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Plasma Metanephrines Are Associated With Glucose Metabolism in Patients With Essential Hypertension

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Abstract: There is a high incidence of glucose intolerance in essential hypertension. Overactivation of the sympathetic system is one of important causes of essential hypertension. Whether sympathetic system affects glucose metabolism in patients with essential hypertension has never been reported previously. The aim of this study was to explore the association between the sympathetic system activity and glucose metabolism in patients with essential hypertension.

A total of 202 essential hypertension inpatients without diabetes were recruited from Shanghai Ruijin Hospital between February 2006 and August 2013. Activity of sympathetic system was quantified by plasma metanephrines (MNs) levels. All subjects received an oral glucose tolerance test.

Fasting plasma glucose and 2-hour plasma glucose increased significantly across the quartiles of plasma MNs. The multiple linear regression analysis revealed that plasma MNs were significantly associated with fasting plasma glucose and 2-hour plasma glucose. The area under curve of plasma glucose increased significantly from the lowest plasma MNs quartile across to the highest quartile. The multiple logistic regression analysis revealed that odds ratios (95% confidence interval) for prediabetes in the highest quartile compared with the lowest quartile of plasma MNs was 4.00 (95% confidence interval, 1.16–13.86).

Plasma MNs levels are positively associated with plasma glucose in patients with essential hypertension. Patients with high plasma MNs levels had an increased risk of prediabetes.

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INTRODUCTION

Essential hypertension is defined as high blood pressure in which secondary causes are excluded, and it accounts for 95% of all cases of hypertension.[1] Essential hypertension and impaired glucose tolerance are closely associated and approximately 75% of diabetes patients have concomitant hypertension, and as such, these two bad companions confer a much increased morbidity and mortality of cardiovascular diseases.[2,3] The sympathetic system is a highly versatile system whose functions are related to circulatory control, immune regulation, metabolism, and emotion.[4–6] It has already been demonstrated that sympathetic activation is strongly associated with many of the components of the metabolic syndrome, such as essential hypertension, obesity, hyperinsulinemia.[7–13] The metanephrines (MNs), including metanephrine (MN) and normetanephrine (NMN), are the O-methylated metabolites of epinephrine and norepinephrine, a process catalyzed by catechol-O-methyltransferase.[14] It has been reported that MNs were reliable markers of sympathetic system activity.[15] In the present study, we aimed to investigate the association between plasma MNs and glucose metabolism in patients with essential hypertension.

METHODS

Study Subjects

A total of 897 consecutive inpatients were diagnosed as essential hypertension between February 2006 and August 2013 in Ruijin hospital affiliated to Shanghai Jiao-Tong University School of Medicine, China. Essential hypertension was defined as blood pressure ≥140/90 mm Hg or previously diagnosed and current taking antihypertensive medication.[16] Causes of secondary hypertension were ruled out based upon normal findings of the following tests: serum and urinary electrolytes, serum creatinine, plasma and urinary catecholamines, plasma MNs, plasma and urinary aldosterone, plasma renin activity, plasma and urinary cortisol, thyroid stimulating hormone, free triiodothyronine and free thyroxine, Doppler studies of the renal arteries, and/or renal scintigraphy or renal angiography. Patients with diabetes or taking drugs of glucose-lowering or insulin, or

those with overweight or obesity, or with the use of β receptor blocker drugs or hypolipidemic were excluded. A total of 202 patients were included in the final analysis. The study was approved by the institutional review board of Ruijin Hospital. Informed consent was obtained from all participants.

MEASUREMENTS

The detailed information about medical history, smoking habits, and alcohol consumption were acquired by trained physicians. Current smoking or drinking status was defined as yes if the subject smoked or drank regularly in the past 6 months. Body height and body weight were measured by experienced nurses according to standard protocol. Body mass index (BMI) was calculated as body weight in kilograms divided by body height in meters squared. Blood pressure was measured on the no dominant arm, using an automated electronic device (OMRON Model1 Plus; Omron Company, Kyoto, Japan) in the seated position 3 times consecutively with 1-minute intervals after at least 5-minute rest. The average of 3 readings was used for analysis.

