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ORIGINAL RESEARCH

Trimethylamine *N*-Oxide, a Gut Microbiota-Derived Metabolite, Is Associated with Cardiovascular Risk in Psoriasis: A Cross-Sectional Pilot Study

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ABSTRACT

Introduction: Trimethylamine *N*-oxide (TMAO), a gut microbiota metabolite from dietary phosphatidylcholine, is involved in the pathogenesis of atherosclerosis and cardiovascular diseases. Psoriasis is associated with increased cardiovascular risk that is not captured by traditional biomarkers. The aim of the present study was to assess TMAO concentration in psoriasis and evaluate the relationship between TMAO and cardiovascular risk in psoriatic patients.

Methods: In 72 patients with psoriasis and 40 age- and sex-matched non-psoriatic controls, we evaluated fasting plasma TMAO, measured by high-performance liquid chromatography, and cardiovascular risk assessed by various scoring systems such as Framingham, QRISK2, AHA/ACC, and Reynolds risk scores.

Results: In patients with psoriasis, TMAO concentration was significantly higher than in the control group (195.68 [133.54–332.58] ng/ml versus 126.06 [84.29–156.88] ng/ml, respectively; $p < 0.001$). Plasma TMAO concentration was significantly correlated with age, total cholesterol, triglycerides, systolic and diastolic blood pressure. Furthermore, the receiver-operating characteristic (ROC) and multiple regression analysis showed that TMAO is an independent predictor of cardiovascular risk.

Conclusion: TMAO is a valuable candidate for biomarker and a translational link between dysbiosis and atherosclerosis in psoriasis.

Keywords: Atherosclerosis; Cardiovascular risk; Dysbiosis; Gut; Microbiome; Psoriasis; Systemic sclerosis; Trimethylamine *N*-oxide; TMAO

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Key Summary Points

Why carry out this study?

A growing amount of evidence suggests a role of gut microbiota in the development of atherosclerosis and cardiovascular diseases. Specifically, a gut microbial metabolite, trimethylamine *N*-oxide (TMAO), has been intensively studied as a mediator between intestinal dysbiosis and vascular pathology.

The disrupted gut barrier in psoriasis may promote translocation of bacterial metabolites into systemic circulation.

The aim of our study was to assess plasma concentration of TMAO in patients with psoriasis and investigate its potential connection with cardiovascular risk.

What was learned from the study?

Plasma TMAO concentration is significantly increased in patients with psoriasis compared with age-, sex-, and body mass index (BMI)-matched nonpsoriatic subjects.

Concentrations of TMAO were found to be an independent predictor of higher Framingham cardiovascular risk score in patients with psoriasis, even after adjustment for traditional risk factors.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article, go to https://doi.org/10.6084/m9.figshare.14510130.

INTRODUCTION

Psoriasis is a chronic inflammatory skin disease associated with accelerated development of atherosclerotic lesions and, consequently, a high incidence of cardiovascular diseases [1]. Large population studies suggest that patients with moderate-to-severe plaque psoriasis have an up to threefold higher risk of cardiovascular events, and significantly reduced life expectancy when compared with matched controls [2–4]. Importantly, even mild psoriasis increases the risk of myocardial infarction [4].

Several studies confirmed aortic vascular inflammation in psoriasis [5–7]. Endothelial inflammatory activation is an established feature of the atherosclerosis process, which may be measured by [18F]-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT). However, high cost, complex and time-consuming methodology, and patient's exposure to a prolonged radiation limit the use of this diagnostic test in clinical practice. Therefore, there is an urgent need to identify circulating biomarkers for more precise stratification of psoriatic patients who are at increased risk for developing major adverse cardiovascular events.

