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ORIGINAL RESEARCH

Association of Betaine, Choline, and TMAO with Type 2 Diabetes in Rural China: A Nested Case–Control Study from the Handan Eye Study (HES)

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Background: Conflicting evidence exists regarding the association of gut microbiota-related metabolites – TMAO and its precursor choline and betaine with type 2 diabetes Mellitus (T2DM), particularly in rural Chinese populations. This study aimed to prospectively examine these relationships in a northern rural Chinese cohort.

Methods: A nested case–control study was conducted within the Handan Eye Study. At baseline (2006–2007), 5,512 participants aged ≥30 years were enrolled. After 6.5 years of follow-up, 209 incident T2DM cases and 394 age- and sex-matched controls were included. Plasma choline, betaine, and TMAO levels were measured using ultra-performance liquid chromatography. Logistic regression and linear models assessed associations with T2DM risk, insulin resistance (IR), and metabolic parameters.

Results: Baseline betaine level was lower in the T2DM group compared to controls (betaine: 7431.4 ng/mL versus 7821.5 ng/mL). After adjusting for BMI, waist-to-hip ratio, and diabetes history, no significant associations were found between choline, betaine, or TMAO and T2DM risk. However, higher betaine quartiles showed a trend toward reduced T2DM risk (Q4 vs Q1 OR: 0.59, 95% CI: 0.34–1.06). Betaine was inversely correlated with HOMA-IR ($\beta = -0.16$), HOMA-β ($\beta = -0.13$), and TyG index ($\beta = -0.21$) ($p < 0.05$). Plasma choline levels were positively associated with fruit intake frequency, while TMAO levels decreased with higher exercise intensity.

Conclusion: Betaine may play a protective role against dyslipidemia, adiposity, and T2DM risk in rural Chinese populations. Further studies are needed to explore TMAO's complex role in diabetes development.

Keywords: type 2 diabetes, choline, betaine, TMAO, nested case–control study

Introduction

Diabetes is a major chronic disease threatening global health and a leading cause of blindness, kidney failure, heart attacks, stroke, lower limb amputation and metabolic disorders. In China, 90% of diabetes cases are Type 2 Diabetes Mellitus (T2DM), and over 20% of people with diabetes are aged 60 years or older.[1] As the population ages, this proportion will continue to rise. T2DM is characterized by hyperglycemia, insulin resistance, and pancreatic β-cell decompensation. Glucose, lipid, amino acid and their metabolites contribute to T2DM pathogenesis through distinct metabolic and immunologic pathways. Gut microbiota dysbiosis has been implicated in adverse metabolic profiles and diabetes development.

Recent studies indicate that gut microbiota is a key factor in developing IR through the production of metabolites and interactions with the host's intestinal cells. A reduction in gut bacterial diversity has been associated with IR, obesity and increased inflammation. Gut microbiota also produces metabolites such as short-chain fatty acids (SCFAs), bile acids (BAs), and trimethylamine N-oxide (TMAO). One crucial metabolic product is TMAO, primarily produced by the bacterial metabolism of substrates such as phosphatidylcholine, choline and betaine in the colon. Elevated levels of choline metabolites—derived from red meat, eggs, and fish—were found to be associated with increased T2DM risk.[2] Choline in the bloodstream can be oxidized to betaine, which is an important

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osmolyte that provides a methyl group in the liver. Intestinal bacteria convert unabsorbed choline into trimethylamine (TMA), which is oxidized in the liver by flavin monooxygenase 3 (FMO3) and transformed into trimethylamine-N-oxide (TMAO). The original compounds are represented by choline, betaine, phosphatidylcholine and carnitine. TMAO has an important role in the onset and progression of T2DM and is correlated with a significant risk of other metabolic disorders, including cardiovascular diseases, hypertension, renal dysfunction.[3–6] Elevated levels of TMAO have been shown to impair glucose-stimulated insulin secretion, reduce β-cell mass, and worsen glucose tolerance, all of which can contribute to the progression of diabetes. Furthermore, choline, as a essential nutrient needed for lipid metabolism and hepatic production of very-low-density lipoproteins (VLDLs), influences glucose and lipid homeostasis through insulin resistance (IR) and the production of TMAO, accelerating prediabetes and diabetes progression.

