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Relationship between Uric Acid and Endothelial Function in Hypertensive Patients with Metabolic Syndrome

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Abstract

Aim: To investigate the association between uric acid (UA) and endothelial function in Chinese hypertensive patients with Metabolic Syndrome (MS).

Methods: 615 hypertensive patients were enrolled, all hypertensives were divided into two groups: hypertensives with MS (MS group, n=239) and hypertensives without MS (NMS group, n=376). 87 age- and sex-matched normotensives served as controls (NC group). Flow-mediated (endothelium-dependent) dilatations (FMD), nitroglycerin-induced (endothelium-independent) dilatation (EID) in the brachial artery were assessed by high-resolution ultrasonography. UA was detected by urease indophenol.

Results: A trend of increase in UA concentration was found among NC, NMS and MS group ((323.77 ± 104.49) μmol/l vs. (353.63 ± 92.83) μmol/l vs. (390.90 ± 101.42) μmol/l, p<0.001). There was a significant difference in FMD (control: (12.03 ± 4.51)% vs. NMS:(8.98 ± 4.32)% vs. MS:(8.23 ± 4.58)%, p<0.001) among groups. After stratification of gender, lower FMD was only seen in male hypertensives with MS accompanied by hyperuricemia <60 years old ((9.98 ± 5.78)% vs (7.12 ± 4.49)%, p<0.05); Pearson correlation analysis showed that the FMD was negatively correlated with UA (r=-0.314, p<0.01); Finally, logistic regression analysis showed that a 50 μmol/L increase in UA levels carried a 41.1% higher risk for endothelial dysfunction in this cohort.

Conclusions: A higher UA level is related to poorer endothelial function in hypertensives with MS. Increased UA can be used as an alternative indicator for monitoring endothelial function and preventing vascular damage in male hypertensives with MS aged less than 60 years old.

Keywords: Uric acid; Endothelial dysfunction; Hypertension; Metabolic syndrome

Instruction

Recently, several studies have indicated that uric acid (UA), the circulating end-metabolite of purine nucleotides of mankind, is associated with subsequent cardiovascular diseases [1,2]. However, it remains controversial whether UA is a relevant and independent risk factor for cardiovascular disease and the mechanisms by which UA results in target organ injury are still unknown. Increasing data suggest that UA is associated with endothelial dysfunction [3,4], which is characteristic of patients with essential hypertension [5]. It is well recognized that endothelial dysfunction is an early stage in atherogenesis and associates with poor cerebro-cardiovascular outcomes [6]. It has been shown that UA disturbs endothelial function by disrupting nitric oxide (NO) synthesis, inhibiting NO bioavailability and activating the renin-angiotensin system.

Metabolic syndrome (MS) is believed to be a clustering of abnormalities of several cardiovascular risk factors in an individual including abdominal obesity, hypertension, and dyslipidemia, including low HDL-C, high LDL-C and hyperglycemia. MS is often associated with elevated UA levels [7] and endothelial dysfunction [8,9]. The prevalence of MS has been increasing in recent years in China. A recent epidemiological study showed that the prevalence of MS among Chinese men and women aged 35 to 64 years old was 9.8% and 17.8%, respectively [10]. As is known to all, MS is quite common in patients with primary hypertension and carries much higher risk of cardiovascular events. It was reported that nearly 90% of Chinese hypertensives were with at least one related risk factor in the outpatient setting [11]. To date, the relationship between UA and endothelial dysfunction has been evaluated in patients with increased cardiovascular risk [12] and in those with preexisting cardiovascular diseases at various levels of risk scores [13,14], but not in hypertensives with MS. Therefore, in this study, we aimed to investigate the association between the UA and endothelial function in hypertensives with MS in a Chinese population.

Methods

Study population

Hypertensives were consecutively enrolled from outpatient care of the First Affiliated Hospital of Fujian Medical University between August 2008 and April 2013. 87 age- and sex-matched normotensives without cardiovascular risk factors were also included as control. The

study protocol was approved by the Ethical Review Board of the First Affiliated Hospital of Fujian Medical University.

Both newly diagnosed and on treated hypertensives were entitled to be included. Hypertension was defined as seated systolic blood pressure of ≥ 140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg, after 15 minutes of rest, measured by mercury sphygmomanometer according to the Chinese Guideline of Hypertension [15]. Diagnosis of essential hypertension was established on the basis of exclusion of secondary hypertension, and with a positive family history. Patients with secondary hypertension including renal hypertension, Reno vascular hypertension, primary aldosteronism, Cushing's syndrome, drug induced hypertension, obstructive sleep apnea, **aortic valve disease**, pregnancy, etc., was established and diagnosed by illness history taking, physical examination, routine tests of blood and urine, and imaging. Those with secondary and severe hypertension (SBP >200 mm Hg or DBP >130 mm Hg), liver or renal dysfunction, acute or unstable coronary artery diseases, type 1 diabetes, severe congestive heart failure (NYHA classes III–IV), taking alcohol >60 ml/day, and using UA-lowering drugs were excluded. Hypertensives were further divided into two groups: with MS and without MS. MS was defined based on the 2004 definition of Chinese Diabetes Society [16]. Patients with three or all of the following four risk factors can be confirmed as MS:

- BMI ≥25.0 kg/ m^2
- TG ≥1.7 mmol/l (150 mg/dl), and HDL–C<0.9 mmol/l (35 mg/dl) for male or HDL–C <1.0 mmol/l (39 mg/dl) for female.
- SBP/DBP ≥140/90 mm Hg or already diagnosed as hypertension.
- Fasting blood glucose ≥6.1 mmol/l (110 mg/dl) and/or 2 hour post-prandial blood glucose >7.8 mmol/l (140 m/dl), or already diagnosed as diabetes.