A growing amount of evidence suggests a role of gut microbiota in the development of atherosclerosis and cardiovascular diseases [8, 9]. Specifically, a gut microbial metabolite, trimethylamine *N*-oxide (TMAO), has been intensively studied as a mediator between intestinal dysbiosis and vascular pathology. Plasma TMAO is a metabolite derived from dietary precursors (choline, phosphatidylcholine, and L-carnitine), through the activity of gut microbiota [10]. Several studies have revealed a relation between plasma TMAO concentration and cardiovascular diseases, such as myocardial infarction, chronic heart failure, atrial fibrillation, or stroke [11–14]. Fecal microbial transplantation in a murine model demonstrated the role of intestinal microbiota in transmission of atherosclerosis susceptibility and overall TMAO production [15].

Our previous study confirmed altered intestinal barrier integrity in patients with

chronic plaque psoriasis [16–18]. The disrupted gut barrier may promote translocation of bacterial metabolites into the systemic circulation. However, this hypothesis has not yet been evaluated in patients with psoriasis. The aim of our study was to assess plasma concentration of TMAO in patients with psoriasis and investigate its potential connection with cardiovascular risk.

METHODS

Subject

All adult patients diagnosed with plaque psoriasis at least 6 months prior to the study visit and not receiving systemic treatment or phototherapy in the previous 3 months were screened for inclusion in this cross-sectional study. Patients were recruited from the Department of Dermatology at Medical University of Warsaw between January 2019 and December 2019.

Exclusion criteria included concomitant chronic gastrointestinal disorder, gastrointestinal infection during the last 3 months prior to the study, dietary restrictions during the last 3 months, intake of agents modulating gut microbiota (proton pump inhibitors, antibiotics, probiotics or prebiotics) within the previous 3 months, unexplained weight loss and major surgery (previous 6 months), chronic liver and pancreatic disease, other autoimmune diseases aside form psoriasis and/or psoriatic arthritis, congestive heart failure (NYHA class III or IV), estimated glomerular filtration rate (eGFR) of < 60 ml/min/1.73 m^2, pregnancy, and breastfeeding.

The control group consisted of individuals matched for age, sex, and body mass index (BMI). Control group subjects followed the same exclusion criteria.

Clinical Assessment

All patients underwent a complete physical examination, and detailed medical history was obtained for all participants. Demographic and clinical data including sex, age, height, weight, blood pressure, psoriasis duration, abuse history, comorbidities, and use of medications were recorded for all subjects.

Psoriasis severity was measured according to Psoriasis Area and Severity Index (PASI). To rule out interobserver variations, PASI was assessed by the same dermatologist in all cases.

Various validated cardiovascular risk scores were calculated, such as Framingham Risk Score (FRAM) [19], QRISK2 [20], Atherosclerotic Cardiovascular Disease 2013 Risk Calculator from AHA/ACC (American Heart Association/American College of Cardiology) [21] Systematic COronary Risk Evaluation (SCORE) [22], and Reynolds Risk Score (RRS) [23].

Laboratory Assessment

The laboratory measurements included complete blood count (CBC), C-reactive protein, fasting blood glucose, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, creatinine, aspartate aminotransferase (AST), and alanine aminotransferase (ALT).

Routine clinical laboratory tests were performed in the Hospital Clinical Laboratory. The estimated glomerular filtration rate (eGFR) was calculated using the Cockcroft–Gault equation.

Blood samples were taken from the cubital vein of all subjects after 8–10 h of fasting. Serum was immediately separated and stored at −70 °C until analysis.

Plasma TMAO concentration was determined using liquid chromatography coupled with triple-quadrupole mass spectrometry as described previously [24, 25]. Briefly, 10 µl of sample was mixed with 100 µl of acetone containing internal standards. After centrifugation, an aliquot was analyzed. The mass spectrometer operated in the multiple-reaction monitoring–positive electrospray ionization mode. The ion transitions used for TMAO quantitation were m/z 76 → 58. The TMAO calibration curve range was 0.1–60 µg/ml, and the limit of quantification was 0.1 µg/ml.

Ethics

The study was approved by the Regional Bioethical Committee (RBC) at Medical University of Warsaw. A written informed consent was obtained from all participants. The study was carried out in accordance with the Declaration of Helsinki and was approved by the Bioethical Committee of the Medical University of Warsaw.

