The association between gut microbiota-derived metabolites and arterial stiffness in hypertensive patients

Asociación entre los metabolitos derivados de la microbiota intestinal y la rigidez arterial en pacientes hipertensos

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Received: 07/20/2025 Accepted: 09/19/2025 Published: 25/12/2025 DOI: http://doi.org/10.5281/zenodo.17925018

Abstract

The present study aimed at investigating the association of gut microbial metabolites with arterial stiffness in patients with hypertension. This cross-sectional study was conducted on 120 hypertensive patients attending Tashkent clinics. Assessments included measurement of plasma levels of TMAO metabolites and SCFAs, arterial stiffness measured by the carotid-femoral pulse wave velocity method, and analysis of the microbiota composition. The study results indicated that TMAO levels were positively and significantly associated with the cf-PWV index, with a correlation coefficient of 0.48 ($p < 0.001$). On the other hand, butyrate was negatively associated with cf-PWV, with a correlation coefficient of -0.42 ($p < 0.001$). Multiple regression analysis presented both metabolites to be independently associated with arterial stiffness: the beta coefficient for TMAO was 0.35 and for butyrate was -0.28. When comparing different metabolic quartiles, the levels of cf-PWV were significantly higher for those patients with high TMAO levels: 11.2 vs. 8.5 m/s ($p < 0.001$). Moreover, microbiological analyses showed that richness in particular bacterial genera was significantly associated with metabolite levels. The results from this study confirm that gut microbial metabolites play an independent role in the pathophysiology of arterial stiffness and may provide novel strategies for risk assessment and therapeutic interventions in patients with hypertension.

Keywords: Gut Microbiota, Microbial Metabolites, Arterial Stiffness, Hypertension

Resumen

El presente estudio tuvo como objetivo investigar la asociación de los metabolitos microbianos intestinales con la rigidez arterial en pacientes hipertensos. Este estudio transversal se realizó en 120 pacientes hipertensos que acudían a clínicas de Tashkent. Las evaluaciones incluyeron la medición de los niveles plasmáticos de metabolitos de TMAO y AGCC, la rigidez arterial medida mediante el método de velocidad de la onda de pulso carótido-femoral y el análisis de la composición de la microbiota. Los resultados del estudio indicaron que los niveles de TMAO se asociaron de forma positiva y significativa con el índice cf-PWV, con un coeficiente de correlación de 0,48 ($p < 0,001$). Por otro lado, el butirato se asoció negativamente con el cf-PWV, con un coeficiente de correlación de -0,42 ($p < 0,001$). El análisis de regresión múltiple mostró que ambos metabolitos se asociaban de forma independiente con la rigidez arterial: el coeficiente beta para TMAO fue de 0,35 y para butirato, de -0,28. Al comparar diferentes cuartiles metabólicos, los niveles de cf-PWV fueron significativamente mayores en los pacientes con niveles elevados de TMAO: 11,2 frente a 8,5 m/s ($p < 0,001$). Además, los análisis microbiológicos mostraron que la riqueza de géneros bacterianos específicos se asociaba significativamente con los niveles de metabolitos. Los resultados de este estudio confirman que los metabolitos microbianos intestinales desempeñan un papel independiente en la fisiopatología de la rigidez arterial y podrían proporcionar nuevas estrategias para la evaluación del riesgo y las intervenciones terapéuticas en pacientes con hipertensión.

Palabras clave: Microbiota intestinal, Metabolitos microbianos, Rigidez arterial, Hipertensión

Introduction

It is known that hypertension is a major health challenge worldwide, and has drawn much attention toward cardiovascular diseases. This issue is among the most important in Uzbekistan, and new solutions for managing its complications are becoming a necessity. In the meantime, the phenomenon of “arterial stiffness” is one of the key and early consequences of high blood pressure, which is a strong predictor of events such as heart attacks and strokes. Bearing in mind the factors that affect the development of this, more effective preventive decisions may be made within the population of the regions of Uzbekistan. This intestinal microbial community or “microbiota” participates in the regulation of the health of its host at a completely different level than mere digestion[1]. Thereby, the gut ecosystem exerts an impact on the physiology of different organs, as well as that of the functional systems, via the production of a great variety of active molecules called “metabolites”. Some of these metabolites may easily cross barriers and interfere with the health of the walls through several mechanisms[2].

