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Original Article

Levels of trimethylamine N-oxide and lipopolysaccharides in vascular and idiopathic erectile dysfunction

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Abstract

The gut microbiota influences endothelial dysfunction through metabolites like lipopolysaccharides (LPS) and trimethylamine-N-oxide (TMAO), affecting cardiovascular health and contributing to atherosclerosis and hypertension development. We evaluated TMAO and LPS levels in patients with vascular and idiopathic erectile dysfunction (ED). In this study of 151 participants (50 vascular ED, 50 idiopathic ED, 51 healthy controls), patients were categorized using comprehensive clinical assessment including International Index of Erectile Function (IIEF), laboratory tests, and imaging methods. While age (mean 55.15±7.17 years) and TMAO levels showed no significant differences between groups ($p>0.05$), LPS levels were significantly elevated in the vascular ED group (497.36±87.83) compared to idiopathic ED (430.62±69.72) and control groups (436.98±105.37) ($p<0.05$). These findings suggest that gut microbiota metabolites, particularly LPS, play a significant role in ED pathophysiology through endothelial dysfunction. Regulating gut microbiota may serve as both a protective factor against ED development and a potential treatment option for existing cases. Further comprehensive studies are warranted to explore these therapeutic possibilities.

Keywords: Vascular erectile dysfunction, Idiopathic erectile dysfunction, Lipopolysaccharide (LPS), Trimethylamine N-oxide (TMAO), Endothelial damage.

1. Introduction

Erectile dysfunction (ED) is the persistent inability to achieve or maintain sufficient penile erection for sexual intercourse [1]. ED is a health issue that has persisted since ancient times, having significant negative effects on both psychosocial and physical aspects of life [2]. The prevalence of ED has been shown to be 52% in men aged between 40 and 70 years [3]. The main identified risk factors include age, coronary artery disease (CAD), obesity, smoking, depression, hypertension (HT), previous pelvic surgery, psychological factors, and spinal cord injury [4]. In the diagnostic phase, the patient's medical, sexual, and psychosocial history should be thoroughly investigated [5].

It has been determined that erectile dysfunction is associated with endothelial dysfunction, and in addition, it is an important indicator of cardiovascular diseases (CVD). A decrease in nitric oxide (NO) production from endothelial cells adversely affects the smooth muscles in the corpora cavernosa, leading to reduced blood flow and less relaxation of smooth muscle cells, resulting in ED [6].

Changes in the gut microbiota have been shown to be associated with many diseases such as CVD, type 2 diabetes mellitus (DM), inflammatory bowel diseases, asthma, and psychiatric disorders [7–11]. Low-grade chronic inflammation resulting from changes in the gut microbiota predisposes to the development of atherosclerosis and HT. Metabolites derived from changes in the microbiota, such as lipopolysaccharides (LPS) which are endotoxins in the outer membrane of gram-negative bacteria, and trimethylamine-N-oxide (TMAO), obtained from dietary intake of red meat, eggs, and fish-derived choline and L-carnitine, have been found to cause endothelial dysfunction, thus affecting cardiovascular health and effectively contributing to atherosclerosis and HT [12,13].

Research conducted on the roles of TMAO and LPS, which have vascular effects, in ED is still very limited. Therefore, in our study, the serum levels of TMAO and LPS in vascular and idiopathic ED were aimed to be evaluated.

2. Materials and Methods

2.1. Patient selection and method

Our study was conducted with approval from the

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Ethical Committee of Elazığ Fırat University, dated January 13, 2022, with reference number 2022-6281. Between February 1, 2022, and February 1, 2023, patients presenting with ED complaints to the Urology Department Clinic of Elazığ Fırat University were evaluated based on anamnesis, physical examination, International Erectile Function Score (IIEF scoring), serum follicle stimulating hormone (FSH), luteinising hormone (LH), prolactin (PRL), thyroid function tests (TSH, T3, T4), testosterone levels, and penile Doppler ultrasonography (USG) results. In our study, patients with an IIEF score below 21 were accepted as having ED. Patients with hormonal ED were excluded, and among those with arterial or venous insufficiency, those with vascular ED were classified, while individuals with no pathological findings on USG were classified as having idiopathic ED. After classifying patients into vascular and idiopathic ED groups, serum TMAO and LPS levels in these patients and those in the control group were examined. Before measuring serum TMAO and LPS levels, factors such as sepsis, acute gastroenteritis, and high-fat food consumption prior to measurement, which can lead to sudden increases in these levels, were taken into account during patient history inquiries, with the aim of preventing false positive results.