Statistical Analysis

Continuous data are presented as mean ± standard deviation (SD) for normal or median with interquartile range (IQR) for non-normally distributed data. Categorical data are expressed as frequencies (number of cases and percentages). The Shapiro–Wilk test was used to assess the normality assumption of continuous variables. Normally distributed continuous variables were assessed with Student's *t* test or one-way analysis of variance (ANOVA), while non-normally distributed continuous variables were assessed through Mann–Whitney *U* test or Kruskal–Wallis test, as appropriate. For comparing categorical data, χ^2 test was performed. Spearman's correlation coefficient was used to evaluate the correlation between two continuous variables. Multiple linear regression analysis with a forward-stepwise procedure was applied to determine the parameters most predictive of cardiovascular risk score. Regression analysis data are reported as a beta coefficient with standard error and *p* value. The receiver-operating characteristic (ROC) curve analysis was applied for testing sensitivity and specificity. A p value < 0.05 was considered statistically significant. All statistical analyses were performed with STATISTICA 13 software (StatSoft, Inc., USA).

RESULTS

In total, 72 patients with psoriasis and 40 nonpsoriatic controls were enrolled in the present study. Table 1 presents the demographic and clinical characteristics of the two groups.

Table 1 Characteristics of the enrolled patients with psoriasis and matched control group

	Psoriasis (*n* = 72)	**Control (*n* = 40)**	***p* value**
Age, years	42 [35–57.5]	44 [35.5–56]	0.935
Sex, men, *n* (%)	56 (77.8%)	25 (62.5%)	0.083
Body mass index, kg/m^2	29.61 (5.34)	28.33 (6.27)	0.672
Omnivorous diet, *n* (%)	72 (100%)	40 (100%)	1
Red meat more than three times per week	72 (100%)	40 (100%)	1
Vegan/vegetarian diet, *n* (%)	0	0	–
Diabetes mellitus, *n* (%)	6 (8.3%)	1 (2.5%)	0.224
Hyperlipidemia, *n* (%)	24 (33.3%)	8 (20%)	0.135
Hypertension, *n* (%)	32 (44.4%)	14 (35%)	0.330
Chronic kidney disease stage 4 or 5, *n* (%)	0	0	–
Current smoker, *n* (%)	34 (47.2%)	13 (32.5%)	0.130
PASI score	12.3 [5.3–17.9]	–	–
Psoriasis duration, years	12.5 (7.4)	–	–
Psoriatic arthritis, *n* (%)	30 (41.7%)	–	–

Table 1 continued

	Psoriasis (n = 72)	Control (n = 40)	p value
Previous treatment, n (%)		–	–
Topical	72 (100%)		
Phototherapy	22 (30.6%)		
Methotrexate	27 (37.5%)		
Ciclosporin	15 (20.8%)		
Acitretin	19 (26.4%)		
Biological drugs	3 (4.2%)		

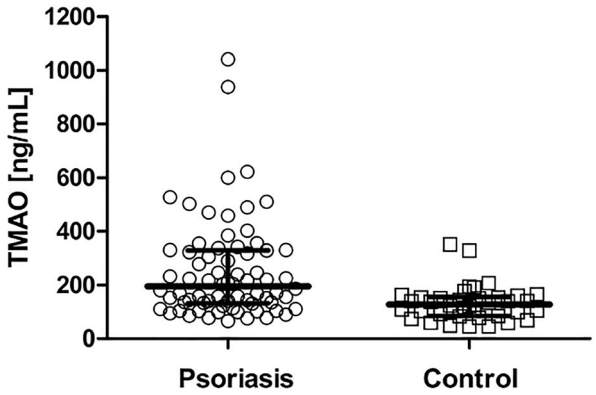

Fig. 1 Plasma concentration of trimethylamine *N*-oxide (TMAO). Results presented as median and interquartile range

Subjects were well matched for age, sex, BMI, and comorbidities.