All participants received the oral glucose tolerance test (OGTT) after an overnight fast, and blood samples were collected at 5 time points (0, 30, 60, 120, and 180 minutes). Plasma glucose concentrations and serum concentrations of triglycerides, total cholesterol, high-density lipoprotein cholesterol and low-density lipoprotein cholesterol were measured using an autoanalyzer (Beckman CX-7 Biochemical Autoanalyzer, Beckman Coulter, Brea, CA). Serum insulin was measured using an electrochemiluminescence assay (Roche Diagnostics, Basel, Switzerland).

In accordance with the 2003 American Diabetes Association criteria, prediabetes was defined as impaired fasting glucose (IFG) (fasting plasma glucose ≥ 5.6 mmol/L and ≤ 6.9 mmol/L) and/or impaired glucose tolerance (2 h OGTT plasma glucose ≥ 7.8 mmol/L and ≤ 11.0 mmol/L). The homeostasis model assessment of insulin resistance was calculated as fasting serum insulin (μIU/mL) $\times$ fasting plasma glucose (mmol/L)/22.5. The area under curve (AUC) of plasma glucose was calculated by trapezoidal method.

Plasma MN and plasma normetanephrine (NMN) were quantified by reverse-phase high-performance liquid chromatography (Agilent 1100 series, Santa Clara, CA) with electrochemical detection (ESA-A Dionex Company, Chelmsford, MA). The lowest detectable plasma MN concentration was 5 pg/mL and the lowest detectable plasma NMN concentration was 8 pg/mL. Plasma MNs were represented as plasma MN plus plasma NMN.

Statistical Analysis

All statistical analyses were performed using SAS version 8.1 (SAS Institute, Cary, NC). Variables were presented as medians (interquartile ranges) or as number with proportion for categorical variables.

The study population was divided into quartiles on the basis of plasma MNs levels, with the first quartile representing the lowest one and the fourth quartile representing the highest one. Demographic and laboratory features were described in each group, P for trend across quartiles was calculated by linear regression analysis for continuous variables and Cochran–Mantel–Haenszel for categorical variables.

Pearson correlation coefficients of plasma MNs with fasting plasma glucose and 2-hour plasma glucose were analyzed in unadjusted model. To allow for covariance and confounders, the multiple linear regression was used to investigate the associations of plasma MNs with fasting plasma glucose and 2-hour plasma glucose after adjusting for age, sex, BMI, systolic blood pressure (SBP), current smoking state, total cholesterol (TC).

Differences of plasma glucose concentrations in different plasma MNs quartiles during the OGTT test were compared by analysis of variance and post hoc comparisons were performed by using Bonferroni correction. To investigate the association of plasma MNs with the AUC of plasma glucose, linear regression analysis was used. Comparisons of the AUC of plasma glucose in different plasma MNs quartiles, the analysis of variance test and Bonferroni post hoc test were adopted.

The crude association between plasma MNs and prediabetes was first evaluated by the univariable logistic regression in model 1. The multivariable logistic regression models were performed to assess the relationships between plasma MNs levels and prevalence of prediabetes. In model 2, age, sex, BMI were adjusted. In model 3, SBP, current smoking state, TC were further adjusted on model 2. The statistical tests were two-sided, a $P < 0.05$ was considered statistically significant.

RESULTS

Characteristics of the Study Population

The clinical and biochemical characteristics of the study population in relation to plasma MNs quartiles are presented in Table 1. Fasting plasma glucose ranges from 4.90 (4.66–5.10) mmol/L to 5.17 (4.81–5.34) mmol/L across plasma MNs quartiles. Two-hour plasma glucose ranges from 5.10 (4.50–6.40) mmol/L to 6.77 (5.44–7.61) mmol/L across plasma MNs quartiles. Fasting plasma glucose and 2-hour plasma glucose were significantly increased with plasma MNs quartiles ($P = 0.004$, $P < 0.001$, respectively, Table 1). We observed that age was increased with plasma MNs quartiles with a significant difference ($P = 0.01$); however, other parameters were not statistically different among the plasma MNs quartiles.

Associations between Plasma MNs and Plasma Glucose Levels

As shown in Table 2, Pearson correlation analysis revealed that plasma MNs were positively and significantly correlated with fasting plasma glucose and 2-hour plasma glucose ($P = 0.003$, $P < 0.001$, respectively). After adjusting for age, sex, BMI, SBP, current smoking state, TC, the multivariable linear regression analysis also demonstrated that fasting plasma glucose and 2-h plasma glucose increased significantly with plasma MNs ($P = 0.008$, $P = 0.001$, respectively).

