


COMMENT AND CONTROVERSY

Edited by Stephen P. Stone, MD

Diet and acne ☆

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Abstract Acne is caused by the action of dihydrotestosterone, derived from endogenous and exogenous precursors, likely acting synergistically with insulin-like growth factor-1. These sources and interactions are discussed. Both a mechanism of action and recommended dietary changes that limit ingestion and production of these hormones are proposed.

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Much has been written on this subject over the past few years.¹⁻³ Those who have denied a link between diet and acne have put forward no convincing evidence to support their contention.^{4,5} Evidence of the link is slowly but surely accumulating. The statistical association between acne and dairy is solid.⁶⁻⁸ Molecular mechanisms postulated as responsible for the stimulation of the pilosebaceous unit are logical and conform to known science. A recent clinical trial has established in a small group that dietary manipulation changes the biochemical and endocrine parameters that are associated with acne metabolism in expected ways, and dietary changes are accompanied by clinical improvement.⁹

Theory

In brief, the postulated mechanism of action consists of an elevated supply of dihydrotestosterone (DHT) acting at the intranuclear androgen receptor of the germinative cell layer

of the various components¹⁰ (sebaceous, hair, and ductal lining) of genetically predisposed pilosebaceous units.¹¹ The effect of the DHT is likely synergized by insulinlike growth factor-1 (IGF-1),^{9,12} an adolescence-related growth factor whose pubertal rise peaks at 15 years in girls and 18 years in boys, and subsequent fall to basal levels is closely associated with the course of clinical acne. Both molecules are present naturally endogenously, but both are also under dietary influence.

Dihydrotestosterone is the 5α -reduced product of the testosterone (T) that is present as part of normal gonadal metabolism in both sexes, but there are also exogenous sources including foods such as milk and meat.^{13,14} The enzyme 5α -reductase in the pilosebaceous unit mediates this reaction, but DHT may also reach the androgen receptor without the influence of 5α -reductase when the precursor molecules are already 5α -reduced. Milk contains at least 2 such molecules, 5α -androstenedione and 5α -pregnandione,¹⁴ and these are prime candidates as the long-term stimulants to pilosebaceous activity. There are several other likely precursors in milk (and its products), and the enzyme systems necessary for their conversion to DHT are all part of the pilosebaceous intracrine system.¹⁵

Elevated production of T may also occur as a result of dietary intake through a reactive rather than an absorptive mechanism. Elevations of plasma glucose, insulin, and

☆ Dr Danby emphasizes that he has no financial interest in the books and Web sites mentioned in this article. The author refers you also to the previous commentary on *Acne and Diet* by Wolf, Matz, and Orion in the September to October 2004 issue.

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IGF-1 are known to occur as a result of ingestion of a significant glycemic load, and these elevations can in turn cause a rise in testosterone and a decrease in sex hormone binding globulin, having the net effect of presenting the pilosebaceous units with more testosterone. This is the mechanism proposed for the acneogenic effect of high glycemic load foods.¹²

Curiously, and unexpectedly, ingestion of milk has been shown to produce an exaggerated hyperglycemic and hyperinsulinemic response, making this liquid dairy product a prime suspect as a stimulant of this reactive increase in testosterone production. The response is about triple that predicted by the carbohydrate content of fluid milk.¹⁶

In addition to the DHT, T, and 5α -reduced DHT precursors, milk also contains a broad selection of about 60 other growth factors.¹⁷ The specific impact of these molecules is speculative at this time, but it must be pointed out that milk's prime function is the stimulation and facilitation of growth. There is little doubt these hormones are absorbed by the infant gut, but whether this is true in adolescents is less clear.

High glycemic load diets also have an impact on testosterone and IGF-1 metabolism. The same mechanism postulated above appears to be operative, with a reactive production of increased amounts of metabolically active testosterone.

This begs the question, "Why do we not see hypertestosteronemia in acne patients?" The explanation is fairly logical. Individual hormone molecules appear in the blood from various sources and at various speeds, and are either free or bound to various proteins. These molecules leave the blood at a speed related to their affinity for their carrier proteins, their affinity for their receptors, the number of receptors, the avidity with which they are bound, and whether they are metabolized at the receptor site (like T, which leaves the receptor as DHT) or reach a steady state in equilibrium with the blood level of identical or similar molecules (like the competitive inhibition between spironolactone and DHT at the nuclear receptor). Because of this swift removal and/or metabolism, measuring the total or even the "free" concentration of a hormone in blood at a single point in time gives relatively little information about the pharmacokinetics of the molecule. If the hormone is produced by the body (or absorbed from the gut or through the skin from an applied cream or gel) quickly and then removed swiftly, the blood level will be low. It has been suggested that androgens will be removed by avid receptors in as few as 2 passes through the circulation, leaving little circulating in the blood for measurement. In essence, these hormones apparently disappear into the pilosebaceous intracrine system,¹⁸ from which their metabolites emerge only as a component of sebum, in which such hormones have been shown to be resident.

The reality is that we really should be measuring tissue levels of all these hormones, and ultimately, we need to know the pharmacokinetics of DHT, its agonists, and its antagonists at the level of the nuclear androgen receptor.

In summary, there are logical biochemical and physiologic mechanisms to explain why low or nonconsumption of dairy is associated with a lower incidence of acne, and adherence to a low glycemic load diet is associated with a clinical improvement when incorporated into the acne therapy regimen.

Practice

To optimize the efficiency of acne therapy, dermatologists can minimize androgen and IGF-1 by reducing consumption of dairy products to zero and reducing the carbohydrate load in the diet. The "no dairy diet" and a version of a low glycemic load diet are illustrated at www.acnemilk.com. Further details are available in a new book "The Clear Skin Diet," which also deals with the relationship of diet to the inflammatory mediators of acne.