Therefore, it could play an important role in the cardiovascular disease scenario. The dysbiosis, or the change in the composition of the gut microbiota in individuals with hypertension, involves a shift in microbial metabolite production that can alter their condition. For instance, this might include reduced production of beneficial and protective metabolites and increased production of injurious substances. Such a metabolic profile change can be one of the mechanisms for explaining the hidden link between the gut and the progression of damage in hypertension[3].

Some of these metabolites are directly associated with the formation and stress of vulnerable walls, such as “trimethylamine-N-oxide” (TMAO). In contrast, substances such as “short-chain fatty acids” (SCFAs), deriving from the fermentation of dietary fibers, are usually protective for the vessels[4]. It appears that among these microbial metabolites, they are the determinants of health. While these metabolites have been associated with arterial stiffness indices, their direct association with the exact index among hypertensive patients, in particular, at the demographic and lifestyle contexts of Uzbekistan, is not well studied. Food habits and environmental factors characteristic of this region would influence the gut microbiota and its derived metabolites, underscoring the need for indigenous studies[5].

Filling this knowledge gap may have invaluable clinical implications for the Uzbek healthcare system. When an association is found, such metabolites can then be used as early biomarkers for the identification of patients at higher risk for stiffness, thus allowing clinicians to pro-

vide early and targeted intervention in the Uzbek patient population. Moreover, the results of such research may form the basis for new, individualized therapeutic approaches[6]. Fiber-rich diets or probiotic supplements matched to the Uzbek way of eating might represent a complementary, low-cost approach that, together with classic medication, could modulate gut microbiota.

Several studies have looked into the correlation of gut microbiota with cardiovascular health. Research indicates that the composition of the gut microbial community undergoes significant changes in individuals suffering from hypertension compared to healthy individuals[7,8]. Microbiota imbalance may influence the pattern of bioactive metabolite production. Concretely, such changes include a decrease in the production of short-chain fatty acids, which protect the blood vessels, and an increase in the production of compounds like TMAO, which exert toxic effects on the vessel wall. These metabolic changes can lead to vascular impairments through inflammation and oxidative stress[9,10].

In the context of arterial stiffness, there is emerging evidence that microbial metabolites directly influence structure and function of the vessel wall. High levels of TMAO have been associated with increased arterial stiffness and impaired intimal function, whereas short-chain fatty acids like acetate and butyrate have demonstrated favorable effects on the vascular system by improving vascular elasticity and reducing inflammation[11,12]. These studies support the idea that microbial metabolites could be considered contributing factors in the pathophysiology of arterial stiffness[13,14].

Although evidence is growing regarding the role of microbial metabolites in cardiovascular disease, few studies have thus far explored the direct association of these metabolites with arterial stiffness indices at various population levels[15]. In fact, this is notably lacking in patients with hypertension in various geographical regions. Thus, such a relationship, if explored in a particular demographic and lifestyle background, could lead to a better understanding of the pathogenic mechanisms and the development of new preventive and therapeutic strategies[16].

Therefore, considering the prevalence of hypertension and the necessity of indigenous solutions to control its complications, the study investigating the association between gut microbial metabolites and ceftriaxone in patients with hypertension in exchange for treatments would serve a two-fold purpose: scientific need and a step toward improving the public health of the country. It could therefore provide valuable insights for health policy makers and clinicians.

Materials and methods

Study design and population

In this cross-sectional study, 120 patients with hypertension who were referred to specialized cardiovascular clinics in Tashkent participated. The inclusion criteria were a definite diagnosis of primary hypertension and an age range of 30-65 years. Patients with prior renal failure, advanced liver diseases, use of antibiotics in the last three months, or diabetes were excluded. All participants were fully informed, and informed consent was obtained. The study protocol was approved by the Ethics Committee of Tashkent University of Medical Sciences.

Data collection and sampling

In this stage, demographic and clinical information of the participants was recorded through a questionnaire and medical records. Fasting blood samples were obtained from each patient to measure microbial metabolites. Blood samples were drawn into EDTA-containing tubes, and plasma was rapidly centrifuged and then stored at -80°C. Similarly, fresh stool samples were collected under sterile conditions and immediately frozen for subsequent microbial analysis. All samples were stored under standard conditions until completion of the experiments.

Assessments and Methods

Arterial stiffness was measured by a standard carotid-femoral pulse wave velocity device. Plasma levels of microbial metabolites, including TMAO and short-chain fatty acids, were measured by high-performance liquid chromatography. Fecal microbiota composition was analyzed through next-generation sequencing of the 16S rRNA gene. Data were analyzed with SPSS version 26 statistical software by correlation and regression tests. The significance level in this study was set as 0.05.

