Acne Vulgaris

A Disease of Western Civilization

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Background: In westernized societies, acne vulgaris is a nearly universal skin disease afflicting 79% to 95% of the adolescent population. In men and women older than 25 years, 40% to 54% have some degree of facial acne, and clinical facial acne persists into middle age in 12% of women and 3% of men. Epidemiological evidence suggests that acne incidence rates are considerably lower in nonwesternized societies. Herein we report the prevalence of acne in 2 nonwesternized populations: the Kitavan Islanders of Papua New Guinea and the Aché hunter-gatherers of Paraguay. Additionally, we analyze how elements in nonwesternized environments may influence the development of acne.

Observations: Of 1200 Kitavan subjects examined (including 300 aged 15-25 years), no case of acne (grade 1 with multiple comedones or grades 2-4) was observed. Of 115 Aché subjects examined (including 15 aged 15-25 years) over 843 days, no case of active acne (grades 1-4) was observed.

Conclusions: The astonishing difference in acne incidence rates between nonwesternized and fully modernized societies cannot be solely attributed to genetic differences among populations but likely results from differing environmental factors. Identification of these factors may be useful in the treatment of acne in Western populations.

Arch Dermatol. 2002;138:1584-1590

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ACNE AFFECTS between 40 million and 50 million individuals in the United States.[1] Although acne mainly affects adolescents, it is also present in children and adults. One study found some degree of facial acne in 54% of women and 40% of men older than 25 years.[2] In this same group, clinical facial acne affected 12% of the women and 3% of the men and persisted into middle age. Cunliffe and Gould[3] reported similar results 20 years earlier. In pediatric populations, the prevalence of acne increases with age. In 10- to 12-year-old children, 28% to 61% of the population has clinically diagnosed acne, whereas 79% to 95% of 16- to 18-year-old adolescents are affected.[4-6] Even a significant percentage of children (aged 4-7 years) are diagnosed with acne.[5] Thus in the Western world, acne is a ubiquitous skin disease affecting primarily adolescents but also a significant portion of adults older than 25 years.

Few studies have evaluated the prevalence of acne in nonwesternized societies. However, there is suggestive evidence in nonindustrialized societies that the incidence of acne is lower than in westernized populations. Schaefer,[7] a general practitioner who spent almost 30 years treating Inuit (Eskimo) people as they made the transition to modern life, reported that acne was absent in the Inuit population when they were living and eating in their traditional manner, but upon acculturation, acne prevalence became similar to that in Western societies.

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Prior to World War II, Okinawa was an isolated island outpost in the South China Sea, and its native inhabitants lived a rural life with few or none of the trappings of industrialized societies. Extensive medical questionnaires by US physicians administered to local physicians who had practiced from 8 to 41 years revealed that, "These people had no acne vulgaris."[8] Dermatological examination of 9955 schoolchildren (aged 6-16 years) conducted in a rural region in Brazil found that only 2.7% of this pediatric population had acne.[9] Dermatological examination of 2214 Peruvian adolescents by pe-

diatricians demonstrated that acne prevalence (grades 1-4) was lower (28%) in Peruvian Indians than in mestizos (43%) or whites (45%).[10]

In South Africa, dermatologists found lower rates of acne among the Bantu[11] than among whites[12] residing in Pretoria. Bantu adolescents (aged 15-19 years; n=510) maintained a 16% incidence rate of acne,[11] whereas among the white adolescents (n=1822), the incidence was 45%.[12] For the entire sample of Bantus of all ages (n=3905), the overall occurrence of acne was 2%,[11] whereas in the total white sample across all ages (n=16676), the incidence of acne was 10%.[12] Among the Zulu it was suggested that acne became a problem only when these people moved from rural African villages to cities.[13] All of these studies suggest that the prevalence of acne is lower among rural, nonwesternized people than in fully modernized Western societies.

Herein we report the absence of acne in 2 nonwesternized populations: the Kitavan people living on the Trobriand Islands near Papua New Guinea and the Aché hunter-gatherers of Paraguay. Additionally, we evaluate how elements in nonwesternized environments may influence the development of acne.

