Acne: Diet and acnegenesis

F. William (Bill) Danby

Adjunct Assistant Professor of Surgery (Dermatology), Dartmouth Medical School, Hanover, New Hampshire, USA

ABSTRACT

Acne is a manifestation of hormonal overstimulation of the pilosebaceous units of genetically susceptible individuals. Endogenous reproductive and growth hormones, exogenous reproductive hormones, insulin and endogenous insulin-like growth hormone-1, sourced from and stimulated by dairy and high glycemic load foods, all appear to contribute to this overstimulation. A postulated molecular mechanism linking food and acne is reported and integrated into the clinical picture.

Key words: Acne, dairy, milk, insulin-like growth factor 1 (IGF-1), glycemic load, androgen receptor

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Address for correspondence:
Dr. F. William Danby,
721 Chestnut Street,
Manchester, NH, 03104-3002 USA.
E-mail:
billd860@gmail.com

HISTORY

The link between acne and diet goes back many years. Bulkley's 1887 book[1] discussed the subject and up until the 1950s, in America, restrictions on various foods, most often dairy products, were presented in dermatology textbooks as part of acne therapy.[2] The 1950s brought tetracyclines, the 1960s brought benzoyl peroxide, the 1970s brought topical retinoids, the 1980s saw isotretinoin, the 1990s were the decade of topical antibiotics, and for the past decade acne phototherapy is being touted. For almost 60 years, dermatologists have been distracted from the diet by concentrating on therapy, diverting them from achieving what Albert Kligman has called 'the ultimate goal in medical practice, namely prevention.'[3]

During this time, only one valid investigation into the dairy component of diet was performed, as far as I can determine, and that was Dr. Jerome Fisher's personal ten-year epidemiological study of over 1000 of his own acne patients in Pasadena, California. He presented a very long and detailed article in 1966, to the American Dermatological Association. Although mentioned in the newsmagazine Time, the article never appeared in the scientific literature. It was rejected for publication by a reviewer who wishes to remain anonymous, on the basis that it was unlikely that hormones could survive the processes of digestion and be absorbed in sufficient quantity to have a clinical effect. It could also have been rejected because it was too long, but it is now available at www.acnemilk.com.[2]

My interest in diet was triggered by the dietary questionnaires I administered to my acne patients when I started practice in 1973. After two years, it was apparent that the only thing that showed up with great regularity was a moderate-to-high intake of dairy products. I gathered what little experimental evidence appeared in the literature over the years and when I moved to the United States in 1997, my new cohort of patients confirmed to me that this was not just a local semi-rural Canadian experience. I approached Dr. Walter Willett, Chair of the School of Nutrition, Harvard School of Public Health, for assistance in investigating the relationship. While this investigation was being considered and undertaken, Loren Cordain, from the University of Colorado, published the first of his three articles on diet and acne, in which he correlated the Western diet with the disorder.[4-6] Despite the fact that his emphasis was on high glycemic load (HGL) food in the Western diet versus the low glycemic load (LGL) in the aborigines, he confirmed to me in a telephone conversation that the two separate tribes his team studied consumed minimal or no dairy products, indeed the Aché in Paraguay considered the practice of drinking another species' milk to be 'abhorrent'.

The study done at Harvard's School of Public Health by the Adebamowo team produced three articles, the first one in 2005, based on 47,355 nurses, and the other two in subsequent years based on the nurses' sons and daughters. In all

three groups, a positive association was made between dairy products (particularly skim milk) and acne.[7-9]

Subsequently, there have been additional attempts to study the link. The articles most widely cited are those of Smith and Mann who published two articles showing a link, in small but carefully monitored prospective clinical trials, between a low glycemic load (LGL) diet and improvement in acne and biochemical markers.[10,11] As my earlier unpublished questionnaire studies had not hinted at this area being suspicious, I was curious about the diet used and the authors kindly provided me with the details. Following a review of the diet (to be published), it now seems apparent that their study is as supportive of the view that low dairy diet improves acne as it is of their thesis, which states that it was the low glycemic load (LGL) diet that resulted in the improvement of acne lesions illustrated in their article.

Ongoing investigations and attempts continue internationally to prove the acne-diet link:

A study sponsored by the Harvard group, in cooperation with the Leeds (UK) group, was designed to look at a population of patients, after clearance with Roaccutane. Two cohorts, one dairy free and one with ad-lib dairy, were to be compared with regard to post-clearance recurrence of their acne. After 14 months of recruiting attempts and only two volunteers, the trial (NCT00132574) was abandoned when it became apparent that the prospect of having their acne return was not attractive to potential recruits.

