Dermatology Practical & Conceptual

Association Between Altered Gut Microbiota and Acne Vulgaris: A Comparative Study of Trimethylamine N-Oxide Levels in Patients and Healthy Controls

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ABSTRACT

Introduction: Microbiota refers to the microorganisms inhabiting specific environments, while the microbiome encompasses these organisms, their metabolites, and environmental factors. Variations in microbiota composition across body regions influence physiological processes, including metabolism, immunity, and skin health. Trimethylamine N-oxide (TMAO), a metabolite linked to gut dysbiosis, inflammation, and systemic diseases, has not been previously investigated in acne patients.

Objective: We aimed to investigate the potential relationship between gut dysbiosis and acne vulgaris by assessing serum TMAO levels in acne patients compared to healthy controls.

Methods: This case-control, cross-sectional study involved 70 acne patients and 70 age- and sex-matched healthy controls. Serum TMAO levels were measured, and acne severity was graded using the Global Acne Grading System (GAGS). Statistical analysis was performed using SPSS 20.0, with p-values <0.05 considered significant.

Results: Acne patients exhibited significantly higher serum TMAO levels (16.74 ± 10.10 ng/ml) compared to controls (13.11 ± 4.28 ng/ml, *P*=0.007). While no significant correlation was found between TMAO levels and acne severity, a weak negative trend was observed (*P*=0.062). Similarly, TMAO levels showed no significant correlation with body mass index (BMI) (*P*=0.933).

Conclusion: This study identified elevated serum TMAO levels in acne vulgaris patients, suggesting a potential link between gut dysbiosis, diet, and acne pathogenesis. While these findings emphasize the role of systemic inflammation and microbiota, further research is necessary to establish causal relationships and to evaluate the impact of dietary and microbial interventions in acne management.

Introduction

The term microbiota refers to microorganisms such as bacteria, fungi, and viruses present in a given environment, while the term microbiome encompasses these microorganisms along with microbial elements, metabolites, and environmental conditions as a whole. The components of microbiota vary across different regions of the body, with distinct compositions observed in areas such as the gut and skin [1]. Studies have shown that the microbiome plays a role in vital physiological processes such as energy balance, metabolism, gut epithelial health, immune activities, and neurobehavioral development [2]. Changes in the microbiome have been associated with diseases such as inflammatory bowel disease, type 2 diabetes, psoriasis, and Parkinson's disease [3].

Trimethylamine N-oxide (TMAO) is a metabolite produced in the liver from trimethylamine (TMA), which is generated by the gut microbiota through the metabolism of dietary nutrients such as choline, betaine, and L-carnitine [4-6]. In the liver, TMA is oxidized to TMAO primarily by flavin monooxygenase (FMO) enzymes, with FMO-3 acting as the rate-limiting enzyme in this process [7]. TMAO has been implicated in promoting oxidative stress and low-grade chronic systemic inflammation, which are key contributors to various chronic diseases [8]. Elevated TMAO levels have been associated with high dietary intake of choline and L-carnitine as well as gut dysbiosis [9,10].

Studies have shown that gastrointestinal health and skin balance are closely linked through the regulation of both the innate and adaptive immune systems. While this regulation is mainly mediated by the gut microbiota, the skin microbiota is also important to maintaining skin immune balance. A disruption of this balance can lead to weakened skin barrier function. This connection has also been implicated in dermatologic conditions such as hidradenitis suppurativa (HS) and acne vulgaris [11].

In the dermatological context, hidradenitis suppurativa (HS), a chronic inflammatory skin disorder affecting the pilosebaceous unit and sharing pathogenic mechanisms with acne vulgaris, has been linked to increased circulating TMAO levels, which correlate with disease severity [4,12].

Acne vulgaris is a common chronic inflammatory disease. While genetic and hormonal factors are known to play a role in its development, the relationship between diet and acne remains unclear. Studies suggest that a high glycemic index diet, dairy products, and chocolate consumption may trigger or exacerbate acne vulgaris [13,14]. Research has shown a bidirectional interaction between gut microbiota and skin homeostasis through immune system regulation. However, the relationship between acne and microbiota has not yet been fully elucidated [15,16].

Objective

TMAO levels, an indirect marker of gut dysbiosis and inflammatory processes, were investigated in this study in patients with acne vulgaris. The aim was to explore the potential role of gut dysbiosis in acne development by comparing patients with a healthy control group.

