Dietary Implications for the Development of Acne: A Shifting Paradigm

a report by
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Loren Cordain, MD, is a Professor in the Department of Health and Exercise Science at Colorado State University in Fort Collins, Colorado. His research emphasis over the past 10 years has focused upon the evolutionary and anthropological basis for diet, health and well being in modern humans. Dr Cordain's scientific publications have examined the nutritional characteristics of worldwide hunter-gatherer diets as well as the nutrient composition of wild plant and animal foods consumed by foraging humans. More recently his work has focused upon the adverse health effects of the high dietary glycemic load that is ubiquitous in the typical western diet. A number of his recent papers have proposed a common endocrine link between dietary induced hyperinsulinemia and dermal manifestations such as acne, ancanthosis nigricans and cutaneous papillomas. Dr Cordain is the author of more than 100 peer-reviewed publications, including a series of three recent papers outlining the central role diet plays in causing acne. He is the recent recipient of the Scholarly Excellence award at Colorado State University for his contributions into understanding optimal human nutrition. He has lectured extensively on the evolutionary aspects of human nutrition world wide, including presentations on how diet plays a key role in the pathogenesis of acne at the annual conferences of the Society for Investigative Dermatology (SID) and the European Society of Dermatology and Venerology (EADV). He has written a popular book, *The Dietary Cure for Acne*, summarizing his research findings.

Following our 2002 publication in *The Archives of Dermatology*[1] demonstrating that acne was not present in two non-westernized populations, there has been renewed interest in the role that diet may play in the pathogenesis of this disease. In the past two years, three studies now support the link between diet and acne.[2–5] Although these reports will need to be followed-up by more extensive experiments, they are important for two reasons: they represent the only well controlled, modern studies of diet and acne that have been published in more than 35 years;[6] and they are contrary to the long-held belief that acne is not caused by diet.[7–9]

Establishing Cause and Effect Between Diet and Disease

One of the challenges faced by nutritional scientists, when they ultimately make recommendations regarding what we should and should not eat, is to establish cause and effect between a dietary element and the subsequent development or prevention of disease. *Figure 1* demonstrates the four primary procedures by which causality is established between diet and disease.[10,11]

No single procedure alone can establish cause and effect,[10,11] nor can any single study prove causality.[12] Observational epidemiological studies can only show relationships among variables and cannot provide decisive evidence by themselves either for or against specific hypotheses.[13] In order to establish cause and effect between diet and disease, it takes more than just observational epidemiological evidence.[13] There must also be biological plausibility in which evidence gathered from tissue, animal and short-term human metabolic studies support causality.[11] When observational epidemiological evidence is augmented by biological plausibility studies and confirmed by randomized controlled trials, the case for causality becomes ever-more convincing.

Diet and Acne: The Most Recent Data

In addition to our ecologic study demonstrating the absence of acne in the Kitavan islanders of Papua New Guinea and the Ache hunter gatherers of Paraguay,[1] two recent observational epidemiological studies also support the notion that diet is linked to acne.[2,3] In a retrospective cohort of 47 and 355 women, after accounting for age, age at menarche, body mass index, and energy intake, Adebamowo and colleagues found a positive association between acne incidence and total (prevalence ratio = 1.22; p=0.002) and skim (prevalence ratio = 1.44; p=0.003) milk intakes.[2] In a prospective cohort of 6,094 girls, aged nine to 15 years studied from 1996 to 1999, milk drinking of all kinds (total, whole, low-fat, and skim) was positively associated with acne.[3] After accounting for age at baseline, height and energy intake, the prevalence ratios and p-values were as follows: total milk (1.20; <0.001), whole milk (1.19; <0.001), low-fat milk (1.17; <0.002) and skim milk (1.19; <0.001). These two observational experiments are important in that they are the first evidence in westernized populations to show that diet (and milk in particular) is associated with acne. In order to establish causality, future randomized controlled trials, in which milk is either added to or excluded from the diet and acne symptoms assessed, will be needed to confirm these preliminary epidemiological observations.

