne in milk drinkers in this study, based solely on memory; more importantly, the self-reported prevalence rates of acne in this study are inconsistent with the well-accepted fact that 70–90% of people are affected by acne at sometime during their teenage years. One who really loves to drink milk could decide to drink 2–3 glasses and be one of the 15,800 (>92%) individuals that had not developed acne.

Another confusing aspect of that study is that a reverse association was reported between the consumption of milk fat and acne. Most of the hormones present in milk, and especially the steroids, partition with the milk fat the same way that the fat-soluble vitamins do. So this result is bewildering, since no matter if the skim milk gets contaminated with the hormones due to the milk processing, still it should be expected to have fewer fat soluble molecules and attribute to a lower prevalence than the whole milk. No matter how many hormones are left behind in the skim milk the whole milk should have a higher concentration of steroids. The steroids share a similar structure and partition to fat as the vitamin D. Skim milk is deficient in lipophilic vitamins and by law has to be fortified with these vitamins after the removal of the fat. To encourage intake of Vitamin D from other sources could be a mistake, since this nutrient plays a great role when calcium is present, which is the case in milk and dairy products. Even if some hormones are left behind in skim milk, no one has evidence on how much of the various ingested growth factors survive the processing and most importantly the human digestive tract.

Indeed the above studies demonstrated a positive association between milk intake and acne, as consuming more milk showed a greater prevalence of acne than less frequent consumption. Even though in absolute value there is an association of milk with acne, AAD[3] was reluctant to implement guidelines based on these data as they were not convincing enough. The low prevalence rates, memory test, self-assessment and hormone speculation were not significant enough to drive a recommendation or report on the association of acne to milk. The recommendations were mainly[3] that *(a) dietary restriction (either specific foods or food classes) has not been demonstrated to be of benefit in the treatment of acne and (b) that there are few clinical studies available in the peer-reviewed literature that directly evaluate the effectiveness of dietary restriction or the consumption of specific foods or food groups to improve acne.*

These studies failed to support a link between the consumption of chocolate or sugar and acne. Thus, no evidence exists on the role of diet in acne.

A very important point is that dermatologists should not ignore the vast amount of literature on the reverse association of milk or calcium to obesity.[60-63] Ignoring other studies on the positive association between lipolysis and calcium, and between calcium consumption and weight loss, would be a mistake,[62-66] especially when recommendations and dietary guidelines target children with acne. Certainly any "milk animosity" that has been created should be mediated.

Interestingly, recent studies have suggested that milk consumption could potentially alter insulin production.[67,68] Even if milk is responsible for elevated insulin levels, it is noteworthy to mention that higher dairy intake, especially low-fat dairy intake, may lower the risk of type 2 diabetes in men and women.[69,70] However, the insulin response could be a far more important factor than the ingested hormones and growth factors. Absolutely would be great to avoid having a cocktail of hormones in our daily diet, but we could not assume that each person in our society has access or can afford organic or hormone free milk. Indeed, insulin and high-glycemic index are perhaps the two most scientifically and clinically, associated factors with acne. There is a relatively adequate amount of research and reports that outlines the significance of the insulin pathway in the sebaceous biology.[70-73] Recent reports also suggest that PPAR agonists could impact skin and the sebaceous gland.[74-76] PPARγ agonists are very well validated as insulin sensitizers, and many dietary omega 6 and 3 metabolites are PPAR agonists as well.[77-79]

Soon after the guidelines of the AAD were published,[3] two clinical studies reported an association between high-glycemic diet and acne. Certainly clinical studies with controlled diets are hard to perform and assure compliance but at least the dermatological community now has clinical data that shed light on the debate over diet and acne.

Findings from the studies of Smith et al.[5,6] have focused on the glycemic load, insulin sensitivity, hormonal mediators and acne. The investigators reported that foods with a high-glycemic index may contribute to acne by elevating serum insulin concentrations (which may stimulate sebocyte proliferation and sebum production), suppress SHBG concentrations, and raise androgen concentrations. On the contrary, low-glycemic-index foods increased SHBG and reduced androgen levels; this is important since higher SHBG levels were associated with lower acne severity.

In these studies, control groups were included and the effects of a low-glycemic-load diet (25% of calories from protein and 45% from low-glycemic-index carbohydrates) on acne and insulin sensitivity were examined. Randomly assigned participants (n = 43, all male, 15–25 years old) were enrolled to the dietary intervention or to the control group and were followed for 12 weeks. Blinded dermatologists assessed the number of acne lesions every four weeks, starting at baseline. Participants on the low-glycemic-load diet experienced greater reductions in total lesion counts and inflammatory lesions compared to those on the control diet. In addition to an improvement in acne, volunteers on the low-glycemic diet also experienced an increase in insulin sensitivity and significant changes in androgen levels.[53] A positive correlation was observed between the change in total lesion counts and the change in insulin sensitivity. Sex hormone-binding globulin (SHBG) levels also correlated negatively with a change in lesion counts.