TMAO concentration was significantly higher in psoriasis patients than in the control group: 195.68 [133.54–332.58] ng/ml and 126.06 [84.29–156.88] ng/ml, respectively; $p < 0.001$ (Fig. 1). Psoriatic patients with non-alcoholic fatty liver disease (NAFLD) had significantly higher TMAO in comparison with patients without liver disease (243.69 [165.55–382.45] ng/ml and 140.82 [95.53–238.16] ng/ml, respectively; $p < 0.001$). A similar trend was observed in patients with psoriasis and concomitant hypertension (333.12 [224.39–450.65] ng/ml) compared with normotensive psoriatic patients (145.69 [100.24–237.22] ng/ml; $p < 0.001$).

Table 2 Correlation of TMAO with clinical and laboratory parameters in patients with psoriasis

	Spearman's rank correlation coefficient	p value
Framingham Risk Score	0.679	< 0.001
QRISK2	0.659	< 0.001
AHA/ACC	0.548	< 0.001
SCORE	0.506	< 0.001
Reynolds Risk Score	0.655	< 0.001
Age	0.408	< 0.01
Body mass index	0.263	0.121
PASI score	0.198	0.246
Systolic blood pressure	0.434	< 0.01
Diastolic blood pressure	0.456	< 0.01
Total cholesterol	0.333	< 0.05
LDL cholesterol	0.211	0.218
HDL cholesterol	− 0.181	0.290
Triglycerides	0.335	< 0.05
Neutrophil-to-lymphocyte ratio	0.117	0.498
C-reactive protein	0.091	0.595
Estimated glomerular filtration rate	0.021	0.905

Plasma TMAO concentration was strongly correlated with all analyzed cardiovascular risk scores (FRAM $r = 0.68$, $p < 0.001$; QRISK2 $r = 0.66$, $p < 0.001$; AHA/ACC $r = 0.55$, $p < 0.001$; SCORE $r = 0.51$, $p < 0.001$; RRS $r = 0.65$, $p < 0.001$). Other characteristics significantly correlated with TMAO included age, total cholesterol, triglycerides, and systolic and

Table 3 Clinical and laboratory characteristics according to the tertile of TMAO concentration in patients with psoriasis