Currently, there are conflicting views on the correlation between choline and TMAO with T2DM. A 19.3 years prospective Finnish cohort study reported a 5.0% lower incidence of T2DM with the highest choline intake,[7] whereas two Puerto Rican Cohorts studies showed neither choline nor TMAO were associated with incidence of T2DM.[8] Conversely, a cohort study involving 13,440 participants from the Atherosclerosis Risk in Communities (ARIC) study in the United States, the incidence rate of T2DM of highest quartile of dietary choline intake was 1.54 times that of the lowest one among women.[9] Plasma TMAO also yields inconsistent results. There have been cross-sectional studies investigating the association between plasma choline, TMAO and T2DM, but few studies are prospective, especially among north rural China population. In addition, some studies were conducted among patients with specific diseases, which calls into question whether such associations can be generalized to a healthy population. This study utilizes data from the Handan Eye Study (HES),[10] a population-based cohort study to determine the prevalence and impact of visual impairment and major ocular diseases in Chinese adults living in a rural region north China. Our prior findings on amino acids with T2DM risk in our population[11] in this cohort align with other studies.[12–14] In this study, we extend this work to investigate associations between gut microbiota-related metabolites (choline, betaine, TMAO) with dyslipidemia, adiposity and the risk of T2DM in healthy China population.

Materials and Methods

Study Participants

Participants were recruited from the Handan Eye Study (HES), a population-based cohort study investigating the prevalence of eye diseases and chronic conditions among adults aged ≥30 years in Yongnian County, Handan City, Hebei Province, China. The study design and baseline data collection methods for HES have been previously described.[10] The baseline survey was conducted from 2006 to 2007, with a follow-up survey from 2012 to 2013. Participants were eligible if they met the following inclusion criteria: (1) subjects of 30 years or above. (2) the household registration was in the local area. (3) the household registration was not in the local area but subjects had lived in the local area for more than half a year. (4) voluntarily participate in the study. A stratified cluster sampling method was employed. From 453 villages: 1) 13 villages were randomly selected, comprising 5,111 residents aged ≥50 years. 2) 6 villages were randomly selected from these 13, yielding 3,532 residents aged 30–49 years. A total of 8,643 subjects were initially selected and 7557 subjects met the criteria. After excluding 727 declined participation and 1318 with incomplete data (missing blood glucose tests, physical examinations, or questionnaires, 5,512 participants remained at baseline. During the 2012–2013 follow-up, 981 were lost to follow-up and left 4531 participants for follow-up. Individuals were further excluded due to the following conditions: 1) 366 with baseline diabetes; 2) 33 missing follow-up glucose tests. Following these exclusions, 4,132 participants remained. Among 4,132 participants: 218 developed T2DM during follow-up. Each case was matched with two controls (1:2 ratio) using propensity score matching (SAS 9.2), balanced for age and sex. After excluding 57 participants with insufficient samples, the final analysis included 209 T2DM cases and 394 matched controls.

Data Collection

Demographic data: At enrollment, demographic data were collected through face-to-face interviews conducted by professionally trained interviewers. The content of standardized survey questionnaire covered demographic information, occupation, educational background, lifestyle variables, medication use and family history of disease, and so on. The

physical examination included blood pressure, height, weight, waist circumference, and hip circumference. Systolic and diastolic blood pressures are the average of two measurements.

