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Maternal serum trimethylamine-N-oxide is significantly increased in cases with established preeclampsia

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ABSTRACT

Purpose: To compare the levels of trimethylamine-N-oxide (TMAO) in sera of normal and preeclamptic pregnancies and to explore whether serum TMAO level was associated with the severity of preeclampsia.
Materials and methods: Eighty-six pregnant women in the third trimester were enrolled in this case control study. Levels of TMAO were quantified by a novel liquid chromatography/tandem mass spectrometry-based method in fasting serum samples from 43 preeclamptic women and 43 normotensive controls. Clinical characteristics, serum biomarkers of inflammation (IL-1β) and biomarkers of endothelial dysfunction (sVCAM-1, sFlt-1) were assessed.
Results: TMAO levels were significantly higher in women with preeclampsia than those with normal pregnancy. The serum levels of TMAO were positively correlated with systolic blood pressure ($r = 0.602$, $P < 0.001$), urinary protein levels ($r = 0.557$, $P < 0.001$) and the serum levels of IL-1β ($r = 0.633$, $P < 0.001$), sVCAM-1 ($r = 0.719$, $P < 0.001$) as well as sFlt-1 ($r = 0.763$, $P < 0.001$) in patients with PE.
Conclusions: Elevated TMAO levels are associated with higher risk of preeclampsia and correlate with increased systemic inflammation and endothelial dysfunction. Further validation of these findings with more robust multicenter prospective and longitudinal characterization of maternal serum TMAO in pregnancy may be carried out in subsequent investigations to determine its suitability as a predictive biomarker for preeclampsia.

1. Introduction

Preeclampsia (PE) is a common pregnancy-specific complication, characterized by hypertension and significant proteinuria at or after 20 weeks of pregnancy, It affects approximately 5–10% of pregnant women worldwide and remains the second leading cause of maternal and perinatal morbidity and mortality [1,2]. Although mounting evidence suggests that maternal endothelial dysfunction and systemic inflammation triggered by placental ischemia are involved in the pathogenesis of PE, the precise cause of PE are not well understood.

A recent metabolomics approach which identified plasma trimethylamine-N-oxide (TMAO) is a gut-derived metabolite that has been linked to cardiovascular diseases and mortality in both humans and animal models [3,4]. TMAO is generated by bacterial conversion of phosphatidylcholine, choline, betaine and carnitine, into gaseous trimethylamine that is taken up and oxidized into TMAO by flavin-containing monooxygenases in the liver [5]. TMAO has been identified as a novel and independent risk factor for promoting atherosclerosis. Recent studies indicate that TMAO accelerates endothelial cell dysfunction and induces vascular inflammation through oxidative stress [6,7].

The accumulation of plasma TMAO is prevalent in various diseases such as obesity, diabetes, metabolic syndromes, and polycystic ovary syndrome [8–10]. Mounting evidences suggested that these population have a higher risk of developing for PE when they are pregnant [11,12]. Microbial composition of gut flora is the major contributing factor in regulating circulating TMAO levels. In 2017, Liu et al. [13] reported that remodeling of the gut microbiota and structural shifts in women with preeclampsia. However, whether patients with PE have higher serum levels of TMAO than those of normal pregnancies is still unknown.

Given the crucial role of TMAO in endothelial dysfunction and vascular inflammation, we hypothesized that elevated levels of circulating TMAO might contribute to the onset of PE and be associated with the severity of the disease (See Fig.1). To test this hypothesis, we first

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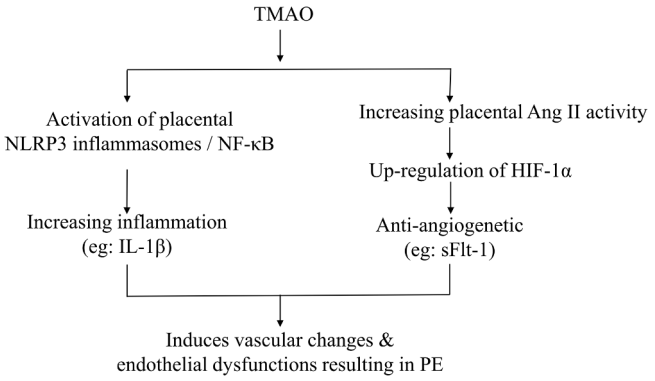

