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Original Article

Effect of *Lactobacillus Plantarum* Supplementation on Trimethylamine-N-Oxide Levels in 30 Patients with Atherosclerotic Cardiovascular Disease: A Double-Blind Randomized Controlled Trial

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Abstract

Introduction: Trimethylamine-N-oxide (TMAO) is a metabolite produced by intestinal microbiota. It is well recognized as an independent risk marker for cardiovascular and renal diseases and mortality.

Aim: The aim of the present study was to investigate the effect of *Lactobacillus plantarum* GLP3 supplementation on TMAO levels in 30 patients with a history of atherosclerotic cardiovascular disease after 12 weeks of treatment.

Materials and methods: Thirty consecutive male patients with a history of clinical atherosclerotic cardiovascular disease were randomized in the study. TMAO levels were evaluated in human plasma samples using high-performance liquid chromatography with triple quadrupole tandem mass spectrometry and results were presented as the median (interquartile range). Microbiome sequencing analysis, focusing on bacteria from the genus *Lactobacillus*, was performed in 21 patients.

Results: Patients receiving probiotic treatment showed a significant decrease in the TMAO levels [from 284 (139) μg/L to 202.5 (96.7) μg/L; p=0.044], with no significant change apparent in the placebo group after the treatment [from 176 (120) μg/L to 178 (150) μg/L; p=0.258]. *Lactobacillus* spp. % in the probiotic group was significantly increased after the interventional procedures [0.6 (0.14) before and 0.79 (0.6) after the treatment; p=0.041].

Conclusion: Probiotic supplementation with *Lactobacillus plantarum* GLP3 reduced the TMAO levels in very high-risk patients for cardiovascular diseases.

Keywords

cardiovascular disease, intestinal microbiome, probiotics

INTRODUCTION

The intestinal microbiota represents the communities of microorganisms inside a human gastrointestinal tract. It has been recognized as an active endocrine organ that affects host metabolism and function through the production of different metabolites.[1] Despite the numerous positive effects of intestinal microbiota, there is growing evidence that some of these produced components are responsible for several adverse consequences.[2]

Trimethylamine-N-oxide (TMAO) is a metabolite that is produced by intestinal microbiota via digestion of food containing different compounds, such as choline and L-carnitine.[3] This molecule was first described by Wang et al. in 2011 [4] and is now recognized as an independent risk marker for cardiovascular and renal diseases and mortality, which has been confirmed by multiple trials and meta-analyses[5-7]. Several studies have shown that increased TMAO levels are related to the degree of coronary atherosclerosis and progression, especially in very high-risk patients.[8,9] The relative risk for all-cause mortality is increased by 7.6% for each 10 μmol/L of TMAO enhancement.[7] TMAO levels are related to the increased risk of coronary plaque instability and rupture and are independent predictors of mortality in patients with acute coronary syndrome undergoing percutaneous coronary intervention.[10,11]

There is growing evidence that TMAO levels are independent predictors of atherosclerosis progression, cardiovascular events, and mortality.[12] This suggests that therapeutic intervention research in order to reduce TMAO levels is needed. It is well established that intestinal microbiota is a necessary component of TMAO synthesis.[4] Several distinct bacterial strains participate in TMAO formation, and TMAO production is increased in dysbiosis.[3,13,14] This led to a hypothesis that changes in microbiota composition to a healthier state may have a favorable impact on TMAO levels. To date, only a few studies have assessed the impact of probiotic supplementation on TMAO levels, and their results are inconsistent.[14]

AIM

The aim of the present study was to investigate the effect of *Lactobacillus plantarum* GLP3 supplementation on TMAO levels in 30 patients with a history of atherosclerotic cardiovascular disease (ASCVD) after 12 weeks of treatment.

MATERIALS AND METHODS

All patients provided informed consent and were given a detailed description of all study procedures before examination and comprehensive information regarding the intervention. The study was approved by the local Ethics Committee of Tsaritsa Yoanna University Hospital in Sofia, Bulgaria. The patients received no compensation for their participation in the study.