As shown in Figure 1, we observed significant higher plasma glucose level for patients with the highest plasma MNs quartile comparing to the lowest plasma MNs quartile at 4 time points (0, 30, 60, and 120 minutes) of the OGTT test (all $P < 0.05$, Figure 1A). The AUC of plasma glucose increased significantly from the lowest plasma MNs quartile to the plasma MNs highest quartile ($P < 0.001$, Figure 1B). Strikingly, the AUC of plasma glucose in the fourth and the third plasma MNs quartiles were significantly higher as compared with the lowest quartile ($P < 0.001$, $P = 0.003$, respectively, Figure 1B).

Association between Plasma MNs and Prediabetes

As shown in Table 3, the univariable logistic regression model indicated patients in the highest quartile and the third

TABLE 1. Clinical Characteristics of the Study Population According to Plasma Metanephrines Quartiles

Variables	MNs Quartiles (pg/mL)				
	Quartile 1 (47.1–92.5)	**Quartile 2 (92.6–113.8)**	**Quartile 3 (113.9–144.2)**	**Quartile 4 (144.3–187.3)**	*P* for Trend
Participants, n	51	50	51	50	
Age, year	44.0 (26.0–60.0)	49.5 (28.0–58.0)	51.0 (34.0–56.0)	51.0 (43.5–62.3)	0.01
Male, n (%)	26 (51.0)	25 (50.0)	28 (54.9)	29 (58.0)	0.41
Current smoker, n (%)	10 (19.6)	8 (16.0)	8 (15.7)	13 (26.0)	0.46
Current drinker, n (%)	8 (15.7)	7 (14.0)	9 (17.6)	5 (10.0)	0.55
BMI, kg/m^2	22.8 (21.5–23.8)	23.0 (20.7–24.1)	22.5 (20.7–24.0)	22.5 (21.5–23.8)	0.96
SBP, mm Hg	145.0 (130.0–151.0)	137.5 (125.8–150.0)	140.0 (126.0–160.0)	140.0 (124.0–152.3)	0.68
DBP, mm Hg	87.0 (80.0–96.0)	87.0 (77.8–95.0)	85.0 (76.0–97.0)	81.0 (72.8–93.5)	0.36
FPG, mmol/L	4.90 (4.66–5.10)	4.95 (4.70–5.20)	5.10 (4.80–5.40)	5.17 (4.81–5.34)	0.004
2hPPG, mmol/L	5.10 (4.50–6.40)	5.82 (5.20–6.95)	6.33 (5.20–7.70)	6.77 (5.44–7.61)	<0.001
FINS, μIU/mL	6.89 (4.20–8.89)	7.36 (4.79–8.63)	5.85 (4.12–8.45)	6.50 (4.69–8.24)	0.78
HOMA-IR	1.48 (0.97–1.94)	1.63 (1.05–1.95)	1.28 (0.83–1.94)	1.44 (1.05–2.03)	0.75
TG, mmol/L	1.33 (0.80–1.72)	1.31 (0.98–1.96)	1.25 (0.84–1.76)	1.42 (0.98–1.89)	0.17
TC, mmol/L	4.11 (3.69–4.66)	4.40 (3.77–5.07)	4.23 (3.85–4.79)	4.35 (3.74–5.02)	0.81
HDL, mmol/L	1.22 (1.07–1.40)	1.14 (0.99–1.39)	1.19 (0.96–1.44)	1.23 (1.06–1.51)	0.68
LDL, mmol/L	2.48 (2.18–2.96)	2.66 (2.12–3.16)	2.66 (2.26–3.00)	2.68 (2.15–3.13)	0.84

Data are presented as median (interquartile ranges) or number (percentage).