2.2. Inclusion criteria

Patients presenting to our clinic with ED complaints, aged between 35-70 years regardless of age category, with an IIEF score below 21, without neurogenic, psychogenic, or hormonal ED, and who gave consent to participate in the study were included.

Excluded from the study were patients who had undergone pelvic radical surgery, had neurogenic erectile dysfunction (history of spinal trauma, multiple sclerosis, Parkinson's disease, etc.), untreated hypothyroidism and hyperthyroidism, exhibited morning erections but had psychogenic ED complaints related to performance anxiety during intercourse, were using antipsychotic or antihypertensive medications that could lead to erectile dysfunction, with alcohol/substance addiction, and those using phosphodiesterase type 5 (PDE-5) inhibitors that could affect the study outcome.

Healthy individuals without comorbidities and ED complaints were included as the control group.

2.3. Laboratory evaluation

5 ml of blood samples were taken from the patient group and the control group into aprotin-containing tubes. Blood samples taken in aprotinin-containing and plain biochemical tubes were centrifuged at 3,500 rpm for 5 minutes (NF1200R, Nuve, Ankara, Turkey) within half an hour, and the sera were separated. Blood samples taken in aprotinin tubes were stored at -80°C until processed. Routine biochemical samples of patients were processed in the Central Biochemistry Laboratory of Fırat University Hospital. After all samples were collected, serum TMAO and LPS levels were measured using the ELISA method.

2.4. Imaging method

The requested penile Doppler ultrasound test (Samsung V8, Gyeonggi-do, South Korea) for patient groups was performed in the ultrasound rooms of the Radiology Department at Fırat University Hospital. Prior to the Doppler ultrasound, a vasoactive agent, 60 mg of papaverine, was administered intracavernosally to the patient. Afterwards, at the 5th, 15th, and 30th minutes post-injection, the peak systolic and end-diastolic flow velocities of the cavernosal artery were measured using Doppler ultrasound. If during the measurement period, the peak systolic flow velocity did not exceed 25 cm/s or the end-diastolic flow velocity did not drop below 5 cm/s, the patient was diagnosed with vasculogenic ED**.**

2.5. Biochemical analysis of samples

Blood collected from participants was taken into sterile 3 mL aprotinin tubes (Hema and Tube Edta K3, Reference No: HG 3081) and left at 25°C for approximately 30 minutes before being centrifuged at 10,000 rpm for 15 minutes (Hettich Universal 1200, Germany). After centrifugation, the plasma obtained was placed in 2 mL Eppendorf tubes and stored at -40°C in a deep freezer (GFL, Italy) until analysis. Plasma TMAO and LPS concentrations were determined using SunRed ELISA kits with reference numbers DZE201127378 and DZE201121792 respectively (Shanghai, China). During the preparation of standard solutions in the study, a VELP ZX3 vortex mixer (Shanghai, China) was used. All incubation steps of the study were carried out in an Allsheng MB100-4A shaking incubator (Zhejiang, China), and washing steps were performed using a BioTek ELx50 microplate washer (California, United States). Samples were measured spectrophotometrically at 450 nm using an Agilent BioTek Epoch 2 microplate reader (California, United States) with BioTek Gen5 software, Version 3.05.

2.6. Statistical analysis

Statistical analyses were performed using the SPSS version 26.0 package program. Descriptive statistics were expressed as mean and standard deviation. The normality of the distribution of variables was examined using visual (histogram and probability plots) and analytical methods (Kolmogorov–Smirnov and Shapiro-Wilk tests). Depending on whether the data showed a normal distribution, numerical variables were compared between three or more groups using the One-Way ANOVA test. In post hoc pairwise comparisons between groups, the Tukey test was used. In the statistical analyses of the study, comparisons with p-values below 0.05 were considered statistically significant.

Since the FSH, testosterone, and glycosylated haemoglobin (HbA1c) values of patients with idiopathic and vascular ED did not follow a normal distribution, they were evaluated using the Mann-Whitney U test. Comparisons were presented as median and interquartile ranges. A p-value of <0.05 was accepted for statistical significance.

3. Results

A total of 151 individuals were included in the study, comprising 50 patients with vascular ED, 50 patients with idiopathic ED, and 51 healthy controls. Table 1 presents the comparison of age, TMAO, and LPS levels among the vascular ED, idiopathic ED, and healthy control groups, and Table 2 presents the comparison of FSH, testosterone, and HbA1c levels between patients with vascular and idiopathic ED.