Fig. 1. A possible role of TMAO in the pathogenesis of preeclampsia.

compare the levels of TMAO in sera of normal and preeclamptic pregnancies. Additionally, we explore whether serum TMAO level is associated with the severity of PE and correlates with systemic inflammation and endothelial dysfunction.

2. Methods

2.1. Patients and study design

The case–control study was conducted at the Department of Obstetrics and Gynecology, Nanfang Hospital of Southern Medical University, Guangzhou, P. R. China. All participants were recruited between May 2016 and December 2017. Written informed consent was obtained from all women participating in the study which was approved by the Institutional Review Board (NFEC-2017-103) of Nanfang Hospital, Southern Medical University.

Of the 86 pregnant women selected in this study, 43 were diagnosed with PE and 43 had normotensive pregnancy without other disease (who were selected as controls). Women with preeclampsia were stratified into two groups according to the disease severity, 26 cases of severe PE (sPE) and 17 of mild PE (mPE). Preeclamptic patients and normotensive controls were matched for maternal age, parity, and body mass index. Exclusion criteria were: age < 18 years or ≥ 35 years, women who were complicated with multiple gestations, fetal congenital malformation, fetal chromosomal disorders, or maternal history of cardiovascular, renal, or other hypertension-associated diseases, or gestational/pregestational diabetes, or auto-immunological diseases. The demographics and clinical characteristics of the pregnant women selected in this study are summarized in Tables.

Preeclampsia in this study was based on the modified criteria introduced by the American College of Obstetricians and Gynecologists [14]: a new onset of hypertension (blood pressure $\geq$ 140/90 mmHg on two occasions, 2 h to 2 weeks apart after 20 weeks of gestation) and proteinuria (urine dipstick with $\geq 2+$ protein at presentation, or24-h urine protein $\geq$ 300 mg/d). Severe PE were defined as the presence of new onset of hypertension during the pregnancy with one of the following features: elevated liver alanine/aspartate aminotransferase (ALT $\geq$ 80 U/L or AST $\geq$ 70 U/L), platelet count $\leq 100 \times 10^9$/L, placenta abruption, pulmonary edema, cerebral hemorrhage, eclampsia, acute renal failure (creatinine $>$ 114.4 μmol/L), disseminated intravascular coagulation, or HELLP (hemolysis, elevated liver enzymes and low platelets) syndrome. The diagnosis of HELLP syndrome was established when at least one of three criteria was present: elevated plasma level of transaminases (AST and ALT $\geq$ 70 U/L), platelet count $\leq 100 \times 10^9$/L, and lactic dehydrogenaseenzyme $>$ 600 IU/mL. Placental abruption was defined as premature separation of the normally implanted placenta before delivery.

2.2. Analysis of TMAO, IL-1β, sVCAM-1 and sFlt-1 in human plasma

Blood samples were collected into EDTA anticoagulant tubes after a 12 h overnight fast. The samples were immediately centrifuged at 3000*g* for 5 min, the serum samples were aliquoted and stored at −80 °C until further analysis to avoid interference due to repeated freeze-thaw cycles.

Routine blood test and plasma levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine and urea in each patients were analyzed with standard laboratory techniques by an automatic biochemical analyzer (Cobas8000, Roche, Germany) at Nanfang Hospital of Southern Medical University. Plasma creatinine was used to estimate glomerular filtration rate (GFR) based on the formula of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) [14]: for females with serum creatinine $\leq$62 μmol/L: GFR = 144 (serum creatinine [μmol/l] × 0.0113/0.7)$^{-0.329}$ × (0.993) age in years, and for females with serum creatinine $>$ 62 μmol/L: GFR = 144 (serum creatinine [μmol/l] × 0.0113/0.7)$^{-1.209}$ × (0.993) age in years).

