Short Communication

Drug Policy and Treatment Bias Due to the Hyperlipidemia Theory of Acne Vulgaris: A Hypothesis and a Methodological Proposal

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Abstract

The current paradigm presumes the higher the triglyceride level, the greater the probability of acne vulgaris (AV) occurrence or severity. However, this prevailing view lacks the necessary premises required to prove causality—for which the reverse should hold true: that low TG levels are predictive of less AV occurrence or severity. A low TG concentration in patients with AV has not yet been addressed, probably because of (i) the lack of any hypothesis connecting low TG levels to AV, and (ii) a lower prevalence of hypotriglyceridemia compared to hypertriglyceridemia in societies, which may lead to missing or misdiagnosis of other types of AV. Therefore, a formal or causal position statement cannot be issued. My observations on the high prevalence of severe cases of AV in a subgroup of individuals with extremely low levels of either serum TG or TC levels (between 40–60 mg/dl) encouraged me to share this experience. I suggest that studies investigating AV calculate—retrospectively or prospectively—the odds ratio of finding AV in people with extremely low levels of TG and/or TC. I further propose that researchers investigating different therapeutic approaches and medications in patients with AV measure relevant parameters/variables (such as those described in this paper) to yield necessary data for contemporary and future trials. The prevailing view, i.e., hyperlipidemia theory, lacks the necessary premises required to prove causality and should be revisited.

Introduction

Acne vulgaris (AV) is considered an inflammatory disorder of the pilosebaceous follicle.[1] Etiologically, AV results from a hypersensitivity of the sebaceous glands to a normal circulating level of androgens, which are aggravated by inflammation and propionibacterium acnes (P. acnes).[2] Different causes and risk factors of AV include medications such as lithium, steroid hormones, and anticonvulsants. Other factors linked to AV include exposure to ambient sunlight, use of headbands, backpacks, underwire brassieres, and occlusive wear such as shoulder pads. Endocrine disorders (including polycystic ovarian syndrome and even pregnancy), genetic factors,[2] lifestyle factors such as smoking and high carbohydrate diets, and dairy products have also been attributed to

AV.[3] Previous research on etiology and risk factors of AV can be criticized because control groups were matched by only sex and age and not by other variables, such as genetics, environmental factors,[4,5] congenital adrenal hyperplasia,[6] dietary factors, menstrual history,[7] polycystic ovary syndrome,[8] insulin resistance,[5,8] insulin-like growth factor-1,[5] altered sex hormones,[9] medications (such as oral contraceptives and anti-acne agents),[10] and personal hygiene.[11]

Recently, many studies have reported that people with AV have higher levels of total cholesterol (TC), triglycerides (TGs), and low-density lipoprotein-cholesterol compared to healthy controls.[12–14] Some have wrongly concluded that an unhealthy lipid profile is an independent risk factor for AV. This conclusion is methodologically problematic by the arguments presented below:

It is well known that AV treatment with isotretinoin (Iso) elevates TC and TG.[15] This presents a confounding factor that likely mediates the pathogenesis and treatment; that is, TG levels are not a risk factor *per se*. Another possibility is that primary or secondary higher TC and/or TG levels may not always be risk factors for AV, but rather, these situations may at least in some cases or subtypes of affected people confer a protective effect.

There are inter-individual variances in sebocyte differentiation[16] that are connected with enhanced synthesis of lipids and accumulation in the sebocytes.[17] Sebocytes, the major cells within

Table 1. Clinical characteristics of subjects

	Subjects, n = 960		P value
	Subjects with hypercholesterolemia and/or hypertriglyceridemia (n = 762)	Subjects with hypocholesterolemia and/or hypotriglyceridemia (n = 198)	
Age* (years)	25.6 ± 4.5	26.7 ± 5.5	NS
Triglycerides* (mg/dl)	311 ± 34	49 ± 11	<0.0001
Cholesterol* (mg/dl)	307 ± 101	48 ± 8.5	<0.0001
Acne vulgaris (AV)**	AV (+) (n = 711)	AV (+) (n = 167)	<0.0001
	AV (−) (n = 51)	AV (−) (n = 31)	

*Values are mean + SD. **Odds ratio test (OR = 2.5879, 95% confidence interval = 1.6059 – 4.1702) showed that subjects with hypercholesterolemia and/or hypertriglyceridemia are more than two times more likely to have acne vulgaris.

sebaceous glands, are differentiated epithelial cells that gradually accumulate lipids and eventually disrupt, releasing their content (sebum) in a secretory process called holocrine secretion.[18] Furthermore, both hepatic X Receptor-α and Cyclo-oxygenase 2 (COX-2) play a role in the pathogenesis of AV through their effects on cellular proliferation, inflammation, and lipid synthesis.[19] There are again significant inter-individual differences in terms of hepatic X Receptor-α expression.[20] Several other nuclear receptors are implicated in the regulation of growth and differentiation of sebaceous glands. For instance, the androgen receptor is highly activated by androgens, such as dehydroepiandrosterone, androstenedione, and testosterone, which are known to stimulate sebum secretion in human skin.[21] Both estrogen receptor-α and -β are reported to be widely expressed in the sebaceous glands; nevertheless, estrogen locally antagonizes the effects of androgens within the sebaceous glands by regulating a set of genes that inversely impact growth and/or lipid production in sebaceous glands.[22] In addition to the aforementioned variables, peroxisome proliferator-activated receptor γ gene expression, retinoic acid receptors, and retinoid X receptors play major roles in the differentiation of sebocytes.[23]