RESULTS

THE KITAVAN ISLANDERS

Population Parameters

Kitava is an island belonging to a group of coral atolls known as the Trobriand Islands located in Milne Bay Province, Papua New Guinea. Kitava has a surface area of 25 km^2 and is home to 2250 native inhabitants who live as subsistence horticulturalists and fishermen. Electricity, telephones, and motor vehicles were absent in 1990. Most Kitavans live in villages of 20 to 400 people. Some Western goods are received from the New Guinea mainland, but the influence of the Western lifestyle has been minimal.

General Health

Cardiac death and stroke are extremely rare among Kitavans.[14] Overweight, hypertension, and malnutrition are also absent.[14,15] Kitavans have low levels of serum insulin,[16] plasma plasminogen activator inhibitor 1 activity,[17] and leptin,[18] which suggests high insulin sensitivity throughout life. A moderately high level of physical activity, roughly 1.7 multiples of basal metabolic rate in male subjects, is another characteristic feature.[16] Three of 4 Kitavan men and women are daily smokers. Infections, accidents, complications of pregnancy, and senescence are the most common causes of death. Life expectancy is estimated at 45 years for newborns and 75 years or more at age 50. Mean age at menarche is 16 years.[19]

Diet

Tubers, fruit, fish, and coconut represent the dietary mainstays in Kitava. Dietary habits are virtually uninfluenced by Western foods in most households. The intake of dairy products, alcohol, coffee, and tea was close to nil, and that of oils, margarine, cereals, sugar, and salt was negligible. Estimated carbohydrate intake was high, almost 70% of daily energy, while total fat intake was low (20% of daily energy). Virtually all of the dietary carbohydrate intake was in the form of low–glycemic load tubers, fruits, and vegetables.

Methodology

During 7 weeks in 1990, one of us (S.L.) visited all 494 houses in Kitava and performed a general health examination in 1200 subjects 10 years or older, including 300 subjects between 15 and 25 years. Dr Lindeberg is a general practitioner whose formal training included detection of acne comedonica, acne papulopustulosa, and acne conglobata. As a practicing physician in Sweden, he regularly examines European patients with acne ranging from grade 1 through grade 4.

All subjects were examined specifically for skin disorders, including acne. However, the examinations were also designed to detect a number of other common Western diseases. Subjects were examined in daylight at a close enough distance to detect acne or scarring. In male subjects, the face, chest, and back were examined, whereas in female subjects, only the face and neck were examined. For the classification of acne the following system was used: grade 1, comedones present (open or closed), few papules present; grade 2, comedones and papules present, few pustules present; grade 3, comedones, papules, and pustules present, few nodules present; and grade 4, comedones, papules, pustules, nodules, and cysts present.

Dermatological Results

Not a single papule, pustule, or open comedone was observed in the entire population examined (N=1200). Although no closed comedones were reported, it is possible that they were present but undetected. Single bruises, scars, papules, or pustules of infectious origin were fairly common, including tropical ulcers, which rapidly healed following treatment with penicillin V. A number of intramuscular abscesses were also encountered.

THE ACHÉ HUNTER-GATHERERS

Population Parameters

The Aché of eastern Paraguay were full-time hunter-gatherers occupying a 20 000-km^2 area between the Paraguay and Paraná rivers until contact with Western civilization in the mid-1970s. Following contact, the Aché people settled in small communities near their traditional foraging range and now follow a mixed hunting-gathering and farming economy. Many aspects of Aché socioecology have been studied over the past 20 years.[20-23]

General Health

Since the late 1970s, multiple lines of evidence have demonstrated that contact with Western civilization was not necessarily beneficial from an overall health perspec-

tive.[22] Over the contact period, the Aché population has decreased by 30% as a result of deaths, primarily of respiratory tract infections. However, chronic diseases prevalent in urban communities (eg, diabetes, asthma, hypertension, and other cardiovascular disease) are still absent or rare.[22,24]