Patient population and study design

This double-blind randomized controlled 12-week study was conducted between January and December 2023 at Tsaritsa Yoanna University Hospital, Sofia, Bulgaria. Thirty consecutive male patients with a history of clinical ASCVD were randomized in the study. The study population included patients who presented for a routine cardiology examination. Inclusion and exclusion criteria are listed in **Table 1**. All patients were screened for eligibility criteria before the study. The patients were invited to participate in the trial after meeting the criteria. All patients were instructed not to consume read meat, fish, eggs, milk products, and energy drinks 2 days before the study and 2 days

Table 1. Study inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Age 45–70 years	Major cardiovascular event within 30 days*
Male sex	EF <40% and/or heart failure NYHA ≥III
History of clinical ASCVD	Glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2
	Active infection
	Antibiotics or probiotics use within 30 days
	Active liver disease
	Malignancy
	Inflammatory diseases, e.g. intestinal bowel disease
	Unsigned informed consent

* acute myocardial infarction, acute coronary syndrome, coronary revascularization and other arterial revascularization procedures, stroke and transient ischemic attack, hospitalization for heart failure; ASCVD: atherosclerotic cardiovascular disease; EF: ejection fraction; NYHA: New York Heart Association Classification for Heart failure; ASCVD: atherosclerotic cardiovascular disease, which include history of myocardial infarction, acute coronary syndrome, coronary revascularization and other arterial revascularization procedures, stroke and transient ischemic attack.

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before the last study visit in order to limit the effect of dietary factors on the TMAO levels. All other study procedures were performed on the same day. The patients were also fasting on the day of the analyses.

The probiotic-to-placebo ratio was 1:1. Interventional procedures lasted for 12 weeks in both groups and the trial was stopped according to the study protocol **(Fig. 1)**.

Data collection

During the screening, data regarding patient history, concomitant conditions, and therapy were collected. Information on arterial hypertension, diabetes mellitus, dyslipidemia, premature history of cardiovascular diseases, and smoking status for each patient was also gathered. The current European guidelines on cardiovascular disease prevention were used to determine the presence or absence of these risk factors.[15] The Fourth Universal Definition of Myocardial Infarction type I was utilized to identify patient history of myocardial infarction, e.g. documented history of rise and/or fall in cardiac troponin level with at least one value above the 99th percentile combined with one of the following: symptoms of acute myocardial ischemia, new ischemic electrocardiogram changes or new pathological Q waves, and imaging evidence of ischemic etiology or identification of a coronary thrombus by angiography.[16]

Information regarding the degree of coronary vessel disease, number and timing of events, and revascularization procedures was also collected.

All patients underwent a standard physical examination and an electrocardiogram. Blood pressure (BP) measurements were performed after 5 minutes of rest in a supine position. Three BP measurements were performed 1–2 minutes apart and a final BP was recorded as the average of the last two measurements. Body mass index was calculated as the patient's weight (kg) divided by height squared (m^2).

Randomization

Randomization was performed at the Center of Applied Studies and Innovation, Sofia, Bulgaria. Prepared bottles containing probiotic and placebo at a ratio of 1:1 (n=30) were supplied for the Cardiology Clinic, Tsaritsa Yoanna University Hospital ISUL. Each bottle was coded at the microbiology department and was given a unique number. The researchers and participants were blinded to the type of study treatment. The interventional products were assigned to the participants according to their recruitment sequence.

Laboratory analyses

The patients were fasted for laboratory analyses. The following parameters were examined: creatinine levels, lipid profile, glycated hemoglobin (HbA1c) levels, and glucose levels. The glomerular filtration rate was estimated using chronic kidney disease epidemiology collaboration formula and was represented in mL/min/1.73 m^2. Homeostatic model assessment for insulin resistance (HOMA-IR) was calculated using the following formula: fasting insulin level (μU/L) × fasting glucose level/22.5.

TMAO measurement

TMAO levels in human plasma samples were assessed at the Central Laboratory of Therapeutic Drug Management and Clinical Pharmacology at Alexandrovska University Hospital in the Faculty of Medicine of the Medical Univer-