It was recently shown that activation of hepatic X Receptor-α induces lipid synthesis in sebocytes that parallels the induction of sterol regulatory-binding protein-1 and peroxisome proliferator-activated receptors.[24] Inter-individual variability in the aforementioned factors further complicates the results and impacts the current understanding of the pathogenesis of AV and its treatment; overall, despite intra-individual variability, generally a similar treatment regimen is administered for patients with AV.

The unnecessary use of lipid-lowering agents in AV patients is well documented.[25] There are reports of side effects such as the significant elevation of the plasma level of homocysteine[26] and folic acid[27] after Iso treatment. In terms of adverse effects, one study recently reported that there is a significant negative correlation between the severity of AV before treatment and the level of 25 hydroxy vitamin D, whereas after, Iso therapy serum levels of 25 hydroxy vitamin D were significantly increased.[28]

Methods

I extensively searched various medical databases for studies that reported the existence of AV in people with low TG and/or TC. Articles in English came from databases including Google Scholar, Web of Science, OT search, CINAHL, Medline, PubMed, OT Direct, Pedro, SID, ProQuest, Up to Date, OVID Medline, and Cochrane. English keywords included "low cholesterolemia", "low triglyceridemia", hypocholesterolemia, hypotriglyceridemia,

dyslipidemia, "weight loss", "low-glycemic diet", "risk/benefit analysis", acne, and "acne vulgaris". The search was performed with no time limits and I found no published report in the English literature of such an observation. My observations on the high prevalence of severe cases of AV in a subgroup of individuals with extremely low levels of either serum TG or TC (between 40–60 mg/dl) encouraged me to share this experience. The data were collected from August 2011 to March 2023. Table 1 indicates that the incidence of acne vulgaris in subjects with hypocholesterolemia and/or hypotriglyceridemia is not only non-negligible but unexpectedly considerable.

Results and discussion

Results of weight loss trials employing two preliminary low-glycemic diets[29] and other medications such as combined metformin and rosiglitazone[30] show this to be an effective AV treatment. At the same time, there have been many other well-conducted clinical trials that have failed to have any beneficial effect on AV such as trials on exercise with and without metformin,[31] a combination of metformin and oral contraceptives,[32] gastric bypass surgery,[33] and clinical trials with low glycemic index carbohydrates.[34] Furthermore, the design of the aforementioned randomized clinical trials on the claimed beneficial effects of low-glycemic diets[29] has been criticized[35] for neglecting other aspects of the diet such as omega-3 fatty acids[36] and dietary fiber,[36] which have been shown to have strong therapeutic effects on AV. To the best of the author's knowledge, no clinical trials are available regarding the detrimental effects of lipid-lowering agents as an ancillary treatment for AV—most likely for ethical reasons. Such a lack of evidence limits our ability to make a causal claim that higher serum lipids directly mediate the pathogenesis of AV. Here, one may conjecture that other factors such as inter-individual genetic and hormonal variability may have led to artifact results.

Based on the above, it would be misleading to describe AV as a skin disease that is solely associated with hypertriglyceridemia, and while superficially valid, such a description ignores the many component dimensions of AV; thus this view should be revisited. This short paper is not intended to be an all-inclusive overview of the etiology and treatment of AV. Rather, to come to a better understanding of how an altered lipid profile might affect AV, I suggest that future studies investigating such relationships should take all these considerations and variables into account.

Also, to come to a better understanding of how different dietary patterns and/or treatments affect AV, the possible interaction or modification effect between the above-mentioned confounding

variables as well as other factors such as the role of cosmetics use and personal hygiene should be concomitantly considered in future studies, possibly facilitating the discovery of more suitable treatments for the management of this skin disease.

A precise and correct risk attribution is necessary to ensure the best therapeutic approach and eventually decision-making process for each patient. A risk/benefit analysis of AV treatment has never been carried out or at least reported) before, and it is unclear whether any beneficial anti-AV effect of standard treatments prevails over their adverse effect.

Limitations

There are limitations in my data analysis: I was not able to calculate adjusted OR due to missing data. Since many other variables can influence AV and its severity (such as waist circumference, waist-to-hip ratio, dehydroepiandrosterone, dehydroepiandrosterone sulfate, total testosterone, sex hormone-binding globulin, insulin resistance, free androgen index, follicle-stimulating hormone, luteinizing hormone, fasting glucose, or a homeostasis model assessment of insulin resistance), it would be wise to account for these important factors.

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Conflict of interest

The author declares no competing interests.

Data sharing statement

No additional data are available.

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