Methods

This case-control, cross-sectional, observational study was conducted between September 2023 and April 2024 at the Dermatology and Venereal Diseases outpatient clinic. Ethical approval was obtained from the Ethics Committee for Clinical Research at Ankara Bilkent City Hospital (approval number: E1-23-3868). All participants were verbally informed about the study, and detailed written informed consent was obtained.

The study included 140 volunteers: 70 patients with acne vulgaris and 70 healthy individuals as controls. The control group was matched to the patient population in terms of age and sex. The inclusion criteria were volunteers aged 18 years or older, no known systemic disease, and first-time hospital admission for acne. The control group consisted of volunteers aged 18 years or older with no history of acne vulgaris or any known systemic disease. Patients diagnosed with seborrheic dermatitis, polycystic ovary syndrome, rosacea, or inflammatory bowel disease were excluded. Patients who had previously been treated for acne with antibiotic therapy within the preceding six months or who were smokers were also excluded.

For eligible participants, demographic data, height, and weight were recorded. Disease severity was assessed using the Global Acne Grading System (GAGS), a standardized tool developed by Doshi et al. (1997), and the corresponding scores were recorded. [17]. Blood samples were collected to evaluate TMAO levels.

Descriptive data are presented as frequencies, percentages, means, standard deviations, and minimum-maximum values. The normality of the data distribution was assessed using Kolmogorov-Smirnov and Shapiro-Wilk tests. Differences in distribution between the two groups were analyzed using the chi-square test. Differences between two group means were evaluated using the Student's T-test, while differences among three group means were analyzed using the one-way ANOVA test. Relationships between two numerical values were assessed using Pearson's correlation test. A p-value of <0.05 was considered statistically significant. Data analysis was performed using SPSS 20.0 software.

Results

The study included 70 acne patients and 70 healthy volunteers matched to the patients in terms of age and sex. The mean age of the acne group was 21.6 ± 3.77 years, while that of the control group was 20.76 ± 3.26 years. Females accounted for 67% of the acne group and 48% of the control group. The mean BMI in the acne group was 22.16 ± 4.43, compared to 22.02 ± 3.58 in the control group, with no statistically significant difference between them. The mean serum TMAO level in the acne group was 16.74 ± 10.10 ng/ml, compared to 13.11 ± 4.28 ng/ml in the control group; this difference was statistically significant (*P*=0.007; Table 1) and is illustrated in Figure 1.

Acne patients were evaluated using GAGS and categorized into three groups: mild, moderate, and severe. Although serum TMAO levels tended to be higher in patients with mild acne (19.75 ± 10.45 ng/ml) and lower in those with severe acne (16.67 ± 10.89 ng/ml), the difference was not statistically significant (*P*=0.062; Table 2). The correlation between TMAO levels and GAGS scores was weakly negative and did not reach statistical significance (*P*=0.084). Similarly, the correlation between TMAO levels and BMI was also weakly negative and not statistically significant (*P*=0.933).

Discussion

This study investigated serum TMAO levels in patients with acne vulgaris, providing insight into the potential involvement of gut dysbiosis in acne pathogenesis. The results indicate that serum TMAO levels, which have been linked to inflammation and cardiovascular risk and are considered a marker of gut dysbiosis [6], were significantly higher in acne patients compared to healthy controls. These findings suggest a possible association between gut microbiota alterations and the development of acne vulgaris.

Similarly, increased TMAO levels have also been observed in hidradenitis suppurativa (HS), a disease of the pilosebaceous unit like acne. In a study by Barrea et al., a correlation was identified between TMAO levels and disease severity. Elevated TMAO, considered a marker of inflammation, may also reflect increased systemic inflammation in HS patients [4]. In this study, while TMAO levels were found to be elevated in acne patients compared to the control group, no significant relationship was observed between acne severity and TMAO levels.

Recent evidence indicates that certain probiotics and prebiotics may reduce systemic TMAO levels by modulating gut microbiota composition. Strain-specific effects have been observed, particularly with *Lactobacillus rhamnosus* GG and *Lactiplantibacillus plantarum* ZDY04, which were shown to lower TMAO concentrations in both animal and limited human studies [18,19]. These findings suggest a potential role for microbiota-targeted interventions in reducing TMAO-mediated inflammation, which may be relevant in acne pathogenesis.

Table 1. Demographic Characteristics, TMAO Levels, and Acne Severity in Compared Groups.