3.1. Age, TMAO, and LPS levels

There were no significant differences in age among the

Table 1. Comparisons of age, TMAO, LPS and hormone profiles among the VED, IED and control groups.

	VED (n=50)	IED (n=50)	Control (n=51)	P Value
Age	56.46±5.57	55.16±6.19	53.78±9.09	0.17
TMAO	2.02±1.11	1.76±1.28	1.81±0.67	0.423
LPS	497.36±87.83	430.62±69.72	436.98±105.37	**<0.001**
IIEF	9.46±2.72	14.46±3.17	27.01±1.34	**<0.001**
Additional disease (DM, HT or CVD)	At least one	None	None	

One-Way ANOVA test was applied for comparisons among the VED, IED and control groups. Post-hoc Tukey test was used for pairwise comparisons between groups.

Table 2. Hormone profiles Bbetween idiopathic and vascular ED groups.

	IED Median Value (IQR) (n=50)	VED Median Value (IQR) (n=50)	U Value	P Value
FSH	5.73 (4.03 –6.92)	5.35 (3.89 – 8.16)	1237	0.929
Testosterone	430.46 (395.96 – 540.37)	439 (342.28 –516.59)	1130	0.408
HbA1c	5.5 (5.2 – 5.8)	6.1 (5.57 – 8.1)	570	**<0.001**

IQR: Interquartile range.

vascular ED (mean age = 56.46 ± 5.57 years), idiopathic ED (mean age = 55.16 ± 6.19 years), and healthy control groups (mean age = 53.78 ± 9.09 years; p = 0.17). Similarly, TMAO levels did not differ significantly between the groups (vascular ED: 2.02 ± 1.11 µM; idiopathic ED: 1.76 ± 1.28 µM; controls: 1.81 ± 0.67 µM; p = 0.423) (Fig. 1). In contrast, LPS levels exhibited significant variation among the groups (p < 0.001). Post hoc Tukey analysis revealed that LPS levels were significantly higher in the vascular ED group (497.36 ± 87.83 ng/mL) compared to both the idiopathic ED group (430.62 ± 69.72 ng/mL; p = 0.001) and the healthy controls (436.98 ± 105.37 ng/mL; p = 0.002). No significant difference in LPS levels was observed between the idiopathic ED and control groups (p > 0.05) (Fig. 1).

3.2. Hormone profiles

Table 2 presents the comparisons of FSH, testosterone, and HbA1c levels between the vascular and idiopathic ED groups. There were no significant differences in FSH (vascular ED median = 5.73 µIU/mL; idiopathic ED median = 5.35 µIU/mL; U = 1237.0; p = 0.929) or testosterone levels (vascular ED median = 430.46 ng/dL; idiopathic ED median = 439 ng/dL; U = 1130.00; p = 0.408). However, HbA1c levels were significantly elevated in the vascular ED group (median = 6.1%) compared to the idiopathic ED group (median = 5.5%; U = 570.00; p < 0.001).

4. Discussion

ED is a commonly encountered sexual dysfunction in men. Today, it is known that endothelial cells, in addition to influencing vascular tone, play a role in processes such as atherosclerosis, cardiovascular diseases, peripheral vascular diseases (PVD), and ED.

In a study published by Russo et al. (2022), the relationship between the gut microbiota and both ED and benign prostatic hyperplasia was demonstrated. In this study, it was proposed that changes in the gut microbiota may indirectly affect prostate health through activation of the immune system and the release of pro-inflammatory cytokines such as interleukin-17 (IL-17), interleukin-23 (IL-23), tumor necrosis factor-alpha (TNF-alpha), and interferon-gamma (IFN-gamma). Sexual dysfunction caused by stress and anxiety, the development of metabolic problems such as obesity and diabetes, changes in hormone levels and metabolic profiles together with HT, and gut dysbiosis have been linked to the onset of ED [14].

Leelani et al. (2023) examined the relationship between ED and the gut microbiome and found strong evidence that the gut microbiome is closely related to known risk factors for ED such as DM, HT, metabolic syndrome (MS), and obesity. For instance, it has been shown that certain bacterial species in the gut flora of obese individuals are found at lower levels. Furthermore, it has been reported that the gut microbiome plays an important role in regulating androgen levels [15].

Okamoto et al. (2020) divided 408 male participants according to their IIEF-5 scores into two groups (IIEF-5 ≤16 and >16), evaluated the relationship between the gut microbiome and ED based on 96 men matched by age, and found no significant differences between the groups in terms of a history of HT, CAD, and PVD. However, statistically significant differences were observed in species of Clostridium XVIII, thought to be associated with gut motility, and Alistipes, associated with anti-inflammation [16].