Diet

The Aché diet contains wild, foraged foods, locally cultivated foods, and Western foods obtained from external sources. By energy, their diet consists of 69% cultigens, 17% wild game, 8% Western foods, 3% domestic meat, and 3% collected forest products.[25,26] The cultigens consist mainly of sweet manioc, followed by peanuts, maize, and rice, whereas the Western goods are mainly pasta, flour, sugar, yerba tea, and bread.[23]

Methodology

The population was examined repeatedly over an 843-day period (September 1997 to June 2001), specifically for acne and for other skin and health disorders. I. Hurtado, MD, a general practitioner from the Instituto Venezolano de Investigaciones Cientifics, Caracas, Venezuela, initially examined all 115 subjects. Dr Hurtado's formal training included the detection and diagnosis of acne using the International Consensus Conference on Acne Classification system[27] with the following categories: *mild*, few to several comedones, papules, and pustules, no nodules; *moderate*, several to many comedones, papules, and pustules, few to several nodules; and *severe*, numerous comedones, papules, and pustules, many nodules. The face, chest, neck, and back of all subjects were examined at a close distance under bright lighting.

Every 6 months following the initial assessment, identical follow-up examinations were conducted by 1 of 6 family practitioner physicians who were also formally trained in the detection and recognition of acne using either the International Consensus Conference on Acne Classification system[27] or the 4-grade classification scheme used in the Kitavan sample. All subjects were regularly screened for any health problems by a health care worker, and all ailments were recorded in a log, including rashes, skin infections, and other dermatological disorders. One of us (M.H.) compiled all of the health care data during the observation period, including the dermatological data used in the present study. Over the observation period, the sample included an average of 115 subjects (59 men and women 16 years or older and 58 boys and girls younger than 16 years), including 15 subjects aged 15 to 25 years.

Dermatological Results

Not a single case of active acne vulgaris (mild, moderate, or severe[27] or grades 1 to 4) was observed in all 115 subjects over the 843-day study period by any of the 7 examining physicians. One 18-year-old man appeared to have acne scars. Not a single papule, pustule, or open comedo was observed in the entire population. Although no closed comedones were reported, it is possible that they could have been present and gone undetected. As in the Kitava sample, skin infections and intramuscular abscesses were common and responded well to treatment with antibiotics such as erythromycin and tetracycline.

COMMENT

GENETIC AND ENVIRONMENTAL CONSIDERATIONS

Of the 300 Kitavans at greatest risk for acne (aged 15-25 years), not a single case of acne was observed. In a similar Western population, some degree of facial acne would be found in at least 120 subjects.[2,4-6] In Western populations the development of acne has hereditary and environmental components. Familial studies have demonstrated that hereditary factors are important in determining susceptibility to acne,[28] whereas twin studies have suggested that although sebum secretion is under genetic control, the development of clinical lesions is modified by environmental factors.[29]

Clearly, genetic susceptibility to acne cannot be ruled out in the interpretation of our observations. However, it is unlikely that the effective absence of acne in the Kitavan and Aché people resulted entirely from genetic resistance to acne, since other South American Indians[10] and Pacific Islanders[30] whose ethnic backgrounds are similar to the Aché and Kitavans but who live in more westernized settings maintain considerably higher acne incidence rates than those we report. Consequently, our observations are suggestive that elements common to the Aché and Kitavan environments but not present in Western settings may operate together with genetic factors to prevent acne.

THE PROXIMATE ETIOLOGY OF ACNE VULGARIS

Acne is well understood 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 increases in sebum production; and (3) colonization of the follicle by *Propionibacterium acnes,* which generates inflammation.[31,32] The ultimate mechanism responsible for factors 1 and 2 is not well understood.[32,33] 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 AND HYPERINSULINEMIA

Although diet is infrequently considered as an etiologic agent in the development of acne,[34] it represents a well-recognized factor in acute[35]and chronic[36,37] 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. Hence, hyperinsulinemic diets may represent a previously unrecognized environmental factor in the development of acne via their influence on fol-

licular epithelial growth and keratinization and on androgen-mediated sebum secretion.