2hPPG = 2h postprandial plasma glucose, BMI = body mass index, DBP = diastolic blood pressure, FIN = fasting insulin, FPG = fasting plasma glucose, HDL = high-density lipoprotein, HOMA-IR = homeostasis model assessment of insulin resistance, LDL = low-density lipoprotein, MNs = indicates metanephrines, SBP = systolic blood pressure, TC = total cholesterol, TG = triglycerides.

quartile of plasma MNs had higher risks of prediabetes compared with those in the lowest quartile (odds ratio [OR] = 4.57, 95% confidence interval [CI] = 1.39–15.07; OR = 4.45, 95%CI = 1.35–14.64, respectively). After adjusting for age, sex, BMI, patients in the highest quartile and the third quartile still had higher risks of prediabetes (OR = 4.04, 95% CI = 1.17–13.95; OR = 4.94, 95% CI = 1.43–17.03, respectively). Moreover, the third model adjusted for age, sex, BMI, SBP, current smoking state, TC revealed that the highest quartile and the third quartile of plasma MNs yielded higher risks of prediabetes compared with the lowest one (OR = 4.00, 95% CI = 1.16–13.86; OR = 5.01, 95% CI = 1.44–17.40, respectively). The tests for trend in three different models were significant (all $P < 0.01$). Each 1 standard deviation increase of plasma MNs was associated with higher risk of prediabetes in 3 models (OR = 1.01, 95% CI = 1.00–1.02).

DISCUSSION

In our study, we performed a retrospective study in large series of patients with essential hypertension excluding known risk factors for glucose intolerance. We found plasma glucose levels were significantly increased with elevated plasma MNs and high plasma MNs level was associated with higher risk of prediabetes.

Essential hypertension is closely associated with reduced glucose tolerance, and commonly coexists with diabetes.[3] Many pathophysiologic mechanisms underlie the impaired glucose metabolism in essential hypertension, such as insulin resistance,[17] central fat accumulation,[18] inflammation, endothelial dysfunction, and albuminuria.[19] In addition to the above mechanisms, our study revealed that activation of the sympathetic system was an important mechanism contributing to the adverse effect of glucose metabolism in essential hypertension.

Previous studies have revealed that the activation of sympathetic system was closely associated with hypertension, glucose metabolism regulation, and other metabolic syndrome components. Flaa et al[20] found that elevated sympathetic reactivity to a cold pressor test was associated with future higher plasma glucose concentration after 18-year follow-up study. Masuo et al[21–23] showed that increased baseline plasma norepinephrine concentration predicted future higher insulin levels and elevated blood pressure over a 10-year follow-up.

TABLE 2. Associations Analysis of Plasma Metanephrines With FPG and 2hPPG

Variables	FPG (mmol/L)						2hPPG (mmol/L)					
	Unadjusted			Adjusted			Unadjusted			Adjusted		
	r	β ± SE	*P*	β ± SE	*P*		*r*	β ± SE	*P*	β ± SE	*P*	
Log MNs	0.210	0.691 ± 0.228	0.003	0.599 ± 0.223	0.008		0.263	3.053 ± 0.791	<0.001	2.663 ± 0.800	0.001	

Variables in adjusted models included age, sex, body mass index, systolic blood pressure, current smoking state, total cholesterol.

β = regression coefficient, 2hPPG = 2h postprandial plasma glucose, FPG = fasting plasma glucose, Log MNs = logarithmically transformed metanephrines, *r* = Pearson correlation coefficient, SE = standard error.
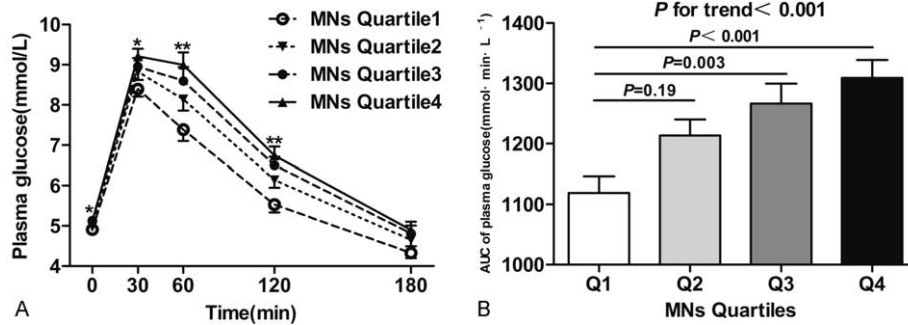
FIGURE 1. Plasma glucose concentrations and the AUC of plasma glucose according to plasma MNs quartiles during the OGTT test. A, plasma glucose concentrations according to plasma MNs quartiles; B, the AUC of plasma glucose according to plasma MNs quartiles. *P* values and *P* for trend were adjusted for age, sex, body mass index, systolic blood pressure, current smoking state, total cholesterol. Data are mean ± SEM; *$^{*}P < 0.05$; $^{**}P < 0.01$. AUC = area under curve, MNs = metanephrines, OGTT = oral glucose tolerance test. This figure suggests significant associations between plasma MNs and plasma glucose levels.