An Internet-based study was conducted at the University of Miami, Florida, in which 1903 volunteers reported the effect on their acne of the low glycemic 'South Beach' diet (SBD). This gave quite positive results, with the acne of more than 80% of those on the popular SBD improved, prompting a reduction of acne treatment, usually within three months.[12] One of the several problems in interpreting this uncontrolled study was simply that the SBD, while basically a low glycemic load diet, did permit dairy products, so the results were not clear-cut.

A third study was conducted in New York City in a predominantly Jamaican immigrant population whose dietary staple is HGL rice. Compliance was a problem, but in a single compliant patient, there was a marked decrease in the comedonal lesion count over the study course.[13]

Just published is a study of 1285 Koreans, a population that does not traditionally consume dairy. The authors report that the IGF-1 level was significantly higher in those with acne, and suggest that, "a high glycemic load diet, processed cheese, a high-fat diet, and iodine play a role in the exacerbation of acne in Koreans."[14]

HYPOTHESIS

How might dairy products, or food in general, impact acne? It is important, first of all, to have a working model of the induction of the primary lesion in acne, the comedo. If one visualizes the infundibular portion of the pilosebaceous unit as a tightly constrained and narrow tube, lined with a germinative epithelium actively producing keratinocytes, and contained within a constrictive sheath of PAS-positive glycoprotein (the glassy membrane), consider what happens when one increases the rate of production of these keratinocytes. Apparently, as we have all seen, a traffic jam occurs and that causes increasing pressure within the duct. As the pressure increases, the duct expands, and either bursts or reaches its limit of expansion. The increased pressure within this closed space apparently produces significant anoxia and also limits the diffusion capacity of the nutrients needed for terminal differentiation of the keratinocytes. In addition to providing a wonderful place for Propionibacterium acnes to grow, the anoxia probably also inhibits the ability of the keratinocytes' metabolism to fully nourish the process of terminal differentiation, to the point where the intercellular desmosomal connections dissolve, freeing the keratinocytes to proceed up the duct where they are normally shed. These keratinocytes, unable to disengage from each other because of immaturity, become the keratinous plug we know as a comedo. For an animated look at this process, see http://www.acnemilk.com/acne_animation

If one accepts this postulated mechanism, then the primary question becomes, "what turns on the germinative epithelium?" The answer is simple, hormones. The mechanism, however, is not simple. The best hypothesis to date has been formulated by Prof. Dr. Bodo Melnik, in a series of recent articles.[15-21] In essence, one needs to understand that anything that sensitizes the androgen receptor and then stimulates that androgen receptor will turn on the processes that lead to acne. It is apparent that a small polypeptide nuclear transcription factor called FoxO1 is at the center of the action. 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. 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. The androgenic hormones present in dairy products (as well as others that are circulating naturally) can then have their natural effect on this androgen-sensitive cell's androgen receptor, thus stimulating the processes that produce sebum, or infundibular lining cell keratinocytes, or indeed hair.

Phosphorylation is accomplished by a two-step process that is induced by elevated levels of insulin or insulin-like growth factor

1 (IGF-1) and is mediated by two enzymes, phosphoinositol-3-kinase and Akt kinase, so ultimately androgen sensitivity is enhanced by elevated IGF-1 and insulin.

That brings us back to the question of what might cause the elevated levels of IGF-1 and elevated levels of insulin. Much of the IGF-1 is endogenous, formed as part of the metabolic changes of puberty. There has been a great debate as to whether or not it is possible to raise one's level of IGF-1 by consuming dairy products that contain (exogenous) IGF-1 or whose consumption induces the production or elevation of endogenous IGF-1 in humans. The dairy industry is on one side of the fence and the human physiologists on the other side.[22] The fact that IGF-1 has been suspected as a cause of breast and prostate cancer explains the different spheres of interest. The question of elevated insulin levels is also complicated by the physiological response of human insulin levels to the consumption of milk. Both skim and whole milk stimulate a hyperinsulinemic response, unexplainable by the amount of carbohydrate present and unaccompanied by a corresponding hyperglycemic response.[23]

In summary, it would appear that milk is 'nature's perfect food' for the creation of acne. Not only does it induce increased amounts of IGF-1 and insulin, which together sensitize the androgen receptor in androgen-responsive cells, but it is also capable of supplying those androgen-responsive cells with dairy-derived androgens and their 5α-reduced precursors to appropriately stimulate them. At the same time, the endogenous androgens produced by the ovaries, testes, adrenal glands, and by the intracrine system of the pilosebaceous units themselves, are given open access to the de-repressed androgen receptors in these androgen-sensitive cells. However, dairy is not alone; other nutritional influences are also at work.[24]