Assessment of Plasma Metabolites

Blood tests include fasting plasma glucose (FPG), lipid profile, and liver and kidney function tests. Blood samples were collected at baseline and follow-up survey, respectively. Blood samples collection requires empty stomach for more than 8 hours. Fasting glucose, glycated hemoglobin and insulin were determined both at baseline and follow-up. Glycated hemoglobin was performed by cation exchange high-performance liquid chromatography (Bio-Rad D10, USA). Fasting plasma glucose (FPG) was measured by the hexokinase method (Olympus AU2700, Japan). Insulin was detected by chemiluminescent immunoassay (Siemens AdviaCP, Germany). Aliquots were coded and stored at −80°C. In the present study, we performed additional metabolomic measurements including plasma choline, betaine and TMAO. These were performed by ultra-performance liquid chromatography (Ultra Performance Liquid Chromatography, UPLC) (Waters, UPLC I-Class, USA).

Diagnostic Criteria for T2DM

Diagnostic criteria for T2DM in follow-up were based on the Chinese Guidelines for the Prevention and Treatment of Type 2 Diabetes (2013 edition) and the recommendations of the American Diabetes Association,[1,15] which is Fasting Plasma Glucose (FPG)≥7.0 mmol/L or glycated hemoglobin ≥6.5%.

Statistical Analysis

We use logistic regression analysis to calculate odds ratios of plasma choline, betaine, TMAO level and T2DM. Further, we divided plasma choline, betaine, TMAO into four group by quartiles and calculate odds ratios and 95% Cis for T2DM. We use linear regression analysis to calculate the correlation between choline, betaine, TMAO and insulin resistance parameter, such as HOMA-IR, HOMA-β and TyG. Spearman correlation coefficient was calculated between choline, betaine, TMAO level and obesity, lipid and insulin resistance parameters. We use ANVOA to analyze the difference between fruit intake frequencies, exercise intensity levels with choline, betaine and TMAO.

The obesity, lipid and insulin resistance parameters calculation formulas were as follows: homeostatic model assessment for insulin resistance, HOMA-IR= FINS (fasting insulin) ×FPG/22.5; homeostatic model assessment for insulin, HOMA-β=20×FINS/[FPG-3.5]; triglyceride-glucose index, TyG= ln(TG*88.6×FPG×18.02/2); visceral adiposity index (VAI), VAIm=[WC/(39.68+1.88×BMI)]×(TG/1.03)×(1.31/HDL-C), VAIf=[WC/(36.58+1.89×BMI)]×(TG/0.81)×(1.52/HDL-C); Chinese visceral adiposity index(CVAI), CVAIm=−267.93+0.68×age+0.03×BMI+4.00×WC+22.00×LgTG-16.32×HDL-C, CVAIf=−187.32+1.71×age+4.32×BMI+1.12×WC+39.76×LgTG-11.66×HDL-C; Lipid accumulation product, LAP, LAPm=WC-65)×TG; LAPf= (WC-58)×TG.

Data were analyzed using SAS 9.2 (SAS Institute Inc., Cary, NC, USA) and GraphPad 8.0. All statistical tests were two-sided at alpha = 0.05.

Results

Participant Characteristics

Table 1 presents the baseline characteristics of participants. Case group had significantly higher levels of blood lipids, FPG, FINS, insulin resistance (HOMA-IR) and hs-CRP compared to controls. Betaine is lower in the case group, but there are no statistical differences between two groups. No differences were observed in fruit intake frequencies and exercise intensity ($p > 0.05$).

Association of Plasma Metabolites with T2DM and IR Risk

Adjusted for age, gender, BMI, WHR, and family history of diabetes, the odds ratios ORs for T2DM associated with choline, betaine, TMAO of T2DM was 0.99, 1.00 and 1.00 ($p > 0.05$). Subsequently, Choline, betaine, and TMAO were divided into four groups by quartiles as Q1 to Q4 from low to high, as shown in Table 2. Compared with Q1, none of the

Table 1 Baseline Characteristics and Laboratory Test Results of the Study Participants