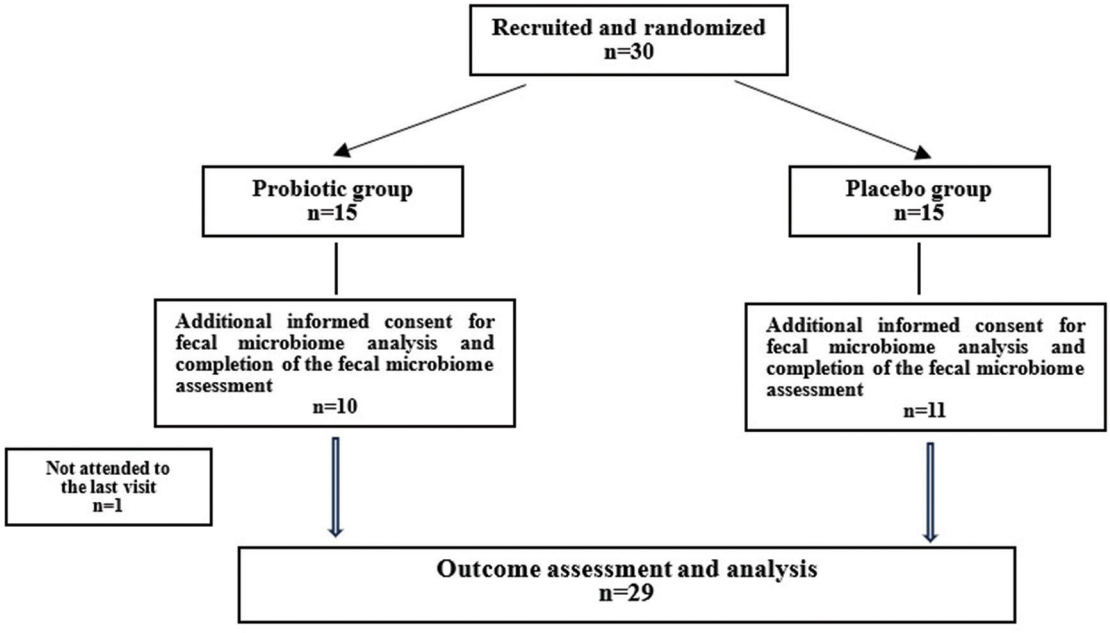

Figure 1. Study design. n = number of examined patients.

sity of Sofia, Bulgaria, using triple quadrupole tandem mass spectrometry (MS) and high-performance liquid chromatography.[8-10]

TMAO levels were determined in external standardization mode after plasma protein precipitation using acetonitrile. Chromatography was performed using a Kinetex RPC8 column, 50 mm×2.1 mm, with 2.6-µm particle size in mobile phase consisting of 10% methanol and 90% 0.02 mM ammonium fluoride buffer. The chromatographic run time was 2.5 minutes with a retention time for the TMAO peak of ~1.34 minutes. Detection was performed in the electrospray positive ion mode. MS/MS monitoring of the column effluent in the SRM mode was set to follow the predominant transitions, where collision energy = 18 at m/z 76–58. Raw mass chromatogram data were collected and processed using specialized software Xcalibur 1.4. All concentrations were calculated in external standard mode using the six-point calibration curve. Area of the mass spectrometry TMAO peak was used as a quantitative measure. Concentration units were µg/L. TMAO levels were measured two times: on the first day of the study before the interventional treatment and on the last day after 12 weeks of treatment.

Interventional procedures

Instructions for the interventional treatment containing information for the investigation product/placebo and prescription data were provided to each patient and explained in detail. Patients were instructed to take the study product two times daily: 1 hour after breakfast and 1 hour after evening. Patients were requested to return the study product on the day of the last (second) visit. Compliance was estimated by obtaining confirmation from patients regarding the medication taken and by the number of tablets returned to the center.

Interventional product

Probiotic consisting of 1×10^9 CFU of *L. plantarum* GLP3, 75 mg of trans-resveratrol, non-alcoholic red wine extract, and prebiotic inulin was the investigational product. The weight of each capsule, including the placebo, was 500 mg.

Fecal microbiome analysis

Additional informed consent for the microbiome analysis was obtained from all patients. In those who agreed to this assessment (n=21), stool samples were collected before (as controls) and after therapy. Microbiome sequencing analysis, focusing on bacteria from the genus Lactobacillus, was performed in a commercial laboratory (GANZIMMUN Diagnostics GmbH, Germany).

Statistical analysis

Statistical analyses were performed using SPSS 23 software for Windows. Kolmogorov Smirnov and Shapiro-Wilk tests were used to assess the distribution of variables. Continuous variables with a normal distribution were presented as the mean ± standard deviation. For variables with a skewed distribution, parameters were presented as the median and interquartile range (IQR) in brackets, where IQR is the difference between the upper and lower quartile. Independent sample *t*-test and Mann-Whitney two-sample tests were used to compare normally and abnormally distributed continuous variables, respectively. Categorical variables were presented as percentages and counts and analyzed using χ^2 or Fisher's exact tests. Relationships between continuous normally distributed variables were determined using Pearson's and Spearman's correlation coefficients according to their distribution.