Thirty-one male acne patients completed sebum tests as part of a larger 12-week, parallel design dietary intervention trial. At baseline and at the end of the period, follicular sebum outflow and composition of skin surface triglycerides were assessed. Subjects on the experimental diet demonstrated increases in the ratio of saturated to monounsaturated fatty acids of skin surface triglycerides when compared to controls; an increase that further correlated with acne lesion counts, implicating a possible role of desaturase enzymes in sebaceous lipogenesis and the clinical manifestation of acne.

Epilogue

The small studies that have been conducted to look at the effect of a low-glycemic diet on acne suggest that a low-glycemic diet may be helpful, but further research is needed to fully elucidate the role that diet may play in acne. The low-glycemic diet induces relatively low amounts of insulin to keep blood glucose levels within the normal range. In contrast, a high-glycemic diet requires more insulin to maintain glucose levels. This could lead to insulin resistance, which in turn can cause numerous health problems including high blood pressure, heart disease, obesity and diabetes.

Since the typical Western diet is more of a high-glycemic diet that often causes insulin resistance, it could potentiate a change in sebum production and therefore inflammation and acne.[5,6] More research is needed to determine whether a low-glycemic diet could effectively mediate acne or possibly even prevent it.

There are still questions as why every obese individual does not have long-term acne, since individuals who are obese demonstrate insulin resistance. In addition if insulin resistance is associated with acne, then everyone who suffers from diabetes would be expected to have acne. PPARγ agonists (such as Rosiglitazone) or dietary fatty acids are known to sensitize cells to insulin in various clinical studies.[77-79] Interestingly, PPARγ agonists are also in trials against Alzheimer disease (AD), which has recently been termed type III diabetes.[80,81] The human brain uses glucose as its primary fuel and insulin secreted by the pancreas crosses the

blood-brain barrier, reaching neurons and glial cells, and potentiates a region-specific effect on glucose metabolism. Glucose homeostasis is critical for energy generation, neuronal maintenance, neurogenesis, neurotransmitter regulation, cell survival and synaptic plasticity, thereby affecting cognitive function.[82,83] There is now an extensive body of evidence demonstrating the efficacy of PPARγ agonists in ameliorating disease-related pathology and improved learning and memory in animal models of AD.[81] Recent clinical trials of the PPARγ agonist rosiglitazone have shown significant improvement in memory and cognition in AD patients.[84] Other studies have shown that omega 3 fatty acids could have similar effect in AD patients.[85,86]

A recent review which referred to the sebaceous gland as the "brain of the skin" has opened the horizons to the newly founded field of dermatoendocrinology.[87] The paper discussed the links between the endocrine system and sebaceous glands. There is an additional link to the relationship between brain and sebaceous cells, if we consider that sebaceous and brain cells are both dependent on an efficient insulin response for maintenance of proper glucose homeostasis. Therefore another similarity between sebaceous gland and brain seems to be the profound role that nutrients as glucose and omega-3 fatty acids play in their physiology. The later could positively affect insulin sensitivity and facilitate the metabolism of the other most important nutrient, glucose. We also know that omega-3 fatty acids are preferentially stored in the brain, and the research cited previously demonstrated that αLA targets sebaceous cells.[40] Could this be another piece of evidence suggesting the sebaceous gland is the brain of the skin? Since their biology is governed by comparable sensitivities in similar nutrients? Does the ectodermic embryonic origin play any role on that similarity? These are questions to be answered by more research in the future.

High-glycemic load seems to be associated with the occurrence of acne, and a recommendation for a low-glycemic load diet cannot harm the patient. How bad this could be when such a diet, which includes a variety of fruits and vegetables, lean protein, and healthy fats, can also protect against cardiovascular disease, type II diabetes and even obesity. It is noteworthy to reiterate that in the studies by Smith et al. the intervention participants[5,6] also lost weight.

Dermatologists should not ignore nutritional studies and perhaps the nutritionist should understand better the complexity of skin and sebum production. They should rather work together in elucidating the "nature of the beast," as it is obvious that much more research is needed to reveal the potential effects of diet or nutrients on acne. We need to understand why people in indigenous societies do not experience acne while, in contrast, acne is wide spread throughout the Western society. Is diet the sole reason, or are other environmental conditions such as stress, sun exposure, and air pollution important? To prevent acne by dietary manipulation may not be possible, but there are scientifically plausible reasons to believe that nutrition can affect acne. To date, the research does not prove that diet causes acne but rather influences it to some degree which is still difficult to quantify.

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