	T2DM Group	Control Group	P value
Number (N)	202	395	
Age (years)	54.0±9.6	54.1±9.7	0.891
Male (%)	78(38.6)	148(37.5)	0.799
Smoking (%)	42(20.8)	89(22.5)	0.621
Drinking (%)	34(16.8)	56(14.2)	0.397
Systolic blood pressure (mmHg)	145.1±23.2	141.9±22.1	0.109
Diastolic blood pressure (mmHg)	79.5±12.7	78.2±11.8	0.247
Obesity indicators			
BMI/(kg/m2)	26.5±4.1	24.5±4.2	0.000
Waist circumference (cm)	92.2±9.7	87.3±8.9	0.000
Waist-to-hip ratio (WHR)	0.91±0.05	0.90±0.05	0.007
VAI	2.92±2.8	2.28±1.9	0.001
CVAI	125.4±37.3	104.9±36.5	<0.001
LAP	63.7±44.1	46.9±44.3	<0.001
Lipid profile			
HDL-C (mmol/L)	1.24±0.3	1.29±0.3	0.044
LDL-C (mmol/L)	2.93±0.6	2.73±0.7	0.000
TCH (mmol/L)	4.90±0.9	4.67±1.0	0.006
TG (mmol/L)	1.9±1.3	1.5±1.1	0.002
Insulin resistance			
Fasting insulin (mU/L)	9.5±5.3	7.6±5.1	<0.001
Fasting glucose (mmol/L)	6.0±0.5	5.5±0.5	<0.001
HOMA-IR	2.55±1.44	1.89±1.29	<0.001
HOMA-β	78.52±48.78	79.72±56.36	0.788
TyG	8.95±0.5	8.64±0.6	0.001
Metabolites			
Choline (ng/mL)	1825.5±470.3	1829.9±495.8	0.917
Betaine (ng/mL)	7431.4±2463.1	7821.5±2677.7	0.08
TMAO (ng/mL)	160.15(98.64~238.30)*	154.00(80.93~223.00)*	0.15
Liver/kidney function indicators			
Albumin (g/l)	45.2±3.2	44.8±3.4	0.152
hs-CRP (mg/l)	2.97±5.33	1.84±2.62	0.001
Unsaturated iron-binding capacity (umol/l)	45.9±13.4	42.9±13.1	0.016
Total iron-binding capacity (umol/l)	66.1±10.7	63.0±9.6	<0.001
GGT (U/l)	20.7±16.9	17.9±24.4	0.163
Urine creatinine (umol/l)	82.0±55.5	85.4±56.6	0.492
GFR (mL/min)	98.7±14.0	100.3±13.9	0.173
Uric acid (umol/l)	261.6±61.8	251.42±63.87	0.078
Frequency of fruit consumption	N (%)	N (%)	0.82
1-7 times/week	51 (25.2)	102 (25.8)	
1-3 times/month	70 (34.7)	127 (32.2)	
Less than 1 time/month	81 (40.1)	166 (42.0)	
Physical activity			0.96
Low intensity	42 (20.8)	85 (21.5)	
Moderate intensity	10 (5.0)	21 (5.3)	
High intensity	150 (74.3)	289 (73.2)	
Family history			
Family history of diabetes (%)	20(9.9)	11(2.8%)	<0.001

Notes: Values are means (SD); *median (IQR).

Table 2 Logistic Regression Analysis of Choline, Betaine and TMAO with T2DM by Quartiles

	T2DM N (%)	Controls N (%)	OR (95% CI)
Choline (ng/mL)	202	395	
Q1 (~1513.38)	51(25.2)	98 (24.8)	
Q2 (1513.38~)	55 (27.2)	95 (24.1)	1.23 (0.76~1.98)
Q3 (1777.35~)	48 (23.8)	102 (25.8)	1.05 (0.63~1.72)
Q4 (2045.30~)	48 (23.8)	100 (25.3)	1.18 (0.69~2.00)
Betaine (ng/mL)			
Q1 (~5837.20)	56 (27.7)	92 (23.3)	
Q2 (5837.20~)	54 (26.7)	97 (24.6)	0.89 (0.55~1.42)
Q3 (7293.30~)	63 (31.2)	128 (32.4)	0.79 (0.50~1.26)
Q4 (9119.03~)	29 (14.4)	78 (19.5)	0.59 (0.34~1.06)
TMAO (ng/mL)			
Q1 (~93.10)	58 (28.7)	92 (23.3)	
Q2 (93.10~)	46 (22.8)	101 (25.5)	0.68 (0.42~1.09)
Q3 (158.55~)	51 (24.2)	100 (25.3)	0.84 (0.52~1.35)
Q4 (230.93~)	47 (23.3)	102 (25.8)	0.74 (0.45~1.21)