Some studies have shown the role of gut-derived metabolites such as TMAO and LPS in the development of chronic diseases and ED [17,18]. TMAO has been repor-

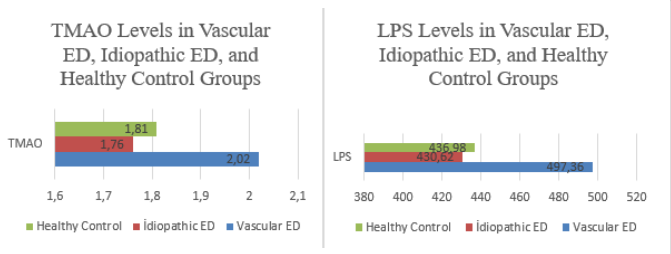

Fig. 1. TMAO and LPS levels in vascular ED, idiopathic ED, and healthy control groups.

ted as an independent determinant in the development of PVD, and it has been stated that diets supplemented with choline/TMAO accelerate atherosclerosis. Phosphatidylcholine, found in cheese, egg yolk, meat, and shellfish, is converted to trimethylamine (TMA) by the TMA lyase enzyme in the gut microbiota. TMA, in turn, is oxidized to TMAO by flavin-containing monooxygenases in the liver [19]. Similarly, because L-carnitine contains a trimethylamine structure similar to TMA, it can also increase TMAO levels and accelerate atherosclerosis [20].

Tsai et al. (2021) drew attention to the close relationship between type 2 DM and cardiovascular diseases and showed that the gut microbiota plays a role in the onset and progression of DM, and therefore the formation of PVD. In this study, the relationship between the gut microbiota of 155 participants and the presence of type 2 DM and subclinical PVD was evaluated, revealing that certain bacterial species are closely related to PVD [21]. In our study as well, we found higher serum TMAO and LPS levels in patients with vasculogenic ED, supporting the relationship between the microbiota and atherosclerosis.

Zhu et al. (2020) showed that TMAO exerts pro-atherogenic properties by influencing traditional risk factors for atherosclerosis, thereby increasing the risk of cardiovascular events [22]. Kang et al. (2023) compared the gut microbiota profiles of 43 men with ED and 16 healthy men, finding that Actinomyces species were negatively correlated with erection quality duration and that some species were positively correlated with IIEF-5 scores. In addition, it was reported that the disruption of the intestinal barrier could lead to chronic inflammation, metabolic and endocrine disorders, and insulin resistance, thereby negatively affecting the spermatogenesis mechanism. Moreover, it was emphasized that dysbiosis in the gut microbiota could contribute to vascular inflammation and ED by increasing circulating TMAO levels [23]. On the other hand, in a study conducted by Osman et al. (2023), no statistically significant difference was found between the gut microbiota of 28 men with ED and 32 healthy men [18].

In our study, similar to that of Osman et al. (2023), no statistically significant difference was observed in TMAO levels. Although the direct effect of TMAO on the pathophysiology of ED has not yet been fully explained, some studies suggest that it may contribute indirectly as an important component of vascular inflammation [24]. Since the half-life of TMAO can change depending on dietary intake, this might influence results. TMAO levels are known to be affected by many factors such as age, sex, diet, gut microbiota composition, kidney function, and flavin monooxygenase activity in the liver [25]. Diet, in particular, holds a significant place among these factors. For example, elements of the Mediterranean diet (e.g., red wine, balsamic vinegar, and cold-pressed olive oil) help suppress TMAO, whereas fatty diets, red meat, and egg yolks can increase TMAO levels [26]. Besides diet, we believe that lifestyle factors (such as exercise, stress, work life, etc.) can also influence TMAO levels. As part of our study, on the days when the patients' TMAO and LPS levels were measured, recent high-fat food consumption was queried; however, because the patients were located in the same geographical area, their overall diet and lifestyle were not examined in detail. It is clear that dedicated, large-scale, and more detailed studies are needed to reach conclusive results in this matter.

In our study, TMAO analysis was not conducted on stool samples. Detecting TMAO in stool samples could have helped predict potential gut microbiota imbalances. Moreover, the presence of factors such as receptor resistance that may affect the conversion of TMA to TMAO may reveal the necessity of examining different metabolites together. Therefore, it is thought that making measurements using more than one serum sample at various time points (e.g., over weeks or months) in future research would yield more accurate results in evaluating the role of TMAO in the pathophysiology of ED.