	TMAO tertial I [75.2–150.3] *n* = 24	**TMAO tertial II [150.3–325.9] *n* = 24**	**TMAO tertial III [325.9–1038.9] *n* = 24**	***p* values**
Age, years	36 [34–39]	47 [38–62]	53.5 [39–60.5]	< 0.001
Sex, men, *n* (%)	19 (79.2%)	19 (79.2%)	18 (75%)	0.923
Body mass index, kg/m^2	28.03 (4.79)	28.44 (4.31)	32.48 (5.97)	< 0.05
PASI	10.7 [4.3–13.0]	14.9 [5.7–19.7]	12.05 [4–17.45]	0.279
Psoriatic arthritis, *n* (%)	11 (45.8%)	10 (41.6%)	9 (37.5%)	0.842
Diabetes mellitus, *n* (%)	1 (4.2%)	2 (8.3%)	3 (12.5%)	0.567
Nonalcoholic fatty liver disease, *n* (%)	11 (45.8%)	15 (62.5%)	20 (83.3%)	< 0.05
Hyperlipidemia, *n* (%)	4 (16.7%)	7 (29.2%)	13 (54.2%)	< 0.05
Hypertension, *n* (%)	4 (16.7%)	10 (41.6%)	18 (75%)	< 0.001
Atrial fibrillation, *n* (%)	0	2 (8.3%)	1 (4.2%)	0.239
Current smoker, *n* (%)	8 (33.3%)	12 (50%)	14 (58.3%)	0.205
Total cholesterol, mg/dl	172.23 (32.63)	175.45 (35.42)	192.67 (27.30)	0.052
LDL cholesterol, mg/dl	114.69 (25.07)	114.00 (37.00)	125.83 (30.81)	0.201
HDL cholesterol, mg/dl	40 [40–45]	41 [35–58]	38.5 [35–45.5]	0.268
Triglycerides, mg/dl	109.46 (30.52)	119.00 (39,85)	134.58 (38.91)	0.079
Neutrophil-to-lymphocyte ratio	1.86 [1.48–4.30]	2.36 [1.44–3.89]	2.40 [1.53–3.46]	0.509
C-reactive protein, mg/dl	2.21 [0.74–4.16]	2.40 [1.45–4.98]	2.19 [0.81–4.62]	0.819
Systolic blood pressure, mmHg	125 [120–135]	130 [125–134]	131 [130–142.5]	< 0.01
Diastolic blood pressure, mmHg	75 [75–80]	80 [70–80]	80 [80–86.5]	< 0.01
Estimated glomerular filtration rate, ml/min/1.73 m^2	94.7 [70.3–124.8]	91.5 [63.9–115.1]	104.5 [65.1–135.5]	0.517
Framingham Risk Score	1.08 [0.17–3.11]	11.09 [0.66–13.28]	11.38 [10.20–14.49]	< 0.001
QRISK2	1 [0–1]	5 [1–7]	4.5 [3.5–6]	< 0.001
AHA/ACC	3 [2–4]	6 [3–10]	9 [5.5–12.0]	< 0.001
SCORE	1 [1–1]	4 [1–6]	5 [2–7]	< 0.001
Reynolds Risk Score	1.06 [0.6–3.3]	8.4 [2.7–19.7]	13.2 [9.15–18.45]	< 0.001

Table 4 Clinical and laboratory characteristics of psoriatic patients with low and intermediate-to-high cardiovascular risk (CVR) according to Framingham Risk Score

	Low CV risk (n = 38)	Intermediate-to-high CV risk (n = 34)	p values
Age, years	38 [35–41]	57 [47–62]	< 0.001
Sex, men, n (%)	28 (73.7%)	28 (82.3%)	0.377
Body mass index, kg/m^2	27.99 (4.50)	30.92 (6.02)	0.052
PASI score	10.7 [4.3–13.0]	12.05 [4–17.45]	0.460
Psoriatic arthritis, n (%)	17 (44.7%)	13 (38.2%)	0.598
Diabetes mellitus, n (%)	0	6 (17.6%)	< 0.01
Nonalcoholic fatty liver disease, n (%)	20 (52.6%)	26 (76.5%)	< 0.05
Hyperlipidemia, n (%)	6 (15.8%)	18 (52.9%)	< 0.01
Hypertension, n (%)	10 (26.3%)	22 (64.7%)	< 0.01
Atrial fibrillation, n (%)	0	3 (8.8%)	0.063
Current smoker, n (%)	12 (31.6%)	22 (64.7%)	< 0.01
Total cholesterol, mg/dl	171.8 (28.7)	189.2 (34.4)	< 0.05
LDL cholesterol, mg/dl	111.7 (23.2)	125.5 (36.5)	< 0.05
HDL cholesterol, mg/dl	43 [40–48]	38 [35–46]	< 0.05
Triglycerides, mg/dl	109.7 (25.8)	133.1 (43.9)	< 0.01
Neutrophil-to-lymphocyte ratio	1.86 [1.43–4.30]	2.63 [1.54–3.89]	0.092
C-reactive protein, mg/dl	2.76 [0.74–4.98]	1.98 [0.95–4.50]	0.488
Systolic blood pressure, mmHg	130 [120–135]	130 [130–135]	< 0.05
Diastolic blood pressure, mmHg	78 [70–80]	80 [80–80]	< 0.01
Estimated glomerular filtration rate, ml/min/1.73 m^2	105.2 [68.0–121.3]	94.6 [65.5–123.0]	0.986
TMAO, mg/ml	134.26 [99.68–178.21]	327.55 [238.16–468.02]	< 0.001

diastolic blood pressure. A detailed list of correlations is presented in Table 2.