metabolites showed a significant association with T2DM risk. However, a trend toward reduced risk was observed for betaine: the ORs for decreased from 0.89,0.79 to 0.59, with the Q4 group showing a 41% lower risk of T2DM compared to Q1 ($p = 0.06$).

Linear regression analysis revealed that betaine was significantly inversely correlated with HOMA-IR ($\beta = -0.16$), HOMA-β ($\beta = -0.13$), and TyG index ($\beta = -0.21$) ($p < 0.05$). Choline and TMAO showed no significant correlation with insulin resistance.

The Correlation of Plasma Metabolites with Obesity, Lipids and IR

As shown in Figure 1, Betaine was negatively correlated with obesity indices, blood lipids and IR markers. The Spearman correlation coefficients for LAP, waist circumference, BMI, VAI, CVAI and TyG were −0.22, −0.21, −0.19, −0.16 and −0.12, respectively. The correlation coefficients for TC, LDLC and TG were −0.19, −0.16 and-0.16. HOMA-IR ($r = -0.15$), INS ($r = -0.14$), HOMA-β ($r = -0.11$)) ($p < 0.05$). Choline showed a weak positive correlation with the obesity indicator CVAI ($r = 0.11$). TMAO was inversely correlated with blood lipids (TG ($r = -0.08$), TyG ($r = -0.09$)) ($p < 0.05$).

The Association of Plasma Metabolites with Diet and Exercise

As shown in Table 3, Plasma choline level is associated with fruit intake frequently, participants consuming fruit less than once per month had lower plasma choline levels than those with higher intake frequencies ($p < 0.05$); and plasma TMAO is associated with exercise intensity, participants reporting high exercise levels had lower TMAO levels ($p < 0.05$).

Discussion

Diabetes is a metabolic disease characterized by hyperglycemia, accompanied by dysregulation of lipid and amino acid metabolism. In this study, baseline levels of FPG, FIN, HOMA-IR, TyG index and lipid profile (TC, TG, LDL) were significantly elevated in the case group. The TyG index, which comprehensively reflects glucose and lipids metabolism, is considered to have relationship with T2DM onset, retinal arteriosclerosis and other metabolic syndrome.[16,17] Central obesity (defined as waist circumference of ≥90 cm in males and ≥85 cm in females) and other adiposity indices such as BMI, WC, WHR, VAI, CVAI and LAP, were also higher in the case group at the baseline. These findings indicated abnormalities in glucose, lipid and amino acids metabolism at least 5 years before diagnosis. No differences were