LPS are large molecules found in the outer membranes of Gram-negative bacteria that trigger a strong immune response. In the case of gut dysbiosis, LPS passes into circulation via increased intestinal permeability and binds to CD14 via LPS-binding protein, initiating the release of pro-inflammatory cytokines (TNF-α, IL-1, IL-6) [27]. LPS causes systemic inflammation; many animal studies have shown that it has metabolic and cardiovascular effects. For example, an LPS infusion 2-3 times higher in mice leads to increases in glucose and insulin levels and weight gain [28]. Masson et al. (2015) also reported increases in heart rate, norepinephrine levels, and blood pressure in rats administered LPS [29].

Zhu et al. (2024) showed in rats that raising LPS levels negatively affects vascular health by activating inflammatory processes; furthermore, it was observed that suppressing inflammation could alleviate ED [30]. The increase in pro-inflammatory cytokines associated with elevated LPS reduces endothelial nitric oxide synthase (eNOS) activity, thereby lowering NO production and increasing the formation of reactive oxygen species (ROS). The resulting decrease in NO and increase in ROS significantly impair the relaxation capacity of corpora cavernosa smooth muscle cells [31]. Furthermore, LPS enhances the expression of adhesion molecules (VCAM-1, ICAM-1) in endothelial cells, promoting leukocyte adhesion and infiltration. This exacerbates the local inflammatory response and further compromises endothelial function [32]. However, no study fully explains the relationship between LPS and ED in humans. In our study, we associate the statistically significantly higher LPS levels in the vasculogenic ED group with inflammation and damage caused by LPS in the endothelial tissue of cavernous smooth muscle. Similarly, in a study by Wu et al. (2019) on diabetic and obese rats undergoing Roux-en-Y gastric bypass, a simultaneous decrease in serum LPS and inflammatory factors, as well as an improvement in the microbiota, was observed [33]. Although our study does not focus directly on patients with DM, the high LPS levels in vascular ED patients support the idea that the relationship between DM and the microbiota may also be significant.

This study has several limitations. First, increasing the sample size could enable stronger conclusions to be drawn in future research. Additionally, because dietary habits and other parameters related to different metabolites (for instance, TMA) could not be fully controlled, the exact role of TMAO in ED cannot be definitively determined. Finally, the half-life of TMAO and the potential changes in patients' dietary habits over time somewhat limit the data obtained from one-time measurements; conducting multiple measurements at various time points with more subjects in future studies may overcome this limitation.

This study makes a significant contribution to unders-

tanding the relationship between metabolites originating from the gut microbiota and ED. Our findings show that LPS levels are significantly higher ($p<0.05$) in patients with vascular ED compared to other groups, whereas there is no statistically significant difference in TMAO levels. Especially the elevation in LPS suggests that it may be related to the underlying inflammatory mechanisms of endothelial dysfunction and that the "gut-vascular axis" could play a role in ED pathogenesis.

Although no statistical significance was found in TMAO levels, the relatively high levels in the vascular ED group point to the importance of factors such as dietary differences and timing of sample collection. In future larger-scale studies, sampling at more than one-time point could clarify the effects of TMAO on ED.

The data obtained suggest that treatments and interventions targeting the gut microbiota may potentially be used in the management of ED. In this regard, it is anticipated that in future research, a detailed investigation of the clinical effects and benefits provided by microbiota-targeted approaches will serve as a potential strategy. This way, the effects of specific diets on gut health and ED symptoms can be more comprehensively evaluated.

Abbreviation

ED: Erectile Dysfunction; CAD: Coroner Arter Disease; HT: Hypertension; CVD: Cardiovascular Disease; DM: Diabetes Mellitus; LPS: Lipopolysaccharides; TMAO: Trimethylamine-N-oxide; IIEF: International İndex of Erectile Function; PVD: Peripheral Vascular Disease.

Conflict of interests

The authors declare that they have no conflict of interest.

Consent for publications

The authors read and approved the final manuscript for publication.

Informed consent

Informed consent was obtained from all patients who participated in our study.

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Ethics approval and consent to participate

This study was performed in line with the principles of the Declaration of Helsinki. Informed voluntary consent was obtained from each of the participants. This study received approval from the Ethical Committee of Elazig Fırat University (dated January 13, 2022, with reference number 2022-6281).

Availability of data and material

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' contributions

AK and MFG designed the study. AAO and FO collected the samples. TK performed the serological tests. AAO and TK also performed data collection and manuscript writing.

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