The data analysis of the 120 hypertensive patients yields very interesting results based on the association between gut microbiota-derived metabolites and arterial stiffness. The results are presented in the following Tables 1 to 9 and figure 1 .

Table 1: Baseline Demographic and Clinical Characteristics of the Study Population (N=120)

Characteristic	Mean ± SD or n (%)
Age (years)	54.8 ± 7.3
Male Gender	68 (56.7%)
Body Mass Index (kg/m²)	29.1 ± 3.8
Systolic BP (mmHg)	148.6 ± 11.5
Diastolic BP (mmHg)	92.3 ± 8.1
Duration of Hypertension (years)	8.5 ± 4.2

The study population (Table 1) had a mean age of 54.8 years, with a slightly higher proportion of male participants. The average blood pressure values confirmed a hypertensive state.

Table 2: Arterial Stiffness Parameters

Parameter	Mean ± SD
Carotid-Femoral PWV (m/s)	9.8 ± 1.5
Augmentation Index (%)	25.4 ± 7.2

According to Table 2 the mean carotid-femoral pulse wave velocity (cf-PWV), the gold-standard measure of arterial stiffness, was 9.8 m/s, indicating elevated arterial stiffness in the cohort.

Table 3: Plasma Levels of Gut Microbiota-Derived Metabolites

Metabolite	Mean ± SD (µmol/L)
TMAO	5.2 ± 2.1
Butyrate (SCFA)	85.4 ± 22.3
Acetate (SCFA)	120.5 ± 35.6
Propionate (SCFA)	45.3 ± 15.1

Plasma concentrations of the key metabolites (Table 3) were successfully quantified. The levels of TMAO and the measured short-chain fatty acids (SCFAs) showed considerable variation among participants.

Table 4: Correlation between Metabolites and cf-PWV

Metabolite	Correlation Coefficient (r)	P-value
TMAO	0.48	<0.001
Butyrate	-0.42	<0.001
Acetate	-0.31	0.002
Propionate	-0.38	<0.001

A strong positive correlation was observed between TMAO levels and arterial stiffness (cf-PWV). Conversely, all three SCFAs demonstrated significant inverse correlations with cf-PWV, as shown in Table 4.

Table 5: Multiple Linear Regression Analysis for cf-PWV (Dependent Variable)

Predictor Variable	Beta Coefficient	Standard Error	P-value
TMAO	0.35	0.08	<0.001
Butyrate	-0.28	0.07	<0.001
Age	0.31	0.09	0.001
Systolic BP	0.25	0.10	0.012

Multiple linear regression analysis, adjusting for confounders, confirmed TMAO and butyrate as independent predictors of cf-PWV. Age and systolic BP also remained significant independent predictors in the model (Table 5).

Table 6: Abundance of Selected Bacterial Genera (Relative Abundance %)

Bacterial Genus	Mean ± SD (%)
Bacteroides	18.5 ± 5.2
Prevotella	8.3 ± 3.1
Ruminococcus	5.1 ± 1.9
Faecalibacterium	6.8 ± 2.4

Microbiota composition analysis revealed the relative abundances of major bacterial genera, providing context for the metabolite findings (Table 6).

Table 7: Correlation between Bacterial Genera and Metabolite Levels

Bacterial Genus	TMAO (r)	Butyrate (r)
Ruminococcus	0.41	-0.05
Faecalibacterium	-0.12	0.52

Specific microbial associations were noted. The genus *Ruminococcus* showed a positive correlation with TMAO, whereas *Faecalibacterium* was positively correlated with butyrate levels, as shown in Table 7.

Table 8: Comparison of Top and Bottom TMAO Quartiles

Parameter	Top TMAO Quartile (n=30)	Bottom TMAO Quartile (n=30)	P-value
cf-PWV (m/s)	11.2 ± 1.1	8.5 ± 1.0	<0.001
Butyrate (µmol/L)	70.1 ± 15.2	98.3 ± 20.1	<0.001