SYNTHESIS

The above is not intended to blame all acne on dairy. Nor is it claimed that all who consume dairy will develop acne. Certainly, there is a solid if circumstantial chain of evidence that implicates dairy products. On the other hand, there have been absolutely no articles that convincingly argue to the contrary. The hormonal link, whether it is through polycystic ovaries producing excessive androgens and their precursors; stress producing unwanted corticotropin releasing hormones; injected anabolic steroids producing acne in bodybuilders; or androgenic progestins producing acne in women exposed to medroxyprogesterone acetate; all are well established. What is new here is the activation, by active de-repression, of the androgen receptor, as a result of the downstream effects of milk, milk products, and high glycemic load foods, but only in those with a genetic predisposition to acne.[25] Milk´s strongest effector mechanism for acne resides in the protein fraction of milk, predominantly the whey protein fraction, as skim milk (nearly fat-free milk) exerts stronger acnegenic effects than whole milk.[7] Basically, anything that produces prolonged elevations of insulin will sensitize the androgen receptor and induce insulin resistance. It is worth noting that the 'transient insulin resistance of puberty', long accepted as a natural, concurrent event during puberty, may actually be enhanced by dietary indiscretions during that period of life. As an aside, one wonders whether such a 'transient insulin resistance' occurs during the pubertal years of the Cordain's Aché and Kitavan tribal populations on their low glycemic load diets.[4]

In our very early lives drinking milk is perfectly natural. What is not generally appreciated is that we actually start our lives with our natural first food laced with anabolic steroids and other growth factors. It is wholly appropriate that the androgen receptor is turned on 'full speed ahead' during this initial growth phase of our lives when the anabolic steroids in our mothers' breast milk must do their work. This natural system is optimized to fuel the highly important initial growth spurt, but it was designed to shut off upon weaning, allowing for a gradual shift to natural non-dairy food. Failure to make this shift to a natural Paleolithic-type diet, moving instead to a western diet with its high glycemic load and dairy consumption, increases the stimulus to insulin production and so induces insulin resistance. As all phases of human growth (neonatal, puberty, pregnancy, as well as cancer growth) are promoted by insulin resistance, this leads to pilosebaceous overgrowth and a high prevalence of acne in industrialized countries.

In those individuals who replace mother's milk with cow's milk, a proportion of the population tends toward obesity, grows taller, more well-muscled, and generally bulkier or more 'heavy-set' than their brothers and sisters. It is likely that the prolonged induced elevation of insulin levels in these individuals is genetically determined, like acne, and simply keeps the androgen receptors open and available for longer than nature intended, yielding a greater growth of fat mass and musculature.

This phenomenon has not been properly examined, but deserves full investigation as part of the chain of events that leads variously to the so-called metabolic syndrome X, obesity, type II diabetes, insulin resistance, polycystic ovarian disease, compromised cognition, hypertension, hirsutism, androgenetic alopecia, HAIR-AN syndrome, and even increased susceptibility to cancer of the breast and prostate gland, as well as the prototype, acne.

Future investigations

Ideally, of course, one should have a prospective randomized double blind study in a large cohort of individuals with the proven ability to develop acne, challenged with appropriate diets. The obvious problem is that it is essentially impossible

to 'double blind' dairy products in a diet. Teenagers are hard to fool. It is also a major challenge to find a large cooperative group of youngsters, under the age of 18 (and thus under the age of consent) whose parents will permit the removal from the diet of something considered as traditionally 'healthy,' such as dairy products. However, as attempts are continuing, the picture is becoming clearer, and meanwhile we need to wrestle with the likelihood that those practitioners among us who choose to wait until unequivocal proof is provided are depriving their young patients of clinically useful advice.

SUMMARY

The epidemiological link between high glycemic load and dairy food having been established, the molecular trigger appears to be based on elevations in IGF-1 and insulin. This pair of polypeptides, stimulated by dairy and high glycemic load food, and working through PI3K and Akt kinases to enable 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. Laboratory substantiation of each link in the chain, the closest we can come to proof, is under way. Meanwhile, 'Nature's Perfect Food' also seems to be nature's perfect acnegen, and high glycemic load foods, a major part of the Western diet, are the co-conspirators.

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