The TMAO levels were quantified using stable isotope dilution liquid chromatography-tandem mass spectrometry (LC/MS/MS) as described previously [6]. Briefly, a 20 μl sample was added to a 1.5 ml Axygen tube containing 80 μl of internal standard mixture (10 μM d9-TMAO in methanol). The mixture was vortexed for 1 min at 4–8 °C and incubated for 4 h at −80 °C to precipitate protein. To obtain the precise levels of TMAO, 20 μl of different concentration standards (0–100 μM) were processed by the same procedure to get a standard curve. Supernatants (70 μl) were injected to a silica column (2.0 × 150 mm, Luna 5 u Silica 100 A; Cat. No. 00F-4274-B0, Phenomenex, Torrance, CA) at a flow rate of 0.4 ml/min using a LC-20 CE Shimadzu pump system, and a SIL-20AXR autosampler coupled to an API 5500Q-TRAP mass spectrometer. Analytes were monitored using electrospray ionization in positive-ion mode with multiple reaction monitoring of precursors and characteristic production transitions of TMAO. The expression level of IL-1β, sVCAM-1 and sFlt-1 was detected by enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's instructions (R&D Systems, Minneapolis, MN, USA).

2.3. Statistical analyses

Data are expressed as mean ± standard deviation or median (10th–90th percentile) as appropriate. Demographics and clinical characteristics were compared between groups by student's *t*-test for continuous and chi square test for proportions. The Pearson's test was used to determine correlations between variables. For the analyses of serum levels of TMAO, IL-1β, sVCAM-1 and sFlt-1, logarithmic values were used to obtain normal distribution. All statistical tests were 2-tailed. A p-value < 0.05 was considered statistically significant. Statistical analysis was performed using SPSS version 23.0 (IBM SPSS statistics).

3. Results

3.1. Baseline characteristics

Table 1 summarizes the clinical and laboratory characteristics with P values for the comparison of all cases with or without PE enrolled in this study. No significant differences were observed in maternal age, gravidity, or pre-pregnant body mass index (BMI), serum urea or estimated GFR among the three groups (all $P > 0.05$). As expected, systolic and diastolic blood pressures at enrolment and proteinuria/24 h of women in the PE group were significantly higher than those in the control group. The gestational age at delivery, neonatal birth weights and placental weight were significantly lower in women with PE compared with normotensive pregnant women.

Table 1
Baseline characteristics of normotensive and preeclamptic pregnant women.

	Control (n = 43)	mPE (n = 17)	sPE (n = 26)
Age (years)	29.46 ± 3.22	30.33 ± 3.07	30.55 ± 3.53
Gravidity	2.11 ± 1.03	2.01 ± 0.99	1.93 ± 1.22
Pre-pregnant BMI, kg/m^2	22.85 ± 4.16	22.26 ± 4.19	22.53 ± 5.68
Gestational age delivery (weeks)	39.08 ± 1.13	37.11 ± 2.16	35.06 ± 4.35
Blood pressure			
Systolic pressure (mm Hg)	109.53 ± 10.16	148.33 ± 18.92[a]	167.23 ± 10.65[a,b]
Diastolic pressure (mm Hg)	69.87 ± 8.52	93.78 ± 9.24 [a]	97.86 ± 12.33 [a]
Serum creatinine(μ mol/L)	55.49 ± 15.13	59.73 ± 10.54	63.39 ± 18.62
Serum urea (mmol/L)	4.76 ± 2.27	4.93 ± 1.78	5.54 ± 1.93
eGFR (ml/min /1.73 m^2)	121.54 ± 16.18	117. 49 ± 11.37	112.31 ± 14.72
Urine protein concentration (g/L)	0.06 ± 0.03	0.93 ± 0.42 [a]	4.82 ± 1.76 [a,b]
Neonatal birthweight (g)	3383.75 ± 311.59	2963.62 ± 486.38 [a]	2719.68 ± 716.52 [a]
Placental weight (g)	657.81 ± 85.34	533.42 ± 95.02 [a]	488.37 ± 78.48 [a]