HYPERINSULINEMIA AND FREE IGF-1 AND IGFBP-3

Chronic and acute hyperinsulinemia initiate a hormonal cascade that favors unregulated tissue growth by simultaneously elevating levels of free insulinlike growth factor 1 (IGF-1) and reducing levels of insulinlike growth factor binding protein 3 (IGFBP-3).[38-41] Because free IGF-1 is a potent mitogen for virtually all body tissues,[42] elevated concentrations of free IGF-1 have a high potential for stimulating growth in all tissues, including the follicle.

In support of the notion that insulin-triggered elevations in free IGF-1 levels may promote acne via hyperkeratinization are data showing that IGF-1 is required for keratinocyte proliferation in humans[43] and that in transgenic mice, overexpression of IGF-1 results in hyperkeratosis and epidermal hyperplasia.[44] Furthermore, women with postadolescent acne maintain elevated serum concentrations of IGF-1[45] and are mildly insulin resistant.[46]

The reductions in IGFBP-3 levels stimulated by elevated serum insulin levels[38,39] or by acute ingestion of high–glycemic load carbohydrates[47] also may contribute to unregulated cell proliferation in the follicle. In murine knockout cells lacking the IGF receptor, IGFBP-3 acts as a growth inhibitory factor.[48] Accordingly, IGFBP-3 is inhibitory to growth by preventing IGF-1 from binding to its receptor. Hyperinsulinemia indirectly increases the number of epidermal growth factor receptors by elevating levels of plasma nonesterified fatty acids,[49] and it also induces production of transforming growth factor β1.[50] Increased concentrations of these cytokines depress localized keratinocyte synthesis of IGFBP-3, thereby increasing the availability of free IGF-1 to its keratinocyte receptors,[51] 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.[52] The body's natural retinoids (*trans* retinoic acid and 9-*cis*-retinoic acid) 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.[53]

Insulinlike growth factor binding protein 3 is a ligand for the RXRα nuclear receptor and enhances RXR-RXR homodimer–mediated signaling.[54] Studies in knockout rodents show that the *RXR*α gene is required for actions of the 2 endogenous retinoic acid ligands (*trans* retinoic acid and 9-*cis*-retinoic acid),[55,56] and RXRα agonists and IGFBP-3 are growth inhibitory in many cell lines.[57] Additionally, RXRα is the major RXR receptor in skin.[58] Consequently, low plasma levels of IGFBP-3 induced by hyperinsulinemia may reduce the effectiveness of the body's natural retinoids to activate genes that normally would limit follicular cell proliferation.

HYPERINSULINEMIA, IGF-1, ANDROGENESIS, AND SEBUM PRODUCTION

Sebum production, essential to the development of acne,[32] is stimulated by androgens.[31,32] Consequently, hyperinsulinemia may promote acne by its well-established androgenic effect. Insulin and IGF-1 stimulate the synthesis of androgens in ovarian[59,60] and testicular[61,62] tissues. Furthermore, insulin and IGF-1 inhibit the hepatic synthesis of sex hormone binding globulin (SHBG),[63,64] thereby increasing the bioavailability of circulating androgens to tissues. Cross-sectional studies demonstrate inverse relationships between serum SHBG and insulin[65] and IGF-1.[66-68] Additionally, sebum production is stimulated not only by androgens,[31,32] but also by insulin[69] and IGF-1.[70] Direct injections of recombinant IGF-1 in humans elicit androgenesis and acne.[71] Higher serum androgen,[72] insulin,[45] and IGF-1[46] concentrations are associated with the presence of acne in women. Taken together, these data suggest that the endocrine cascade induced by hyperinsulinemia enhances sebum synthesis and the development of acne.

POLYCYSTIC OVARY SYNDROME

Acne is a characteristic feature in patients with polycystic ovary syndrome, who are also frequently hyperinsulinemic, insulin resistant, and hyperandrogenic.[73] These patients typically maintain elevated serum concentrations of androgens and IGF-1 and lower concentrations of SHBG.[73-75] Androgen levels can be lowered and disease symptoms alleviated by improving insulin sensitivity through weight loss[76] or by use of pharmaceuticals such as metformin[77] that improve insulin metabolism. Numerous studies[78-80] have reported that tolbutamide, an antihyperglycemic drug similar to metformin, is therapeutically effective in treating acne.