Paired sample *t*-test and Wilcoxon signed-rank tests were applied to compare the effect of interventional procedures on variable levels and to determine the differences between the groups. A two-tailed p value of <0.05 was considered statistically significant.

RESULTS

Clinical and demographic patient characteristics

The mean age for all examined patients was 58.5±8.16 years. Nineteen patients (65.5%) had a history of myocardial infarction, and eight patients (27.6%) had type 2 diabetes mellitus. There was no statistically significant difference in terms of age and risk factor profile between the patient groups. The main clinical and demographic characteristics of the patients are presented in **Table 2**.

Baseline TMAO levels in patient groups

Baseline TMAO levels before the intervention procedures were 284 (139) µg/L in the probiotic group and 176 (120) µg/L in the placebo group, with no statistically significant difference between them (p=0.19). Other evaluated baseline laboratory parameters, including lipid profile, HbA1C level, glucose level, insulin level, and HOMA-IR, are presented in **Table 3**.

TMAO level differences as the primary outcome after interventional procedures in different patient groups

After 12 weeks of the interventional procedure, the patients receiving the probiotic treatment showed a significant decrease in TMAO levels [from 284 (139) µg/L to 202.5 (96.7) µg/L; p=0.044]. There was no significant difference in TMAO levels in the placebo group after the treatment [from 176 (120) µg/L to 178 (150) µg/L; p=0.258] **(Fig. 2)**.

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Table 2. Main clinical and demographic characteristics of examined patients by groups

Parameter	Placebo group n=15	Probiotic group n=14	*p*
Demographics			
Age (years)	58.86±9.38	58.14±7.09	0.82
Medical history			
Obesity, n (%)	13 (86.7%)	9 (64.3%)	0.22
Arterial hypertension, n (%)	13 (86.7%)	14 (100%)	0.48
Diabetes mellitus, n (%)	4 (26.7 %)	4 (28.6%)	1.00
Smoking, n (%)	5 (33.3 %)	2 (14.3%)	0.39
Family history for CVD, n (%)	2 (13.3 %)	3 (21.4)	0.10
Myocardial infarction, n (%)	10 (66.7 %)	9 (64.3%)	1.00
PCI, n (%)	12 (80 %)	12 (85.7%)	1.00
ACB, n (%)	1 (6.7 %)	1 (7.1%)	1.00
Stroke, n (%)	1 (6.7 %)	2 (14.3%)	0.59
PAD, n (%)	1 (6.7 %)	0 (0.0)	1.00
Medical therapy			
ACE inhibitor therapy, n (%)	10 (66.7 %)	12 (85.7)	0.39
B-blocker in therapy, n (%)	8 (53.3%)	10 (71.4%)	0.45
Metformin therapy, n (%)	4 (26.7%)	4 (28.6%)	1.00
SGLT2 inhibitor therapy, n (%)	2 (13.3)	3 (21.4)	0.65
Insulin therapy, n (%)	0 (0.0)	2 (14.3)	0.22
Moderate statin dose, n (%)	4 (26.7%)	3 (21.4%)	1.00
Intensive statin dose, n (%)	11 (73.3)	11 (78.6)	1.00
Ezetimibe therapy, n (%)	1 (6.7)	5 (35.7)	0.08

CVD: cardiovascular diseases; PAD: peripheral artery disease; ACE inhibitor: angiotensin converting inhibitors; SGLT2 inhibitor: sodium-glucose cotransporter-2 inhibitor; n: number of patients Fisher's exact test.

Table 3. Baseline characteristics of the laboratory measurements in the patient's groups

Parameter	Placebo group n=15	Probiotic group n=14	*p*
TMAO levels (μg/l)	176 (120)	284 (139)	0.19
Total cholesterol (mmol/l)	4.14±0.9	4.5±1.29	0.40
LDL cholesterol (mmol/l)	2.19±0.8	2.33±0.7	0.63
HDL cholesterol (mmol/l)	1.06±0.25	1.10±0.23	0.69
Non-HDL cholesterol (mmol/l)	3.08±0.96	3.4±1.28	0.45
Triglycerides (mmol/l)	1.8±1.22	1.76±1.36	0.81
Glucose (mmol/l)	6.45±0.93	5.56±0.8	0.03
Insulin (micro U/l)	17.9±7.9	10.8±4.2	0.02
HOMA IR	4.80 (4.35)	2.49 (1.42)	0.007
HBA1C (%)	5.77±0.48	6.52±1.72	0.12

In variables with normal distribution, results are presented as a median and standard deviation and independent sample t-test was used to compare the differences. In cases of skewed distribution, results are presented as the median and IQR in brackets, and Mann-Whitney 2 test was applied. HOMA IR: homeostatic model assessment for insulin resistance; HBA1C: glycated hemoglobin A1C.