Abbreviations: mPE, mild preeclampsia; sPE, severe preeclampsia; BMI: body mass index. eGFR, estimated glomerular filtration rate. a. $P < 0.05$ when compared with control group; b. $P < 0.05$ when compared with mPE group.

3.2. Increased serum levels of TMAO, IL-1β, sVCAM-1, and sFlt-1 in preeclamptic pregnancies

Serum concentrations of TMAO, IL-1β, sVCAM-1, and sFlt-1 are presented in Table 2. Compared with the normotensive pregnant, the serum levels of TMAO, IL-1β, sVCAM-1, and sFlt-1 were significantly elevated in patients with sPE. Moreover, the serum levels of TMAO and sFlt-1 were higher in sPE groups when compared to those in the mPE group, whereas no significant differences of circulating IL-1β, sVCAM-1 levels were observed.

3.3. Associations between serum levels of TMAO and clinical parameters as well as biomarkers of inflammation/endothelial dysfunction

The serum levels of TMAO were positively correlated with systolic blood pressure ($r = 0.602$, $P < 0.001$), urinary protein levels ($r = 0.557$, $P < 0.001$) and the serum levels of IL-1β ($r = 0.633$, $P < 0.001$), sVCAM-1 ($r = 0.719$, $P < 0.001$) as well as sFlt-1 ($r = 0.763$, $P < 0.001$) in patients with PE, but not with estimated GFR ($r = -0.218$, $P = 0.15$). In contract, no statistically significant correlations were observed between TMAO and systolic blood pressure, serum IL-1β, sVCAM-1as well as sFlt-1 in the control group (data not shown).

4. Discussion

In this case control study, we explored the maternal serum TMAO in patients with established PE and normotensive pregnancies, the principal findings were as follows: 1) TMAO levels were significantly higher in women with preeclampsia than those in women with normal pregnancy; 2) Serum TMAO was associated with the severity of PE; 3) Serum levels of TMAO were positively correlated with systolic blood pressure, urinary protein levels, as well as biomarkers of inflammation/endothelial dysfunction in patients with PE.In 2017, Liu et al. [13] reported that a significant structural shift of the gut microbiota (an overall increase in pathogenic bacteria, but a reduction in probiotic bacteria) in patients with PE.

Several mechanisms may be involved in the association between increased serum levels of TMAO and clinical manifestation of PE. A possible role of TMAO in the pathogenesis of PE is demonstrated in **Figure1**.Recently, Ufnal et al. [15] evaluated the effect of TMAO on arterial blood pressure in rat model. Their results showed that TMAO did not affect blood pressure in normotensive animals. However, it prolonged the hypertensive effect of angiotensin II(Ang II). The blood TMAO concentration may depend on several factors, including diet, gut microbiota activity,the gut permeability, and TMAO excretion [9,16]. Microbial compositions of gut flora are the major contributing factor in regulating circulating TMAO levels. Apart from the structural shifts of gut microbiota in women with preeclampsia [13], it has been suggested that hypertension in rats is associated with an increased permeability of the gut-blood barrier to bacterial metabolites such as TMA (a TMAO precursor) [16]. Previous studies have demonstrated that TMAO was strongly related to renal function in chronic kidney disease (in subjects with eGFR < 90 mL/min/1.73 m^2) [17]. Given the importance of the kidney in eliminating TMAO, we raises the question: could higher TMAO level be due to renal impairment in the present study. Our data showed that no significant differences of maternal renal function were observed between preeclampsia and control groups. Moreover, serum TMAO was not significantly correlated with eGFR, which suggested that high TMAO in patients with preeclampsia was not due to compromised renal function.