Mann and colleagues recently completed a more powerful randomized controlled trial evaluating the effect of a low glycemic load, high protein diet upon acne symptoms in 43 male acne patients aged 18. 3 + 0.4 years.[4,5] Subjects were randomly assigned to either an experimental group with a diet consisting of 25% energy from protein and 45% energy from low glycemic index carbohydrates or to a control group consuming their usual diet. Following the 12-week dietary intervention, total and inflammatory lesion counts decreased significantly (p<0.05) in the treatment group compared with the control group.[4] The hormonal profile of the treatment group improved concomitantly with the reductions in acne lesion counts as measured by significant declines in dehydro-epiandrosterone sulfate and the free androgen index.[5] Milk and dairy products were a component of the treatment diet in this study, hence it is unclear if further improvement in lesion counts would have occurred had these foods been excluded.

Diet and Acne: Underlying Physiological Mechanisms

Acne results from the interplay of six proximate factors:

- increased proliferation of basal keratinocytes within the pilosebaceous duct;
- delayed keratinocyte apoptosis;
- incomplete separation of ductal corneocytes from one another during desquamation via impairment of desmosomal disintegration and subsequent obstruction of the pilosebaceous duct;
- androgen mediated increases in sebum production;
- colonization of the comedone by *Propionibacterium acnes*; and
- inflammation both within and adjacent to the comedone.[14–18]

Despite the wholesale dismissal of diet as a potential environmental factor underlying the development of acne,[7–9] a large body of evidence now exists that demonstrates how certain foods and food substances may adversely influence hormones and cytokines that influence five[1–4,6] of the six previously listed proximate causes of acne.[1,6,19]

The Dietary Glycemic Index

The glycemic index, originally developed in 1981, is a relative comparison of the blood glucose raising potential of various foods or combination of foods based upon equal amounts of carbohydrate in the food.[20] In 1997, the concept of glycemic load (glycemic index x the carbohydrate content per serving size) was introduced to assess blood glucose raising potential of a food based upon both the quality and quantity of dietary carbohydrate.[21] *Table 1* lists the glycemic indices and loads of various foods and demonstrates that refined grain and sugar products nearly always maintain much higher glycemic loads than unprocessed fruits and vegetables. From an endocrine perspective, the importance of the glycemic index and load is that they are closely related to the insulin response.[23] An exception to this general rule is dairy products, which exhibit low glycemic indices and loads, but paradoxically elicit high insulin responses similar to white bread.[24] Highly glycemic and insulinemic foods are ubiquitous elements in western diets and comprise 47.7% of the per capita energy intake in the US.[25] *Figure 2* shows how high glycemic and insulinemic foods, including dairy products, set off a hormonal cascade that may ultimately result in acne.

Dairy Products and Acne: New Findings

In addition to having a potent insulin response, similar to eating a slice of white bread,[24] a recent dietary intervention showed that a high milk diet for only seven days caused insulin resistance in a group of 24 eight-year-old boys.[26] Insulin resistance in turn may promote acne via the hormonal cascade depicted in *Figure 2*.

Milk is essentially filtered blood and as such contains the full complement of hormones that are also present in blood.[27] Traditional theory held that consumption of cow's milk would not result in the transfer of cow hormones into human circulation for a number of reasons. First, in industrialized countries, milk is usually consumed many hours or days after it is initially procured. Many hormones such as the insulin secretagogues (GIP, GLP-1) have very short half-lives (<10 min)[28] and simply would not be present in commercial milk. Secondly, the heat of pasteurization (149°F for 30 min) may degrade or inactivate thermally

Figure 1: Analytical Procedures for Establishing Cause and Effect Between Diet and Disease

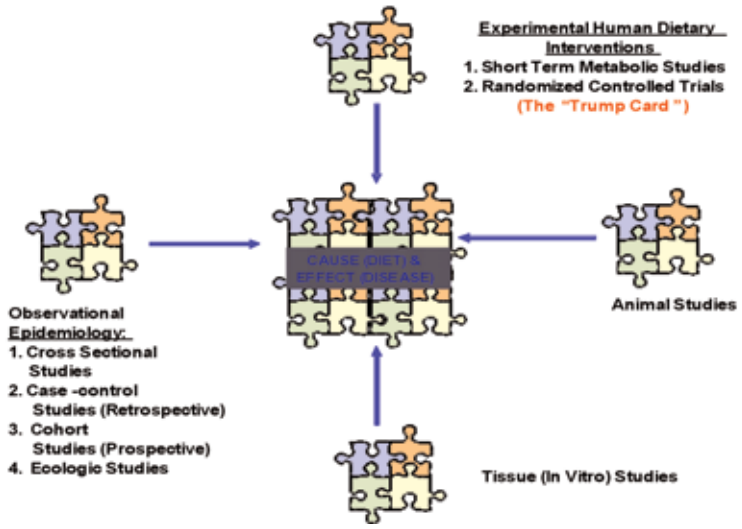


Figure 2: Hormonal Changes Elicited by High Glycemic Load Diets, Which Promote Acne[6]