Further, patients with psoriasis were categorized according to the tertiles of plasma TMAO concentration. As presented in Table 3, subjects with higher TMAO were more likely to be older, be obese, and have hypertension or NAFLD. Cardiovascular risk scores showed a significantly higher value with increased TMAO tertiles. In contrast, a history of smoking, concomitance of psoriatic arthritis, and PASI score were similar across three groups.

When patients were grouped according to Framingham Risk Score, low cardiovascular risk was seen in 53% (38/72) and intermediate-to-high risk in 47% (34/72) of psoriatic patients. Statistically significant differences were observed between groups with respect to age, smoking, comorbidities (NAFLD, hyperlipidemia, hypertension, diabetes), lipid profile,

Table 5 Multiple linear regression analyses of the relationship between Framingham Risk Score (as a dependent variable) and TMAO (as an independent variable)

Model	Beat ± standard error	*p* value	R^2
Unadjusted	0.49 ± 0.10	< 0.001	0.237
Adjusted for age, sex, body mass index	0.31 ± 0.09	< 0.001	0.655
Adjusted for age, sex, body mass index, PASI, smoking	0.21 ± 0.08	< 0.01	0.717
Adjusted for age, sex, body mass index, PASI, smoking, nonalcoholic fatty liver disease, systolic and diastolic blood pressure, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides	0.30 ± 0.08	< 0.001	0.829

and systolic and diastolic blood pressure, as well as concentration of TMAO (Table 4). The results of multiple regression analyses to identify factors associated with Framingham Score in patients with psoriasis are presented in Table 5 and confirmed a significant association of TMAO with cardiovascular risk.

At last, to assess the predictive power of TMAO for cardiovascular risk, we performed an ROC analysis. Our results showed that the area under curve (AUC) of TMAO was 0.913 (95% CI 0.848–0.979, $p < 0.001$, Fig. 2). Plasma TMAO concentration around 210.63 ng/ml is a cutoff for intermediate-to-high cardiovascular risk score. Patients with TMAO concentration above the cutoff threshold showed higher values of age, total cholesterol, triglycerides, systolic blood pressure, and estimated cardiovascular risk (Table 6).

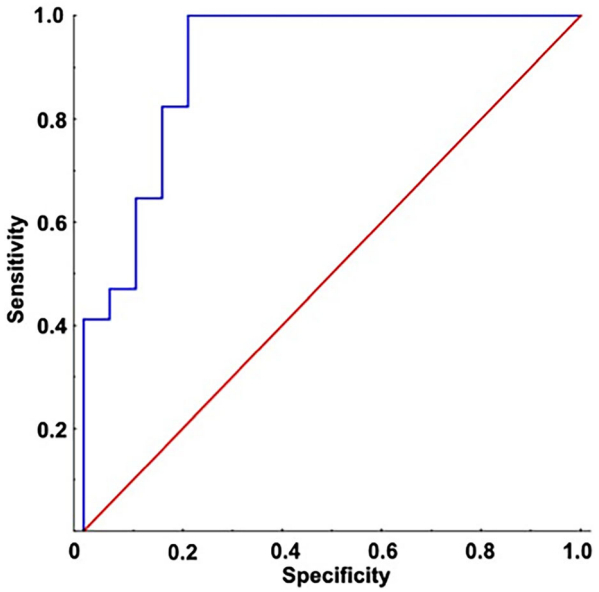

Fig. 2 ROC for predictive values of plasma TMAO concentration in detecting intermediate-to-high cardiovascular risk according to Framingham Risk Score

DISCUSSION

This is the first study demonstrating that plasma TMAO concentration is significantly increased in patients with psoriasis compared with age-, sex-, and BMI-matched nonpsoriatic subjects. Increased TMAO level was associated with age, NAFLD, hypertension, hyperlipidemia, and risk of cardiovascular diseases as assessed by various cardiovascular risk scoring systems. Furthermore, concentrations of TMAO were found to be an independent predictor of higher Framingham cardiovascular risk score in patients with psoriasis, even after adjustment for traditional risk factors.