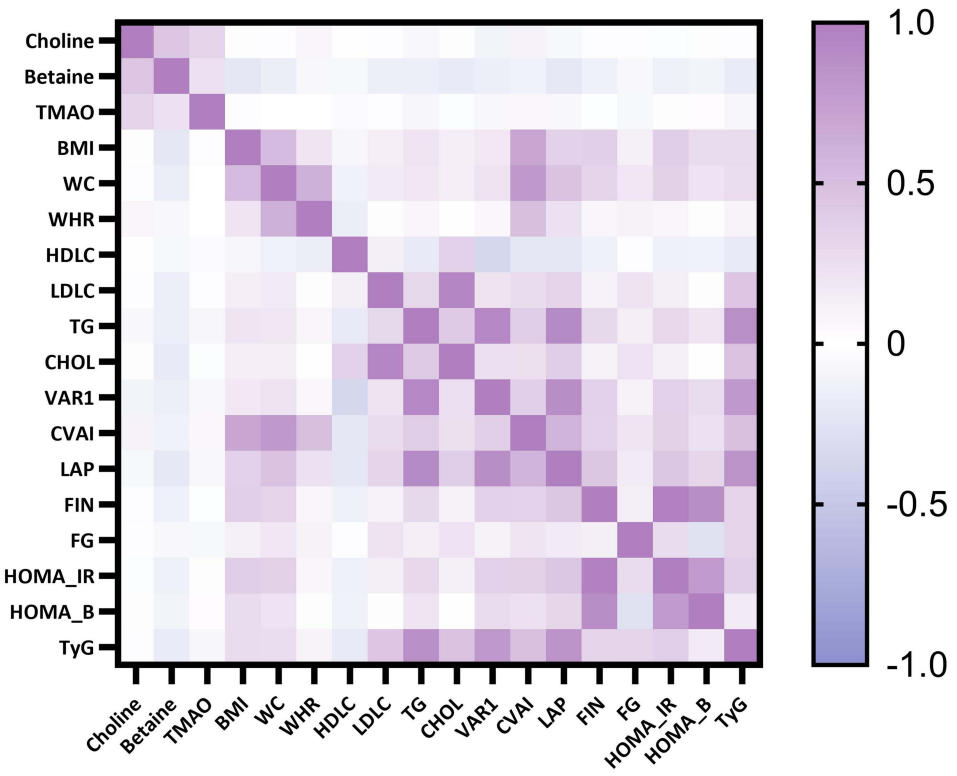

Figure 1 Correlation coefficients between plasma metabolites and metabolic parameters.

observed in liver and kidney function between the two groups, but hs-CRP was significantly higher in the case group at baseline. Collectively, these results suggested that in the early stage of diabetes, IR, lipid metabolites and inflammatory factors all contribute to the process of disease development.

Beyond conventional metabolites, we examined gut microbiota-derived TMAO and its precursors choline and betaine. Choline and betaine are important methyl donors in the body, mainly participating in the methionine cycle and re-methylation of homocysteine (Hcy). They played important roles against metabolic diseases through reducing Hcy levels in the body, alleviating oxidative stress or stabilizing DNA methylation. Previous studies reported that higher serum betaine correlates with lean body tissue in middle-aged and elderly individuals and reduced risk of diabetic complications. A dietary survey questionnaire study in Newfoundland found inverse associations between betaine and choline intake and IR.[18] In cohort studies, plasma betaine levels were negatively correlated with blood glucose, insulin, HbA1c and IR and betaine was also associated with a 22% lower

Table 3 Comparison of Plasma Choline Levels with Different Fruit Intake Frequencies and Exercise Levels

	N (%)	Cholin (ng/mL)	P	Betaine (ng/mL)	P	TMAO (ng/mL)	P
Fruit intake frequencies			0.012		0.719		0.379
1-7/weekly	247	1893.7±572.1		7787.1±2705.9		156.8(92.85~227.15)*	
1-3/monthly	197	1837.1±572.1		7664.6±2586.0		147.2(85.50~224.00)*	
<1/monthly	153	1757.9±371.7		7575.1±2430.5		166.1(99.80~256.50)*	
Exercise intensity			0.169		0.892		0.021
Low	127	1897.4±547.7		7784.4±2764.8		179.10(109.50~252.70)*	
Moderate	31	1786.2±455.9		7658.4±2711.2		156.75(77.53~257.98)*	
High	439	1810.5±468.4		7662.8±2561.4		150.30(90.20~224.60)*	

Notes: Values are means (SD); *median (IQR).