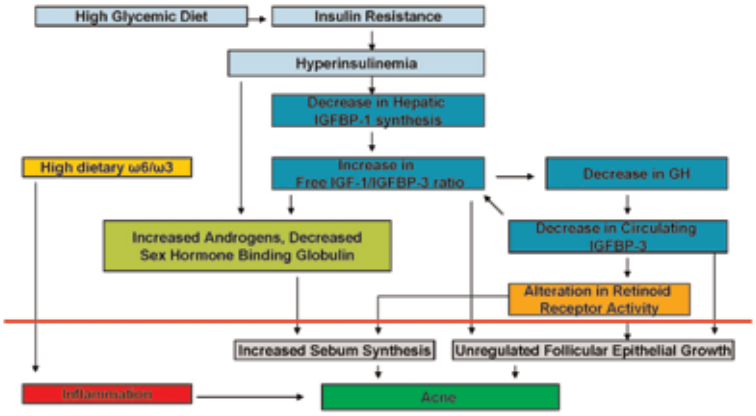


Figure 3: Route by Which Bovine BTC Reaches Systemic Circulation in Humans

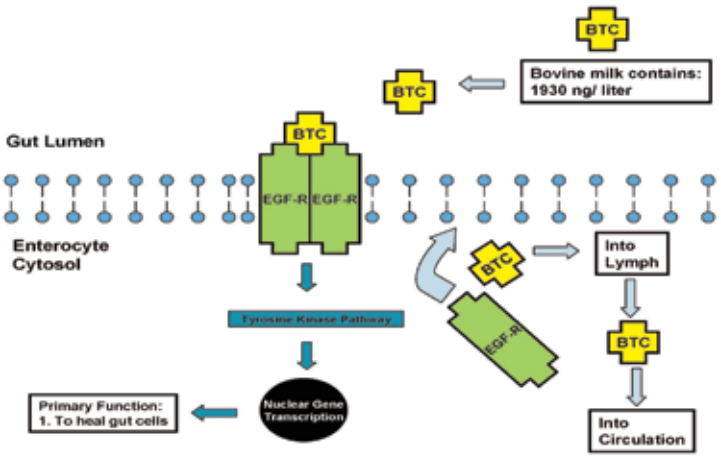
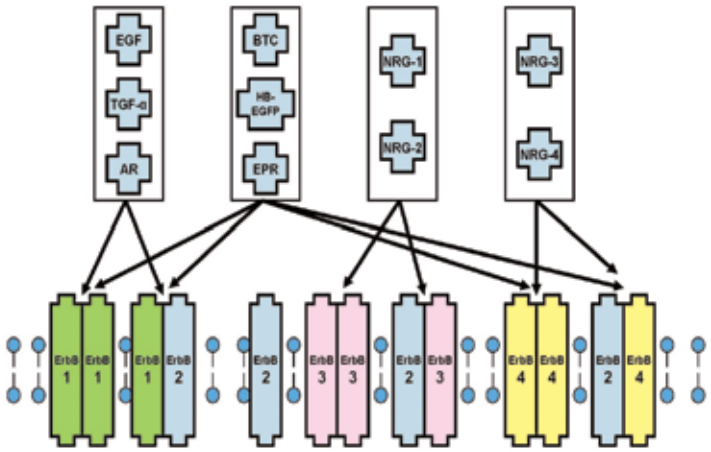


Figure 4: The Four Families of the Epidermal Growth Factor Receptor



The four families of the epidermal growth factor receptor (ErbB1, ErbB2, ErbB3 and ErbB4). Each of the four receptors combines to form a pair with a different receptor (a heterodimer) or itself (a homodimer). The 10 hormones which can bind the various receptors are depicted in boxes above the receptors. Their binding specificities are indicated by the arrows.[34]

labile hormones. Further, the acidity of the stomach and peptidase enzymes in the small intestine would also make it difficult for any peptide hormones in cow's milk to reach the intestines intact with full biological activity. Finally, the most daunting task of all would be for intact peptide hormones to cross the gut barrier that normally prevents intact proteins and large peptides from entering the epithelial cells lining the gut.

