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Hormonal and dietary factors in acne vulgaris versus controls

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ABSTRACT

Background: Acne vulgaris is an inflammatory skin disorder with not as yet fully understood pathogenesis. In this controlled study, we assessed acne vulgaris patients for several possible pathogenic factors such as vitamin D deficiency, vegan diet, increased body mass index (BMI) and positive anti-transglutaminase antibody. **Methods**: We screened 10 years of records at a family medicine clinic for patients diagnosed with acne vulgaris. In eligible subjects, we collected data regarding 25-hydroxylvitamin D levels, BMI, dietary preference and serum IgA tissue transglutaminase levels. Controls were age- (+/− 12 months) and sex-matched patients seen during the study period without a diagnosis of acne vulgaris. **Results**: 453 patients were given a diagnosis of acne vulgaris during the study period. Compared with controls, we found significant associations between vitamin D deficiency (<50nmol/L), and/or positive transglutaminase antibody level (>4.0U/mL) and a diagnosis of acne vulgaris. **Conclusions**: Our study adds important information to the current body of literature in pursuit of elucidating the pathogenesis of this complex multifactorial disease.

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Acne vulgaris; vitamin D deficiency; anti-transglutaminase antibody; obesity; diet

Introduction

Acne vulgaris is a chronic inflammatory disorder of the pilosebaceous unit typically affecting areas with a high density of hormonally-responsive sebaceous glands such as the face, neck, chest, upper back, and upper arms.

Pathogenesis is complex and remains incompletely understood. Follicular hyperkeratinization, sebum production, Propionibacterium acnes and inflammation appear to be involved.[1] The role of factors such as vitamin D, diet, obesity and autoinflammation is evolving.

In vitro, vitamin D has been shown to regulate proliferation and differentiation of keratinocytes and sebocytes, and may also have anti-comedogenic properties. Associations between acne vulgaris and vitamin D deficiency have been demonstrated in a few small cohorts.[2-4]

Studies investigating the influence of diet on acne pathogenesis have been unconvincing and focused mainly on specific foods (e.g. milk),[5-7] which may be artificial in place of diet category. The relationship between body mass index (BMI) and acne has received limited attention and remains uncertain.

Anti-tissue transglutaminase antibody (anti-TTG) is a serum autoantibody utilised primarily in the diagnosis of coeliac disease. Anti-TTG positivity has been associated with vitamin D deficiency in coeliac disease, and has also been seen in several other autoinflammatory conditions.[8-10]

The aim of this study was to determine if there are any associations between serum vitamin D levels, vegan diet, increased BMI and/or anti-TTG, and acne vulgaris in a large Australian population.

Results

453 patients (205 males and 248 females) were enrolled in the study and their mean age was 22.8 years. The control group comprised 101 males and 149 females with a mean age of 23.1 years. Serum vitamin D levels, diet, body mass index, and positive tissue transglutaminase antibodies for both groups are detailed in Table 1.

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Table 1. Hormonal and dietary factors in acne patients vs controls.

	Patients (n = 453)	Controls (n = 250)	Chi^2 (1df)	*P* value
Vitamin D deficiency	192 (42.4%)	61 (24.4%)	22.62	$P<0.0005^*$
Vegan diet	8 (1.7%)	9 (3.6%)	2.3	$P = 0.1297$
Increased BMI	128 (28.2%)	67 (26.8%)	0.17	$P = 0.6798$
Positive tissue transglutaminase antibody	32 (7.0%)	5 (2.0%)	8.29	$P = 0.0040^*$

Coexistence of vitamin D deficiency and positive tissue transglutaminase in patients versus controls was statistically significant (chi^2 (1) = 5.10, Fisher's exact = 0.042). No other significant associations existed between any of the measured factors.

Results (Table 1) showed a statistically significant difference between acne and control groups for vitamin D deficiency (chi^2 (1) = 22.62, $p < 0.0005$) or positive tissue transglutaminase antibody (chi^2 (1) = 8.29, p = 0.004). The difference was not significant for vegan diet (chi^2 (1) = 2.3, $p = 0.1297$) or increased BMI (chi^2 (1) = 0.17, $p = 0.6798$).

When all possible combinations of factors were assessed for association with acne vulgaris vs controls, only Vitamin D deficiency occurring with positive tissue transglutaminase antibody was statistically significant (chi2 (1) = 5.89, Fisher's exact = 0.041).