A significant process in the pathogenesis of PE is placental ischemia/hypoxia [18], which leads to overproduction and secretion of inflammatory cytokines as well as anti-angiogenic factors into the maternal circulation. These cause endothelial dysfunction which ultimately result in multi-system organ injury. As a significant gut flora-dependent metabolite, TMAO has been linked to cardiovascular

Table 2
Serum concentrations of TMAO, IL-1β, sVCAM-1, and sFlt-1 in normotensive and preeclamptic cases.

	Control (n = 43)	mPE (n = 17)	sPE (n = 26)
TMAO (μM/L)	5.9 (2.9–15.3)	21.6 (5.6–65.8)[a]	43.5 (28.6–96.3)[a,b]
IL-1β (pg/mL)	8.2 (4.2–19.7)	47.3 (15.8–52.5)[a]	58.2(32.8–87.9)[a]
sVCAM-1 (ng/mL)	471.8 (383.5–586.8)	772.6 (523.1–1102.6)[a]	833.5 (599.5–1273.2)[a]
sFlt-1 (ng/mL)	5.6 (2.3–11.9)	25.5 (6.8–49.7)[a,b]	46.6 (25.2–63.6)[a,b]

Abbreviations: mPE, mild preeclampsia; sPE, severe preeclampsia; BMI: body mass index.
[a] $P < 0.05$ when compared with control group.
[b] $P < 0.05$ when compared with mPE group.

diseases and mortality in both human and animal models. A growing evidence suggested that TMAO plays a critical role in up-regulation of inflammatory pathways, e.g. c-Jun N-terminal kinase and nuclear factor-kappa B [19,20]. Recently, Boini et al. [21] demonstrate the critical role of TMAO in the activation of NLRP3 inflammasomes and IL-1β production, which could be associated with subsequent endothelial dysfunction. Moreover, it has been reported that TMAO accelerates endothelial cell senescence and vascular aging, which might contribute to the placental ischemia/hypoxia [22].

SFlt-1, a soluble vascular endothelial growth factor (VEGF) protein, has been shown to be a molecule of interest associated with the pathogenesis of the PE. SFlt-1 has the ability to bind with VEGF and placental growth factor (PlGF), thereby neutralizing their angiogenic functions [23]. This attribute can potentially induce an angiogenic imbalance causing endothelial dysfunction.Previous studies indicates that increased expression of sFlt-1 in in-vivo and in-vitro models of human placenta is mediated by hypoxia-inducible factor-1alpha (HIF-1α) [24,25]. Given the fact that Ang II has been shown to upregulate HIF-1α [26], and TMAO could prolong the effects of Angiotensin II in rats [15], it is proposed that TMAO might induce sFlt-1 over-production through Ang II/ HIF-1α pathways in placental trophoblasts and trigger consequently systemic and local endothelial dysfunction.

To the best of our knowledge, this is the first report that compares the levels of TMAO in sera of normal and preeclamptic pregnancies and investigates whether serum TMAO levels are associated with the severity of preeclampsia. Importantly, our study found that elevated TMAO level is associated with higher risk of preeclampsia and correlates with increased systemic inflammation and endothelial dysfunction. However, two limitations should be also addressed. First, in this study, the plasma sample was taken in cases with established preeclampsia during the third trimester. Therefore, we could not figure out whether serum TMAO was increased before or after the onset of PE. Second, the total number of cases selected in this study is relatively small and single-hospital based.

In conclusion, our data demonstrated that increased maternal serum TMAO levels are associated with established PE and may determine the disease severity. We proposed that decreasing serum levels of TMAO might have utility as an adjuvant therapy for established preeclampsia due to its capacity to resolve some aspects of endothelial dysfunction. Further studies with more robust multicenter prospective and longitudinal characterization of maternal serum TMAO profiles in pregnancy are necessary to verify the causal relationships between TMAO and PE.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.preghy.2018.12.001.

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