DIETARY CHARACTERISTICS AND INSULIN RESISTANCE IN NONWESTERNIZED SOCIETIES

Both the Aché and Kitavan diets are composed of minimally processed plant and animal foods and are virtually devoid of typical Western carbohydrates that yield high glycemic loads that may acutely[35] or chronically[36,37] elevate insulin levels (**Table**). Recently acculturated hunter-gatherer populations who have adopted Western diets frequently are hyperinsulinemic and insulin resistant and have high rates of type 2 diabetes,[81,82] whereas hunter-gatherer and less westernized populations living in their native environments rarely exhibit

Glycemic Loads of Western Refined and Unrefined Traditional Foods*

Western Refined Foods			Unrefined Traditional Foods		
Food	Glycemic Index	Glycemic Load	Food	Glycemic Index	Glycemic Load
Crisped rice cereal (Rice Krispies)	88	77.3	Parsnips	97	19.5
Jelly beans	80	74.5	Baked potato	85	18.4
Toasted corn cereal (Cornflakes)	84	72.7	Boiled millet	71	16.8
Hard candy (Life Savers)	70	67.9	Boiled broad beans	79	15.5
Rice cakes	82	66.9	Boiled couscous	65	15.1
Table sugar (sucrose)	65	64.9	Boiled sweet potato	54	13.1
Shredded wheat cereal	69	57.0	Boiled brown rice	55	12.6
Graham crackers	74	56.8	Banana	53	12.1
Wheat and barley cereal (Grape-Nuts)	67	54.3	Boiled yam	51	11.5
Toasted oat cereal (Cheerios)	74	54.2	Boiled garbanzo beans	33	9.0
Rye crispbread	65	53.4	Pineapple	66	8.2
Vanilla wafers	77	49.7	Grapes	43	7.7
Corn chips	73	46.3	Kiwi fruit	52	7.4
Candy bar (Mars)	68	42.2	Carrots	71	7.2
Stoned wheat thins	67	41.9	Boiled peas	48	6.8
Shortbread cookies	64	41.9	Boiled beets	64	6.3
Granola bar	61	39.3	Boiled kidney beans	27	6.2
Angel food cake	67	38.7	Apple	39	6.0
Bagel	72	38.4	Boiled lentils	29	5.8
Doughnuts	76	37.8	Pear	36	5.4
White bread	70	34.7	Watermelon	72	5.2
Waffles	76	34.2	Orange	43	5.1
Bran cereal (All-Bran)	42	32.5	Cherries	22	3.7
Whole wheat bread	69	31.8	Peach	28	3.1
Croissant	67	31.2	Peanuts	14	2.6

*Glycemic load = glycemic index × carbohydrate content in 100-g portions. The glycemic reference is glucose with a glycemic index of 100.

these symptoms,[83-85] including other unacculturated South American Indian tribes.[86] Neither the Kitavan islanders nor the Aché hunter-gatherers manifest the classic symptoms of insulin resistance. The Kitavans are not overweight or hypertensive,[14,15] and they maintain low serum concentrations of insulin,[16] plasminogen activator inhibitor 1,[17] and leptin,[18] which are indicators of high insulin sensitivity.

Dietary interventions using low–glycemic load carbohydrates may have therapeutic potential in the treatment of acne because of the beneficial endocrine effects of these diets. Low–glycemic load diets are associated with a reduced risk for type 2 diabetes,[87] and dietary interventions using low–glycemic load carbohydrates improve insulin sensitivity.[88] Furthermore, a large-scale intervention[89] has demonstrated that diets rich in low–glycemic load foods reduced serum testosterone and fasting glucose levels while improving insulin metabolism and increasing concentrations of SHBG.[89] These endocrine changes are consistent with those known to promote normal follicular cell proliferation and to reduce sebum production. It is possible that low–glycemic load diets may have therapeutic potential in reducing symptoms of acne, a disease virtually unknown to the Aché and Kitavans.

Accepted for publication March 16, 2002.

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