The animation

The acceptance of a no dairy diet and a low glycemic load diet requires that acne patients (and their parents) understand the mechanism of production of blackheads and blemishes. An animation has been developed to illustrate the concept of comedo production and is available on the Web site. It illustrates the concept that the hormones that govern reproduction of the cells lining the pilosebaceous duct are responsible for overproduction of these cells. This overproduction is postulated to produce increased intrafollicular pressure, metabolic stasis, and secondary anoxia leading to anaerobic colonization.

A working hypothesis is illustrated showing that such metabolic stasis likely causes intrafollicular keratinocytes to fail to mature to the point of terminal differentiation and desquamation, so they fail to separate from each other, leading to retention hyperkeratosis and thus comedo formation. This failure of terminal differentiation is postulated to be due to impaired nutrition on a cellular level, likely due to the hypoxia produced by internal pressures within the pilosebaceous duct. The pressure is the result of hormone-mediated excess production of these cells within the limited confines of the pilosebaceous duct. The presence of anoxia is indicated by the existence of colonies of the anaerobic *Propionibacterium acnes*.

Featured segments of the animation include the following:

1. The view illustrating the restrictive "glassy membrane" that limits the centrifugal expansion of the infundibulum.
2. The cross-section of the duct, showing the "glassy membrane" colored pink (it is periodic acid-Schiff positive) and the concentric centripetal production of lining keratinocytes.

3. The aberrant metabolic process, resulting in failed terminal differentiation, represented by the accumulation of lipids instead of production of mature keratohyalin, and failed completion of terminal differentiation, resulting in failed desquamation.
4. The central hypoxia, represented by the incremental dark bluish discoloration, is proposed as the prime cause of the impaired metabolic activity that leads to comedo formation.

The hormone explanation

Once patients have an understanding of the dynamics in the duct, they are educated about the various sources of the hormones that initiate the comedo. There are 3 sources: gonadal, adrenal, and dietary.

Men have no problem with the concept of hormones from the testes driving beard hair growth. The same stimulation process causes the overproduction of the cells that line the pilosebaceous ducts. Regrettably, no prophylactic hormonal therapy is available for men to counteract this. Women easily make the link between monthly cycles and flares of their acne. This provides a basis for discussion of the wisdom of controlling hormones.

Most teens know that the adrenal glands make adrenaline, which is part of the acute stress response, but very few know that these glands also respond to the chronic stresses of daily life with hormones that make acne. Unfortunately, except for drospirenone and spironolactone for women, no safe specific way of blocking these stress hormones is available.

The dairy connection

By the time the subject of hormones in dairy products is introduced, the hormonal link between hormones and acne is usually understood. Patients and their parents are invited to review Fisher's original scientific work, available on the same Web site. Patients are told that total avoidance of all dairy products is an essential part of their acne therapy, no matter what adjunctive therapy is used. The list includes cheese, butter, ice cream, cottage cheese, cream cheese, cream and all forms of fluid milk, dried milk, organic milk, Lactaid milk, and whey protein-based powdered supplements.

Patients are given the option of either simply avoiding all dairy products and eating low glycemic load foods, or stopping all dairy products and supplementing those they miss with low glycemic nondairy substitutes, whether from soy, rice, nuts, or other sources. A superb list of 2500 dairy-free foods has recently been completed by the organization that supports the "Go Dairy Free" Web site at <http://www.godairyfree.org/>.

A low glycemic load diet should be integrated as well.

Therapeutic options

Three therapeutic options are offered: the natural (no therapy) therapy, standard (routine acne care) therapy, and aggressive (pedal to the metal) therapy.

Natural acne therapy is achieved by simply stopping all dairy products and high glycemic load foods, and waiting for the unnatural process of acne to resolve. This choice is welcomed by a committed minority, and they must take great care to select a balanced diet. A nutritionist's assistance is suggested, and the use of supplemental vitamins is recommended. These individuals usually need no calcium supplementation because of its availability in their diet but may need supplemental vitamin D₃.

Standard therapy starts with full dairy restriction. Faster improvement is to be expected by adding a low glycemic load diet. Some patients will choose to remain faithful to their previous standard antiacne medications. Most dermatologists will find it necessary to provide some fine tuning, whether this is an explanation of the value of comedolytics such as the retinoids, or addition of combined therapy with benzoyl peroxides and topical antibiotics or judicious selection and administration of oral antibiotics. Many patients who come from primary care physicians or are self-referred have little idea of the fine points of the use of these various products, so an educational session is essential.

Aggressive therapy must be explained by the dermatologist and understood by the patient. It is impossible to shrink sebaceous glands down to prepubertal size with standard topical therapy. Isotretinoin is routinely offered as the only option available to empty out the present plugged pores, calm the fires of active acne, miniaturize the oil glands themselves, and decrease the size of the hormone-manufacturing apparatus in the sebaceous ducts and the sebaceous glands themselves. The patient must understand that only total clearance of the pores, total "putting out of the fires," and total control of the hormones will give the best long-term results. These results are seen first as clearance of the present acne and secondly as freedom from, or minimization of the risk of, recurrences.

Patients must understand that the hormones from different sources "stack up" on each other. There is nothing one can do to reduce the hormones from male testes; the acnegenic hormones from the adrenals cannot be controlled with any medicines; the ovarian hormones can be controlled to a certain degree with "birth control pills"; but only time will allow a gradual decrease in the level of normal growth hormone that acts through IGF-1. This means that maintenance, after discontinuation of the isotretinoin, is essential. Dairy avoidance and a low glycemic diet must become a part of everyday life. Patients must know that "the low glycemic load lifestyle will help your acne, your weight, and will actually lighten your environmental footprint on this planet's increasingly limited resources."

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