Characteristics	Case	Control	p-value
Number of participants	70	70	
Age (year) (mean ± SD)	21.61 ± 3.77	20.76 ± 3.26	0.153
Sex [N (%)]			
Male	24 (34.3)	22 (31.4)	0.719
Female	46 (65.7)	48 (68.6)	
BMI (mean ± SD)	22.16 ± 4.43	22.02 ± 3.58	0.840
TMAO (mean ± SD)	16.74 ± 10.10	13.11 ± 4.28	**0.007**
GAGS (mean ± SD) (min-max)	21.90 ± 8.65 (8-42)		

SD: standard deviation; GAGS: Global Acne Grading System; BMI: body mass index; TMAO: Trimethylamine N-oxide.

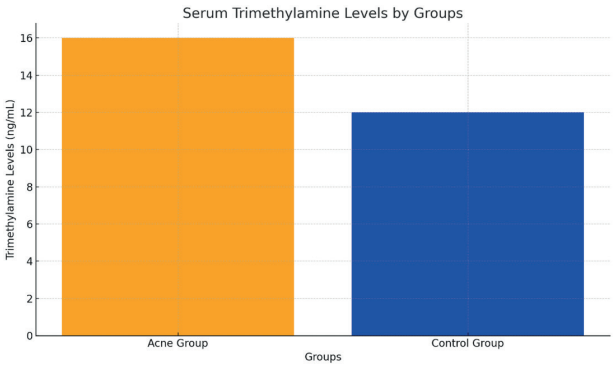

Figure 1. Comparison of mean serum trimethylamine N-oxide (TMAO) levels between the acne group and the control group. TMAO levels were significantly higher in the acne group (P=0.007).

Table 2. Demographic Characteristics, TMAO Levels, and Acne Severity by Severity Groups.

Characteristics	Severe	Moderate	Mild	p-value
Number of participants	16	25	29	
TMAO (mean ± SD)	16.67 ± 10.89	13.28 ± 8.29	19.75 ± 10.45	0.062

Diet plays a significant role in shaping the microbiota, which has been associated with various systemic diseases. Research has shown that dietary changes can significantly alter microbiota composition within 24 hours [20]. For example, a red meat-based diet increases *Bacteroides* and *Clostridia spp.*, while reducing *Bifidobacterium spp.* In contrast, a plant-based protein diet promotes *Bifidobacterium* and *Lactobacillus* growth, while reducing *Bacteroides* and *Clostridium* populations. Similarly, diets rich in saturated and unsaturated fatty acids or high in carbohydrates also influence microbiome composition [21]. Foods rich in choline and carnitine, such as red meat, eggs, milk, and cheese, promote TMA production by *Firmicutes* and *Proteobacteria* [22].

Moreover, short-chain fatty acids (SCFAs) such as acetate and butyrate, produced by beneficial gut microbes, are recognized for their anti-inflammatory properties and roles in maintaining gut epithelial integrity. In acne patients, dysbiosis has been linked to reduced acetate levels and a decline in SCFA-producing bacteria like *Fecalibacterium* spp., which may contribute to systemic inflammation and increased intestinal permeability [23,24]. These findings further support the relevance of gut-derived metabolites in acne and suggest new directions for microbiota-based therapeutic approaches.

This study has several limitations. First, its case-control design restricts causal inferences regarding the role of TMAO in acne pathogenesis. Although significantly higher TMAO levels were observed in acne patients compared to healthy controls, no significant association was found between TMAO levels and acne severity; this may be attributed to the limited sample size, which could have reduced statistical power. While the study discusses gut dysbiosis, no microbial profiling was performed, preventing identification of specific TMA-producing or SCFA-reducing bacterial taxa. Additionally, dietary intake was not recorded, despite the known influence of red meat, eggs, and fish on TMAO production. Other potentially influential factors such as probiotic use, menstrual status, stress, sleep, and physical activity were not systematically assessed. Finally, inflammatory markers such as CRP or IL-6 were not measured, limiting direct confirmation of systemic inflammation.

Conclusion

In this study, serum TMAO levels, an indirect marker influenced by diet and gut microbiota, were found to be elevated in patients with acne vulgaris, suggesting that dietary factors may contribute to acne pathogenesis. Previous research has reported associations between high glycemic index diets, dairy consumption, and acne development, which may support a potential link between diet, gut-derived metabolites such as TMAO, and acne [25,26].

This study investigated TMAO levels in acne vulgaris patients. Further research is warranted to clarify the potential role of gut microbiota and diet in acne pathogenesis.

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