Patients with psoriasis are at greater risk for developing and dying from a myocardial infarction [2]. The risk of other vascular complications in psoriasis is also increased, including stroke [26], peripheral vascular disease [27], and thromboembolism [28]. Additionally, this increased cardiovascular risk is more pronounced in younger patients than in the

Table 6 Clinical and laboratory characteristics of patients with psoriasis divided in terms of plasma TMAO concentration cutoff point for intermediate-to-high cardiovascular risk score

	TMAO < 210.63 ng/ml (*n* = 32)	**TMAO ≥ 210.63 ng/ml (*n* = 40)**	***p* values**
Age, years	38 [34.5–40]	53.5 [40–62.5]	< 0.001
Sex, men, *n* (%)	26 (81.2%)	30 (75%)	0.526
Body mass index, kg/m^2	28.78 (4.67)	30.32 (6.05.72)	0.224
PASI score	10.8 [7.2–16.1]	13.25 [5.2–17.9]	0.289
Psoriatic arthritis, *n* (%)	13 (40.6%)	17 (42.5%)	0.916
Diabetes mellitus, *n* (%)	0	6 (15%)	< 0.05
Nonalcoholic fatty liver disease, *n* (%)	16 (50%)	30 (75%)	< 0.05
Hyperlipidemia, *n* (%)	5 (15.6%)	19 (47.5%)	< 0.01
Hypertension, *n* (%)	8 (25%)	24 (60%)	< 0.01
Atrial fibrillation, *n* (%)	0	3 (7.5%)	0.113
Current smoker, *n* (%)	10 (31.2%)	24 (60%)	< 0.05
Total cholesterol, mg/dl	169.8 (29.2)	188.2 (32.2)	< 0.05
LDL cholesterol, mg/dl	111.2 (23.7)	123.7 (34.1)	0.082
HDL cholesterol, mg/dl	42 [40–47.5]	38.5 [35–52]	< 0.05
Triglycerides, mg/dl	106.2 (29.4)	132.4 (38.1)	< 0.01
Neutrophil-to-lymphocyte ratio	2.07 [1.45–4.46]	2.33 [1.52–3.39]	0.896
C-reactive protein, mg/dl	2.48 [0.72–4.14]	2.18 [1.02–4.86]	0.689
Systolic blood pressure, mmHg	125 [120–132.5]	130 [130–137.5]	< 0.001
Diastolic blood pressure, mmHg	80 [75–80]	80 [78–82.5]	0.092
Estimated glomerular filtration rate, ml/min/1.73 m^2	106.1 [70.3–121.9]	97.9 [64.9–120.5]	0.529
Framingham Risk Score	1.06 [0.2–4.1]	11.81 [10.2–14.5]	< 0.001
QRISK2	1 [0–1]	5 [2.5–6]	< 0.001
AHA/ACC	2.5 [2–4]	9 [5–12]	< 0.001
SCORE	1 [1–1]	4.5 [2–6]	< 0.001
Reynolds Risk Score	2.15 [0.6–3.4]	13.2 [7.8–19.1]	< 0.001

general population. Therefore, there is a need for novel biomarkers that, in combination with traditional cardiovascular risk assessment, may improve risk stratification and enhance the selection of patients for preventative strategies [29].

Premature atherosclerosis in psoriasis is associated with endothelial dysfunction caused by an inflammatory process and concomitant

diseases, such as insulin resistance, obesity, hyperlipidemia, or hypertension [30, 31]. Recent studies suggest that alteration in gut microbiome composition is another factor that may influence formation and progression of atherosclerotic plaque [32]. Moreover, gut dysbiosis has also been linked to psoriasis and its comorbidities [33]. One of the current hypotheses for the pathophysiological mechanism linking alteration in gut microbiome with increased cardiovascular risk states that the bacterial metabolites are translocated via impaired gut barrier into the circulation and exert systemic effects [14]. Several studies confirmed intestinal barrier damage in psoriasis [16–18] as well as increased blood concentration of bacterial components (lipopolysaccharide, DNA) in psoriatic patients [34, 35].