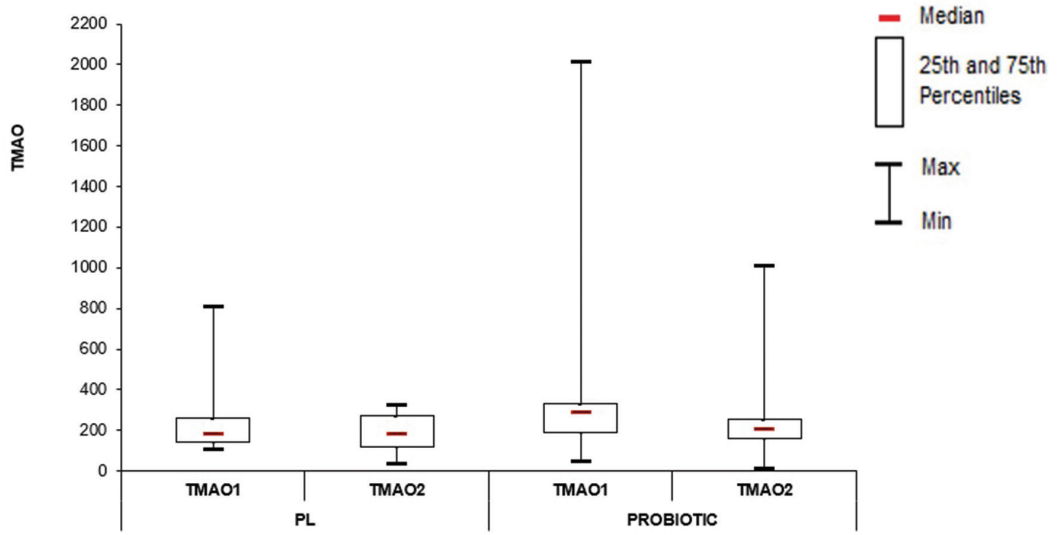

Figure 2. Differences in the primary outcome (TMAO levels) after 12 weeks of treatment. In the probiotic group (n=14) TMAO levels were decreased after the treatment. In the placebo groups, TMAO levels were not changed after 12 weeks of treatment. The difference in the TMAO levels after the interventional study procedure was statistically significant between the groups (p=0.044). Wilcoxon Rank Sum Test; TMAO: trimethylamine-N-oxide.

Differences in lipid profile and glucose control after interventional procedures in different patient groups

There was no statistically significant difference in the levels of total cholesterol, LDL cholesterol, non-HDL cholesterol, and triglycerides after the interventional study procedures in both probiotic and placebo groups. Significant differences in glucose and HOMA-IR index were not observed after 12 weeks of treatment in patients receiving probiotic and placebo treatments **(Tables 4, 5)**.

Differences in microbiome analysis after interventional procedures in different patient groups

The study results showed that *Lactobacillus* spp. % was not statistically significantly changed in the placebo group (2.01 (0.56) before and 0.74 (0.27) after the treatment; p=0.333). In the probiotic group, *Lactobacillus* spp. % was significantly increased after the intervention procedures (0.6 (0.14) before and 0.79 (0.6) after the treatment; p=0.041).

DISCUSSION

Despite numerous efforts, cardiovascular diseases remain the leading cause of morbidity and mortality worldwide.[15] Therefore, identifying new factors related to increased cardiovascular risk and strategies to mitigate these factors is a necessary area of research.

Intestinal microbiota-derived metabolite TMAO has a significant role in the development of atherosclerotic events.[17] However, the exact mechanisms of its action are under investigation.