incidence of T2DM; however, choline, and TMAO showed no significant associations.[8,19] The "REACTION" cohort study that conducted in Lanzhou China in 2011 found dietary choline intake was below the recommended amount in local residents and there was no change in the incidence of T2DM as choline intake increased, though non-diabetic females exhibited increased risk with higher intake.[20] In our cohort, no difference was observed in plasma choline and betaine levels between the two groups at baseline. When analyzed by quartiles, decreased risk was observed as betaine level increased, while choline exhibited no association. Choline positively correlated with obesity index CVAI (r = 0.11), potentially reflecting dietary intake from animal sources, since plasma choline mainly comes from animal-derived foods. Additionally, choline levels were found to be related to the frequency of fruit intake. Lower plasma choline was observed in participants consuming fruit <1/month. It is speculated to be related to gut microbiota metabolism of less conversion to TMAO. Betaine demonstrated consistent inverse correlations with lipid profiles, obesity indices and IR. Betaine was negatively correlated with HOMA-IR (β = −0.16), HOMA-β (β = −0.13) and TyG (β = −0.21). This supports that betaine, as a methyl donor, plays a protective role in T2DM development through reduced lipid accumulation.

TMAO, derived from dietary phosphatidylcholine, choline, betaine, and carnitine (abundant in seafood, eggs, and meat), exhibits complex metabolic effects. Animal studies showed high TMAO levels have been associated with impaired glucose tolerance, disordered insulin signaling, and inflammation in adipose tissue, via TMAO-mediated oxidative stress and inflammatory responses. Cross-sectional studies showed association of plasma TMAO with T2DM, especially gestational diabetes mellitus (GDM).[4,21,22] One meta-analysis on the association between TMAO and obesity reported a dose–response relationship between TMAO and BMI (with a 0.58 kg/m^2 increase per unit in TMAO),[23] consistent with our finding that higher exercise intensity correlated with lower TMAO. Another meta-analysis based on cohort studies suggested increased diabetes risk with elevated TMAO (OR = 1.71).[24] However, a 2-year ORIGINS cohort study in the United States[25] found no association with TMAO and fasting blood glucose, HbA1c, or HOMA-IR. While a strong inverse prospective association was documented between plasma TMAO concentrations with T2DM risk in Spanish elderly Mediterranean individuals.[26] In our study, no significant association was found between baseline TMAO concentration and the incident of diabetes. Divided by quartiles, ORs from the lowest to the highest quartiles of TMAO with T2DM were 1.00, 0.68 (95% CI: 0.42~1.09), 0.84 (95% CI: 0.52~1.35), 0.74 (95% CI: 0.45~1.21). Baseline TMAO levels exhibited a nonlinear relationship with the risk of T2DM and the second quartile showed negative association compared with the lowest group (OR = 0.68). Several factors may account for these discrepancies: 1) this is a prospective study instead of cross-sectional with average follow-up of 6.5 years, the participants were healthy adults aged 30 and above. In cross-sectional study with high-risk population or specific metabolic diseases TMAO seem to be high a risk factor; 2) TMAO levels fluctuate based on diet and an individual's gut microbiome composition, as well as FMO3 expression. Population of different races and dietary habits are of great influence. Early-stage TMAO may primarily reflect dietary intake rather than pathological processes. Thus, TMAO's role in metabolic regulation is multifaceted, with its production being influenced by diet, microbiome composition, and liver function. Given that the potential value of TMAO in early T2DM interventions still needs to be explored.

Limitations of this study: The cohort population was from north rural areas of China and could not represent whole population, for a variety of dietary and environment differences in China. The sample size was limited, which may introduce selection bias. There was a lack of an oral glucose tolerance test and may result in underdiagnosis of T2DM, leading to potential biases in the results. Third, we only tested baseline plasma metabolites and may not fully reflect changes during the disease development process. The narrow scope of analyzed metabolites limits the ability to fully capture the complex interactions within gut microbiota-derived metabolic networks, while the absence of dietary assessment data in the study cohort further restricts the interpretation of potential nutritional influences on these metabolic pathways.

Conclusion

This study indicates that betaine plays a positive regulatory role in resisting obesity and early metabolic disorders of diabetes. While dietary betaine supplementation and microbiota modulation may represent promising strategies for early diabetes intervention, further research is needed to define optimal dosing, mechanistic pathways linking dietary betaine, host metabolism, and gut microbiota.

Ethics Approval

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Beijing Tongren Hospital (TREC2006-22), and all subjects have written informed consent.

Disclosure

The authors report no conflicts of interest in this work.

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