The Epidermal Growth Factor Receptor

Only 12 short years have elapsed since the discovery that humans bear a hormonal receptor in their gastrointestinal tract called the epidermal growth factor receptor (EGFR). This trans-membrane, hormonal receptor is very unusual in that it is expressed luminally—meaning that it faces the gut contents rather than the bloodstream.[29,30] The location of the EGFR puzzled scientists for years—why was it expressed luminally and what was its function?[31] Since, hormones always arrive at tissues from the circulation, why should the EGFR face the gut contents, which in effect are outside the body?

It turns out that the primary function of the luminally facing EGFR is to stimulate healing and maintain the integrity of the cells lining the gastrointestinal tract[30,32] In humans, the primary source of the hormone (EGF) which binds to the EGFR in the gut comes from saliva.[33] Hence by swallowing saliva, the residual EGF contained in saliva helps to maintain the integrity and promote healing of the epithelial cells lining the gut.

The EGFR is a promiscuous receptor in that it doesn't just bind a single hormone (EGF), but rather binds a large family of hormones including transforming growth factor alpha (TGF-α), heparin binding EGF(HB-EGF), epiregulin (EPR), amphiregulin (AR), neuregulins 1, 2, 3, and 4 (NRG1, NRG2, NRG3, NRG4), and betacellulin (BTC).[34] Cow's milk contains no EGF, but does contain high concentrations of BTC, amounting to 1.930ng/liter,[35,36] Additionally, BTC is quite stable and survives the pasteurization process and is even found in high concentrations in cheese,[36] Further, a low ph, such as may be found in the gut, does not impair or prevent BTC from binding its receptor.[37] Finally, bovine milk contains peptidase inhibitors that prevent human gut enzymes from degrading EGF receptor ligands.[38] In summary, BTC maintains all the physical characteristics needed to arrive in the gut intact and with full biological activity. But more importantly, it can breach the gut barrier and enter circulation by the transcellular EGFR route as depicted in *Figure 3*.

Once within circulation, BTC then has the capacity to bind EGF receptors bound in all epithelial cells, including keratinocytes. BTC can bind the specific receptors depicted *in Figure 4*.[34]

BTC from ingested bovine milk may contribute to the pathogenesis of acne by its ability to increase keratinocyte cell proliferation and to decrease keratinocyte apoptosis.[39] Further, BTC up-regulates its own receptor,[34] thereby causing additional signaling through the EGF receptor pathway. In support of the notion that increased flux through the EGF receptor pathway by exogenous BTC from milk may promote acne is the observation that EGF receptor blocking pharmaceuticals cause non-comedonal acne in most patients who are administered these drugs.[40,41]

Table 1: Glycemic Indices and Glycemic Loads of Various Food Groups[22]

	Glycemic Index	Glycemic Load		Glycemic Index	Glycemic Load
Grain Products			**Vegetables**		
Rice Krispie cereal	82	72.0	Baked Potato	85	21.4
Cornflakes	81	70.1	Sweet potato	61	14.8
Rice cakes	78	63.6	Yam	37	8.4
Shredded wheat cereal	75	62.0	Rutabaga	72	6.3
Graham wafers	74	56.8	Beets	64	6.3
Cheerio cereal	74	54.2	Carrots	47	4.7
Rye crisp bread	64	52.6			
Vanilla wafers	77	49.7	**Fruits**		
Stoned Wheat thins	67	41.9	Banana	52	11.9
Corn chips	63	39.9	Grapes	46	8.2
Muesli bar	61	39.3	Kiwi fruit	53	7.5
Bagel	72	38.4	Pineapple	59	7.3
Doughnuts	76	37.8	Apple	38	5.8
White bread	70	34.7	Pear	38	5.7
Whole wheat bread	71	32.7	Watermelon	72	5.2
All bran cereal	42	32.5	Orange	42	5.0
Sugar, sweets			**Dairy foods**		
Jelly beans	78	72.6	Ice cream	61	14.4
Lifesavers	70	67.9	Yogurt, low fat	27	5.3
Table sugar (sucrose)	65	64.9	Skim milk	32	1.6
Mars bar	65	40.4	Whole Milk	27	1.3

Glycemic load = (glycemic index x carbohydrate content in 100g portions. The glycemic reference is glucose with a glycemic index of 100.

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