TMAO synthesis and steps to influence TMAO levels

TMAO is synthesized by conversion of bacterial enzyme trimethylamine (TMA) lyases from L-carnitine, choline, and betaine-containing foods. This leads to the synthesis of TMA, which is the precursor of TMAO. TMA is then converted to TMAO in the liver via the liver enzyme flavin-dependent monooxygenase 3.[18] TMAO is predominantly excreted by the kidneys.[19] Therefore, diet changes, microbiota composition, FMO activity, and kidney function play an important role in the TMAO levels. Vegetarian diet is related to decreased TMAO levels as opposed to high-fat or Western diet, which is associated with increases in TMAO.[20] Other therapeutic factors affecting TMAO levels are currently under investigation. These include the inhibition of microbiota enzymes that convert choline and carnitine to TMA.[21] Balance and diversity in the microbiome are a key factor for healthy host-gut interaction.[22,23] Thus, intestinal microbiota modulation in order to decrease TMAO levels seems to be a safe and reasonable approach.

TMAO levels and probiotic supplementation

Despite the positive results for TMAO reduction after probiotic treatment in animals, studies evaluating the effect of probiotic supplementation on TMAO levels in humans have produced controversial results.[17] Moreover, the results from meta-analyses including 270 patients from eight randomized trials did not show statistically significant changes in TMAO levels after the probiotic treatment. Nevertheless, it can be concluded that probiotic treatment can decrease TMAO levels in individuals younger than 50 years old.[24]

Table 4. Differences in laboratory measurements between baseline evaluation and after treatment in the probiotic group

Parameter	Probiotic group, baseline n=14	Probiotic group, outcome n=141	*p*
TMAO levels (μg/l)	284 (139)	202.5 (96.77)	0.044
Total cholesterol (mmol/l)	4.5±1.29	4.5±1.18	1.00
LDL cholesterol (mmol/l)	2.33±0.7	2.56±1.00	0.189
HDL cholesterol (mmol/l)	1.10±0.23	1.08±0.25	0.668
Non-HDL cholesterol (mmol/l)	3.4±1.28	3.41±1.15	0.964
Triglycerides (mmol/l)	1.76±1.36	1.67±1.11	0.529
Glucose (mmol/l)	5.56±0.8	6.02±1.38	0.520
Insulin (micro U/l)	10.8±4.2	12.51±3.53	0.244
HOMA IR	2.49 (1.42)	2.72 (2.22)	0.173

In variables with normal distribution, results are presented as a median and standard deviation. A paired samples t-test was applied to compare the results. In cases of skewed distribution results are presented as the median and IQR in brackets, and Wilcoxon Signed Ranks test was used. HOMA IR: homeostatic model assessment for insulin resistance.

Table 5. Differences in laboratory measurement between baseline evaluation and after the treatment in placebo group

Parameter	Placebo group, baseline n=15	Placebo group, outcome n=15	*P*
TMAO levels (μg/l)	176 (120)	178 (150)	0.258
Total cholesterol (mmol/l)	4.14±0.9	4.08±0.78	0.759
LDL cholesterol (mmol/l)	2.19±0.8	2.12±0.72	0.901
HDL cholesterol (mmol/l)	1.06±0.25	1.04±0.17	0.638
Non-HDL cholesterol (mmol/l)	3.08±0.96	3.04±0.75	0.852
Triglycerides (mmol/l)	1.8±1.22	1.73±0.95	0.603
Glucose (mmol/l)	6.45±0.93	6.08±1.69	0.623
Insulin (micro U/l)	17.9±7.9	18.77±11.78	0.481
HOMA IR	4.80 (4.35)	3.90 (6.78)	0.814

In variables with normal distribution results are presented as a median and standard deviation. A paired samples t-test was applied to compare the results. In cases of skewed distribution, results are presented as the median and IQR in brackets, and Wilcoxon Signed Ranks test was used. HOMA IR: homeostatic model assessment for insulin resistance.

The present study results showed a slight statistically significant decrease in TMAO levels in patients receiving the probiotic treatment. In addition, the probiotic treatment group showed significantly increased *Lactobacillus* spp. levels after the probiotic supplementation. The present study population had a very high CVD risk, and the probiotic was administered for 12 weeks. Another probiotic supplementation trial with the same study period failed to confirm the efficacy of *L. casei* in decreasing TMAO levels in 30 metabolic syndrome patients.[25] The pilot trial design, the lack of beneficial effects on LcS in these patient groups, and the influence of nutritional factors were the main explanations for these results.