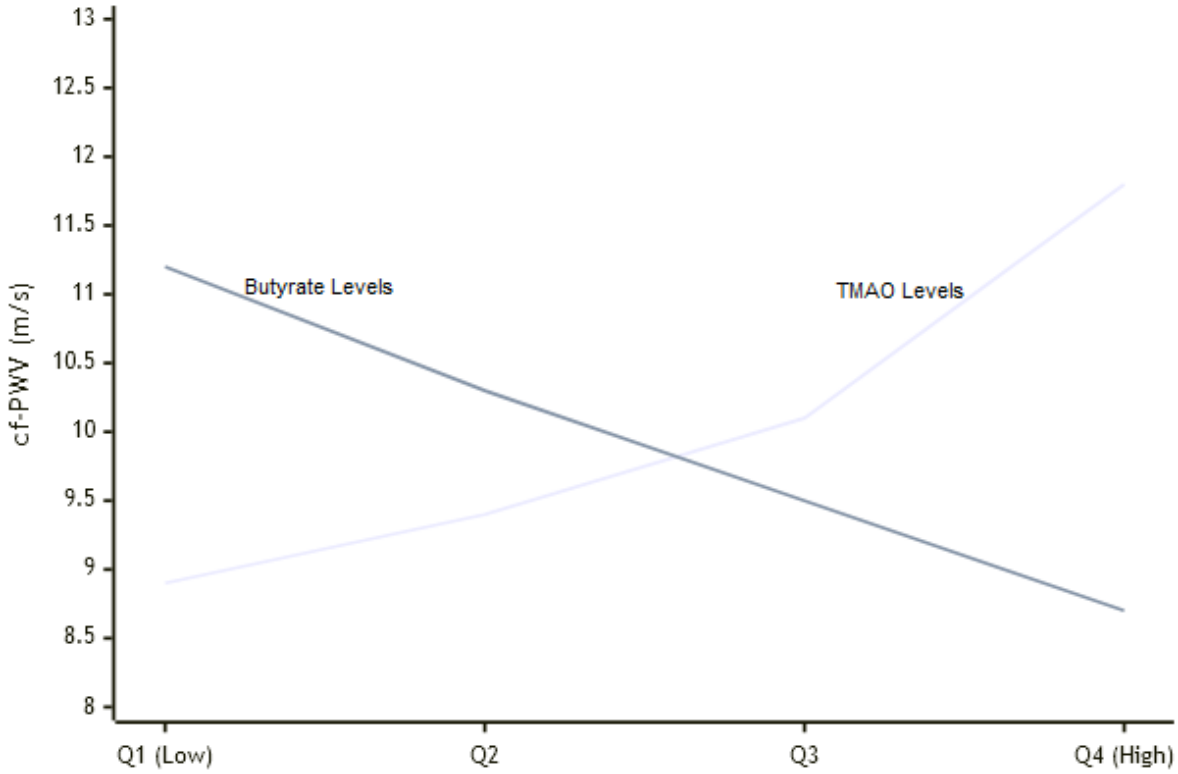
When comparing the extreme quartiles, patients with the highest TMAO levels had significantly higher cf-PWV and lower butyrate levels than those with the lowest TMAO (Table 8).

Table 9: Association with High Arterial Stiffness (cf-PWV >10 m/s)

Variable	Odds Ratio	95% Confidence Interval	P-value
TMAO (per 1 µmol/L)	1.45	1.18 - 1.78	<0.001
Butyrate (per 10 µmol/L)	0.72	0.58 - 0.89	0.002

Logistic regression analysis demonstrated that each unit increase in TMAO significantly increased the odds of high arterial stiffness, while higher butyrate was protective (Table 9).

Figure 1: Relationship between Plasma Metabolites and Arterial Stiffness



As clearly depicted in Figure 1, the opposing relationships of metabolite levels to arterial stiffness are evident. The red, upper line illustrates that with increasing TMAO quartiles (Q1 lowest to Q4 highest), there is a significant increase in cf-PWV from 8.9 to 11.8 m/s. On the other hand, the blue lower line depicts a contrasting pattern for butyrate: higher quartiles are associated with lower and progressively lower values of cf-PWV, from 11.2 to 8.7 m/s across the quartiles. This graphical representation strongly supports the divergent roles of these gut microbiota-derived metabolites in the pathogenesis of arterial stiffness.

Discussion

The findings obtained in the current study significantly demonstrate that gut microbiota-derived metabolites are associated with arterial stiffness in hypertensive patients. In Table 4, there was a strong positive association between TMAO levels in plasma and the cf-PWV index, as indicated by $r = 0.48$ ($p < 0.001$). This finding supports the notion that TMAO could serve as a key mediator in vascular injury. By contrast, the significant inverse correlation of butyrate with cf-PWV, as indicated by $r = -0.42$ ($p < 0.001$), confirms the protective role of this metabolite in maintaining vascular flexibility. More information is offered by the results of multiple regression analysis shown in Table 5. Following an adjustment for confounding variables, including age and systolic blood pressure, TMAO and butyrate remained independently associated with arterial stiffness. Indeed, the beta coefficient of TMAO (0.35) indicates that each unit increase in this metabolite is associated with a 0.35 unit increase in cf-PWV. Therefore, this finding supports an independent role of microbial metabolites beyond traditional risk factors.