Discussion

We found higher prevalence of vitamin D deficiency in patients compared with controls which has been reported previously in smaller series. Vitamin D supplementation has been shown to produce improvements in acne inflammation.2 There is consistency at a molecular level where Vitamin D has been demonstrated to reduce serum inflammatory biomarker expression (e.g. IL-6, IL-8, MMP-9) and inhibit P. acnes-induced Th-17 differentiation with decreased IL-17 expression, as well as induce antimicrobial peptide production in sebocytes.[11–13] The association between vitamin D deficiency and anti-TTG is explained by impaired absorption across an inflamed intestinal epithelium.

Acne patients were more than twice as likely to have a non-vegan diet compared with controls. Fundamentally, vegan diets contain no milk and generally lower glycemic index foods. Multiple studies have shown an association between acne and milk intake.[5–7] Low glycemic loads, with or without metformin, has been associated with greater reduction in acne lesion counts compared with high loads.[14,15] Milk consumption and high glycemic loads have been independently associated with increased levels of serum insulin growth factor-1, offering a possible mechanism.[16–19]

We found no significant association between increased BMI and acne vulgaris. Past study results have varied on this connection. Positive correlations have been found between low BMI and reduced risk for acne, and equally, rising BMI and increased risk.[20,21] Vitamin D deficiency has been shown to occur at higher rates in obesity compared with controls, possibly because of decreased bioavailability from dietary and cutaneous sources due to deposition in body fat compartments.[22] Based on our findings, any effect of vitamin D deficiency on acne pathogenesis appears to be independent of BMI.

In recent years, acne vulgaris has been increasingly described as a symptom of various autoinflammatory syndromes (e.g. PAPA, PASH).[23–26] Autoinflammatory diseases are signified by presence of an inheritance pattern and dysregulated innate immunity. Pathogenesis is not fully understood but is thought to be mediated primarily by abnormal interleukin-1 signaling.27 This mechanism has received additional support from successful treatment with IL-1 antagonists.[28]

Coeliac disease has been associated with several autoimmune conditions and autoinflammatory diseases overlap with, and may even mimic autoimmune diseases.[29] Innate immunity has been shown to play an important role in coeliac pathogenesis and may be necessary to trigger the gliadin-specific T-cell response in genetically-predisposed individuals.[30] Anti-TTG-positive coeliac disease was associated with acne diagnosis in a single study.[31] Future studies might better explore this association after exclusion of vitamin D deficiency.

Our study is limited by its retrospectivity. We categorised patients simply as either having, or not having a vegan diet. There is a variety of vegan diets featuring different food types. For this reason, breakdown of subtypes of vegan diets might have proved more

enlightening. This study might also be criticized for not confirming acne diagnoses with a skin specialist, however family physicians have demonstrated equivalence with dermatologists for diagnosis of several common skin diagnoses, including acne.[32]

Our findings reaffirm vitamin D and dietary factors as potential pathogenic players in clinically-evident acne vulgaris. In addition, we introduce a novel association between anti-tissue transglutaminase antibody and acne, which may act independently or dependently of Vitamin D status. This, along with our other identified associations warrant further investigation prospectively in larger cohorts. We lend credence to acne vulgaris as a highly complex disease with developing pathogenesis.

Materials and methods

We retrospectively screened records from January 2008 to May 2017 at a family medicine clinic for consecutive patients 16 years or older diagnosed with acne vulgaris who had presented primarily about their skin. In this population, BMI and 25-hydroxyvitamin D levels had been recorded within one month of acne diagnosis. Vitamin D testing was performed as part of general health screening. Vitamin D deficiency was defined as <50 nmol/L.

Routine Workup of vitamin D deficiency at our practice included enquiry about patients diet and testing of serum IgA tissue transglutaminase and total IgA antibody levels. Increased BMI was defined as >30 kg/m^2 and a tissue transglutaminase antibody level >4.0 U/mL was considered positive.

Controls were age- (+/− 12 months) and sex-matched patients seen during the study period without a diagnosis of acne vulgaris presenting for wellness checks. Patients were excluded if they had therapeutic interventions (within 3 months) which might have affected vitamin D levels including bisphosphonates, systemic corticosteroids, vitamin D or calcium supplementation, or IgA deficiency.

Statistical analyses were performed using STATA V14.2. Pearson's chi-squared and Fisher's exact tests were used to statistically analyse the data from the patient and control groups. P values of <0.05 were considered statistically significant.

Internal board review or ethics approval was not sought as all study data had been collected as part of the patients routine care at a private institution and is owned in its entirety by the second author. Study procedures were carried out in accordance with the Helsinki Declaration of 1975.

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