It is important to state that treatment was administered for different periods of time in most trials assessing the effect of probiotic supplementation on TMAO levels, which may explain the discrepancy in the results. In particular, four or 12 weeks of probiotic supplementation was utilized. The differences in patient population in terms of inclusion criteria are also important. For example, one of the randomized trials comprised very young healthy patients aged 20–25 years who received the probiotic treatment for four weeks. Statistically significant differences were not present in the TMAO levels between the groups. However, more participants in the probiotic groups showed that the TMAO levels decreased after the intervention.[26]

In addition, the data from human and animal studies suggested that there are only a few probiotic strains that affect the TMAO levels.[27] These outcomes showed a decrease in TMAO levels after treatment with *L. rhamnosus* GG, *L. plantarum* ZDY04, *L. amilovorus* LAM 1345, *L. plantarum* LP1145, and *Enterobacter aerogenes* ZDY01.[28-31] Results from intervention studies using multi-strain probiotic VSL#3 did not show significant results in reducing TMAO levels.[32]

L. plantarum GLP3 was used in the present trial in combination with resveratrol, which is a natural plant antioxidant with probiotic activity that has also been shown to decrease the TMAO levels.[33]

The present study did not show a statistically significant difference in the lipid profile or glycemic status of both the probiotic and placebo groups after the interventional procedure.

Study strengths

The present study had several strengths. First, it was a randomized blind trial, which helped to avoid confounding factors and more reliably evaluate the results. The study population consisted of very high-risk patients with established ASCVD, where an increase in TMAO is of prognostic importance. Furthermore, the study only included male patients in order to decrease the population heterogeneity. All patients had preserved renal function, thereby reducing the influence of renal excretion on the TMAO levels. In order to eliminate the influence of dietary habits on the TMAO levels, patients were instructed to follow the same dietary restrictions two days before baseline and outcome analyses.

Study limitations

This was a single-center study with a very small population size. In addition, even though TMAO levels were influenced by diet, dietary status during the whole study period was not taken into consideration. Finally, only 21 patients in the trial provided consent for microbiome analysis.

CONCLUSIONS

The present study demonstrated that probiotic supplementation with *L. plantarum* GLP3 reduced the TMAO levels in very high-risk patients. More studies are needed to confirm these findings. Whether the decrease in TMAO levels reduces cardiovascular risk is an important key question that needs to be addressed in future research studies.

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Влияние добавки *Lactobacillus Plantarum* на уровень триметиламин-N-оксида у 30 пациентов с атеросклеротическим сердечно-сосудистым заболеванием: двойное слепое рандомизированное контролируемое исследование

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Резюме

Введение: Триметиламин-N-оксид (TMAO) – это метаболит, вырабатываемый кишечной микробиотой. Он общепризнан как независимый маркер риска сердечно-сосудистых и почечных заболеваний и смертности.

Цель: Целью настоящего исследования было изучение влияния добавки *Lactobacillus plantarum* GLP3 на уровни TMAO у 30 пациентов с анамнезом атеросклеротического сердечно-сосудистого заболевания после 12 недель лечения.

Материалы и методы: Тридцать последовательных пациентов мужского пола с анамнезом клинического атеросклеротического сердечно-сосудистого заболевания были рандомизированы в исследовании. Уровни TMAO оценивались в образцах плазмы человека с использованием высокоэффективной жидкостной хроматографии с тройной квадрупольной тандемной масс-спектрометрией, а результаты представлялись в виде медианы (межквартильного диапазона). Анализ последовательности микробиома, сосредоточенный на бактериях из рода *Lactobacillus*, был проведён у 21 пациента.

Результаты: У пациентов, прошедших курс лечения пробиотиками, наблюдалось значительное снижение уровней TMAO [с 284 (139) μg/L до 202.5 (96.7) μg/L; $p = 0.044$], при этом в группе плацебо существенных изменений после лечения не наблюдалось [с 176 (120) μg/L до 178 (150) μg/L; $p = 0.258$]. Процент Lactobacillus spp. в группе пробиотиков значительно увеличился после интервенционных процедур [0.6 (0.14) до и 0.79 (0,6) после лечения; $p = 0.041$].

Заключение: Добавка пробиотиков с *Lactobacillus plantarum* GLP3 снизила уровни TMAO у пациентов с очень высоким риском сердечно-сосудистых заболеваний.

Ключевые слова

сердечно-сосудистые заболевания, кишечный микробиом, пробиотики