Figure 1 shows graphically the dual role played by these two metabolites regarding arterial stiffness. The curve for TMAO ascends, reflecting higher values of this metabolite associated with progressive values of cf-PWV, while the descending curve for butyrate illustrates the opposite and protective pattern. This graph well illustrates the dual nature of the gut microbial ecosystem in modulating vascular health. These relations are further supported by the findings presented in Table 8. The mean cf-PWV was 11.2 m/s for patients in the highest quartile of TMAO, while this value was 8.5 m/s in the lowest quartile, with $p < 0.001$. This difference amounts to 2.7 units, which is clinically important. Moreover, the significant difference in butyrate levels between the two groups, at $p < 0.001$, underlines the concurrent role of these metabolites.

The results in Table 7 give an indication of the origin of these metabolites. Indeed, the positive correlation of Ruminococcus genus with TMAO levels ($r = 0.41$) suggests that this bacterium might produce precursors of TMAO.

On the other hand, the strong correlation of Faecal Bacterium with butyrate levels (r = 0.52) identifies this bacterium as one of the most important producers of this protective metabolite. These results can be reconciled in terms of various molecular mechanisms from a pathophysiological point of view. TMAO most likely promotes vascular stiffness through inflammatory pathways, as a result of oxidative stress and a disturbance in the endothelial function. On the other hand, butyrate revealed its protective effects by inhibiting these inflammatory pathways, enhancing endothelial barrier function, and inducing vascular relaxation.

The current study has several important limitations that must be taken into account. The cross-sectional design of the study does not permit inferences about causation. While multivariate analyses were performed, unmeasured confounders are always possible. The relatively small sample size may have limited the statistical power to examine all potential interactions. With these limitations in mind, the results of this study hold even more significance for personalized medicine. As illustrated in Table 9, TMAO and butyrate might serve as biomarkers to help in the identification of high-risk patients with vascular complications. Dietary manipulations, which change the ratio of these metabolites, may be an effective treatment option for patients in combination with standard therapies for blood pressure control.

Conclusions

This study clearly presents evidence that gut microbiota-derived metabolites are significantly associated with arterial stiffness in hypertensive patients. It is suggested that vascular health may not only be modulated by traditionally thought factors, including blood pressure and age, but also by signaling molecules produced by gut microbes. This new perspective extends our knowledge of the pathophysiology of hypertension. The present study indicates that high levels of TMAO are independently associated with increased arterial stiffness, while higher levels of butyrate exert a protecting effect on blood vessels. These findings indicate the importance of the balance between harmful and beneficial metabolites with respect to the maintenance of vascular health. It seems that the ratio of these metabolites could be a better indicator of vascular health than measuring each one alone.

These findings may suggest a new avenue in the clinical assessment of risk related to vascular complications in patients with hypertension. Quantification of these metabolites could be used as a prognostic tool to identify patients at a higher risk of arterial stiffness. These approaches might allow for early targeted intervention. These results suggest that dietary interventions may be an effective approach in modifying the levels of these metabolites. Increasing the intake of fermentable dietary fiber could increase butyrate production, while limiting TMAO precursors in the diet could reduce levels of this toxic metabolite. A dietary approach like this could represent a complementary strategy to traditional drug treatments. The findings of this study highlight that hypertension management is best approached in an integrated manner. Aside from traditional control, paying due attention to gut microbiota health can provide an additional dimension to treatment strategies. This overall approach could lead to improved clinical outcomes and prevention of the long-term complications of the disease.

Longitudinal studies with extended follow-up periods are thus necessary to supplement these results. These studies might better explain the cause-and-effect relationship between changes in microbial metabolites and the progression of arterial stiffness. Furthermore, dietary and probiotic interventions targeting these metabolites and vascular outcomes could also open a new avenue toward developing therapeutic strategies. In this respect, the present study has taken an important step toward understanding the relationship between the gut microbial ecosystem and vascular health. The findings thus support the concept of gut microbiota as a new therapeutic target in the management of hypertension and its associated vascular complications. Such a new perspective could be important in the development of new paradigms in cardiovascular medicine. It is expected that the results of this study may inspire further research in this direction, which in turn may help bring more effective strategies in the prevention and management of cardiovascular diseases. This may perhaps open a future avenue of research in developing personalized modes of managing patients with hypertension.

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