One of the biologically active metabolites of gut microbiota, which has been extensively studied recently, is trimethylamine *N*-oxide. Intestinal microbial enzymes metabolize dietary L-carnitine, choline, and lecithin into a trimethylamine (TMA), which is subsequently oxidized to TMAO in the liver [10]. This is the first study comparing TMAO concentration in patients with psoriasis and nonpsoriatic controls. However, in psoriatic arthritis, TMAO concentration correlates significantly not only with joint involvement but also with severity of skin lesions [36]. We found no significant relationship between TMAO levels and the PASI score. It cannot be ruled out that the damage of the intestinal barrier increases not only because of the severity of psoriasis but also the duration of high disease activity.

It was shown that TMAO is involved in all stages of atherogenesis, from the initial plaque formation to the terminal stage of thrombotic complications [37]. Several mechanisms for the role of TMAO in the development of atherosclerosis have been proposed, including the modulation of inflammation, cholesterol metabolism, and platelet activity.

An increase in TMAO concentration stimulates the inflammatory response within endothelial and vascular smooth muscle cells by activation of mitogen-activated protein kinase (MAPK), a signaling cascade of nuclear factor-kB (NF-kB), activation of NLRP3 inflammasome, release of proinflammatory cytokines, and expression of adhesion molecules [38, 39]. In addition, TMAO significantly triggers oxidative stress, contributing to the decrease of nitric oxide availability and endothelial dysfunction [40, 41]. Other findings have reported that TMAO promotes atherosclerosis through formation of foam cells [42].

Hepatic flavin monooxygenase 3 (FMO3), the enzyme responsible for forming TMAO from gut microbe-generated TMA, appears to have a regulating function on lipid metabolism. Knockdown of FMO3 in mice on a high-cholesterol diet lowered intestinal lipid absorption and hepatic cholesterol production, and stimulated reverse cholesterol transport [43], while TMAO administration significantly increased concentrations of triglyceride, total cholesterol, and low-density lipoprotein cholesterol [44].

Lastly, TMAO was reported to augment the intracellular release of Ca^{2+} through adenosine diphosphate (ADP), thrombin, arachidonic acid, and collagen, increasing platelet reactivity, which promotes thrombosis [45].

Most of the cited studies were carried out in vitro or on animal models; however, clinical studies confirmed increased plasma TMAO concentration in myocardial infarction [13], stroke [11], and peripheral artery disease [46]. There is a growing number of articles suggesting that not TMAO itself, but rather its precursor—TMA, is responsible for toxic effects on the cardiovascular system [47, 48]. TMAO, as the product of oxygenation, may be a biomarker of the increased intestinal translocation of TMA. We assume that translocation of bacterial metabolites by altered intestinal barrier in psoriasis is a potential mechanism linking gut dysbiosis with increased cardiovascular risk.

Limitations of the study include its small sample size and cross-sectional nature. It should be mentioned that there are a number of other factors that influence cardiovascular risk, such as diet. The classic risk scoring scales may underestimate cardiovascular risk in patients with inflammatory disorders.

CONCLUSION

We showed increased concentration of TMAO in patients with psoriasis. A measurement of plasma TMAO can be a valuable biomarker for assessing cardiovascular risk in psoriasis. A better understanding of the causal relationship between psoriasis and TMAO may highlight several pathophysiological pathways for targeted therapies to reduce cardiovascular risk in psoriatic patients.

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Compliance with Ethics Guidelines. The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Bioethical Committee of the Medical University of Warsaw (KB/106/2017 of 04 July 2017). Informed consent was obtained from all subjects involved in the study.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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