Moreover, Huggett et al[13] revealed that in patients with essential hypertension combined with type 2 diabetes, their peripheral sympathetic activity were greater than that in patients with essential hypertension alone. The above-mentioned studies revealed the sympathetic system was closely related to blood pressure and glucose metabolism; however, few studies have focused on the individual effect of sympathetic system activity and hypertension on glucose metabolism.

Indeed, the current results confirmed the role of sympathetic system in regulating glucose metabolism in essential hypertension. Both fasting plasma glucose and 2-hour OGTT plasma glucose were significantly associated with plasma MNs. The AUC of plasma glucose increased significantly with elevated plasma MNs levels.

Several explanations may be applied for this effect. Patients with essential hypertension had activated sympathetic system, accompanying by overproduction of catecholamines and their metabolites.[15,24–26] Catecholamine regulated carbohydrate metabolism directly through adrenoreceptors and indirectly by modulation of insulin action.[27] Catecholamines regulated both hepatic glucose production and glucose uptake in peripheral tissues. Epinephrine promoted gluconeogenesis in fasted states and increased glycogenolysis in fed states.[28] In skeletal muscle, epinephrine inhibited insulin-stimulated glucose uptake through β-receptor.[29] Norepinephrine also increased hepatic glycogenolysis, but to a less extent than epinephrine.[30,31]

In addition, long-term overproduction of catecholamines may result in chronic low-grade inflammation,[32–34] which was a characteristic of essential hypertension and contributed to reduced glucose tolerance in patients with essential hypertension.[35–37] Chronic sympathetic overstimulation activated the adrenoreceptors in immune cells and increased cytokines production overstimulation.[38] Patients exhibited higher levels of inflammatory markers as CRP, interleukin-1, interleukin-6 and tumor necrosis factor-α were positively correlated with blood pressure[39] and insulin level.[40-42]

Activation of the sympathetic system may be the common pathogenesis of elevated blood pressure and impaired glucose metabolism in patients with essential hypertension. High levels of plasma MNs may therefore be used as early markers for detection of reduced glucose tolerance in essential hypertension. Inhibiting sympathetic activation, such as central sympatholytic agents or β-blockers may prevent the occurrence of impaired glucose metabolism in patients with essential hypertension.[43]

This was the first study to explore the association between plasma MNs levels and glucose metabolism in patients with essential hypertension. None of the enrolled patients had taken glucose-lowering drugs or insulin and they were free of diabetes, overweight, and obesity. Confounding factors associated with glucose levels have been excluded.

Nevertheless, several limitations should be taken in considerations. First, this was a retrospective study and the sample

TABLE 3. Associations of Plasma Metanephrines Levels With Prediabetes

Prediabetes	MNs Quartiles				P for Trend	1 SD Increase of MNs
	Quartile 1	Quartile 2	Quartile 3	Quartile 4		
Cases/number at risk	4/51	9/50	14/51	14/50		
Model 1	1.00	2.58 (0.74–9.00)	4.45 (1.35–14.64)	4.57 (1.39–15.07)	0.007	1.01 (1.00–1.02)
Model 2	1.00	2.46 (0.67–8.97)	4.94 (1.43–17.03)	4.04 (1.17–13.95)	0.015	1.01 (1.00–1.02)
Model 3	1.00	2.49 (0.68–9.14)	5.01 (1.44–17.40)	4.00 (1.16–13.86)	0.017	1.01 (1.00–1.02)

Model 1: unadjusted; Model 2: adjusted for age, sex, body mass index; Model 3: adjusted for age, sex, body mass index, systolic blood pressure, current smoking state, total cholesterol.
MNs = metnephrines, SD = standard deviation.

size was relatively small. Prospective studies and validation in an even larger series should be performed. Second, the association with HbA1c was lacking and this should also be clarified in future study. Furthermore, this finding should also be confirmed in other ethnicities.

In conclusion, our study demonstrated in patients with essential hypertension, high level of plasma MNs contribute to higher plasma glucose level, suggesting activation of sympathetic system might be a pathogenic factor causing impaired glucose metabolism. Prospective studies with larger sample sizes are needed to confirm our findings.

ACKNOWLEDGMENTS

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