A smoker was defined as those with a pack-year smoking index >0 (calculated as packs of cigarettes per day multiplied by years of smoking).

Subjects provided with written informed consent underwent a screening protocol consisting of medical history taking, physical examination recording, electrocardiogram and laboratory testing in the morning after 8 h of fasting. Three days later, all the participants were arranged to determine endothelial function.

Assessment of endothelial function

All subjects were instructed to fast for at least 4 h, and not to smoke, take alcohol or caffeine for at least 8 h prior to the measurements. All subjects were asked to rest in the supine position in a quiet, dark, air-conditioned room (at temperature of 25°C) for 15 min. Then, the FMD measurement was conducted according to the guidelines for ultrasound assessment of FMD [**17**].

Briefly, using high-resolution with 10 MHz linear array transducer (LOGIQ7 system, American GE Company), longitudinal images of the right brachial artery were recorded at the baseline, at 90 s after the cuff deflation after 5 mins' occlusion of brachial artery and at 5 min after sublingual administration of 0.4 mg glyceryltrinitrate. Vasodilation was evaluated based on the change of artery diameter after release of occlusion (percentage of FMD) and change of artery diameter after administration of nitroglycerin (percentage of EID) as described previously by our group [18,19].

Marietta had demonstrated that with optimal sonographer training and adherence to strict and standardized protocols, endothelial function can be assessed serially using flow-mediated dilatation in a multicenter setting in patients with coronary artery disease [20]. There were two observers in our study, performing for all these measurements, blinding for design of experiment and all information's of subjects, and a statistic specialist analyzing for the data independently. The interobserver and intraobserver coefficient of variation of FMD was 6.92% and 1.90% separately [21,22].

Laboratory measurements

Blood samples were obtained after 8 h fasting. UA was measured by the method of uricase peroxidase system. The coefficient of variation of UA was approximately 2% in our laboratory [**19**]. Hyperuricemia was defined as UA ≥ 420 μmol/L in men and menopause women or UA ≥ 357 μmol/L in menstrual women. White blood cell counts (WBC) was performed with analyze (ADVIA2120). Serum creatinine (Scr), fasting blood glucose (GLU), total cholesterol(TC), high density lipoprotein cholesterol (HDL), triglycerides (TG), were determined using standard methods with Automatic Biochemical Analyze (OLYMPUS AU2700).

Statistical analysis

All data were fed into Excel to set up a data base. Statistical analysis was performed using SPSS software, version 13.0 (SPSS Inc., Chicago, Ill., USA). The normality of the distribution of the variables was firstly performed by the Kolmogorov–Smirnov test. Variables not in a distribution of normality were log-transformed (Log) before statistical analysis was carried out. Continuous variables were expressed as mean ± SD while categorical variables were expressed as percentages. Comparisons between groups of normally distributed variables were made by one-way ANOVA or independent t test, as appropriate. The χ^2 test was performed for comparison of categorical variables. Pearson's correlation analysis was employed to test the relationship between UA and FMD. Multiple regression model and multivariate logistic regression model were used to determine whether UA is independently associated with FMD after adjusting for potential confounding variables. A p-value<0.05 was considered to be statistically significant.

Results

Demographic characteristics of patients

615 hypertensives and 87 age- and sex-matched normotensive controls were included. Clinical characteristics of the participants were summarized in (Table 1) of the 615 hypertensives, 239 (38.9%) patients were with MS and 240 (39.0%) were with hyperuricemia. Values of WC, BMI, GLU, TG, Scr and WBC count were significantly higher in MS patients, compared with those in NMS and control group. The number of patients with diabetes mellitus and hyperuricemia in MS group was significantly greater than that in NMS group, so were the values of Scr and WBC. Except for higher blood pressure in hypertensives, no significant differences in other indexes were found among the groups.

	All patients (n=615)	NC group (n=87)	NMS group (n=376)	MS group (n=239)	p
Age (years)	59.97 ± 12.02	59.21 ± 10.98	59.87 ± 11.94	60.14 ± 12.16	0.821
Male (%)	53.80%	52.90%	50.50%	59.00%	0.12

WC (cm)	89.12 ± 10.36	84.46 ± 10.67	85.25 ± 9.67	95.20 ± 8.27*#	0
BMI (kg/m^2)	24.38 ± 3.07	23.46 ± 2.70	23.41 ± 2.87	25.90 ± 2.74*#	0
Smoking (%)	84 (13.7%)	9 (10.3%)	44 (11.7%)	40 (17.4%)	0.091
Duration of EH (months)	98.03 ± 24.62		98.82 ± 26.87	96.71 ± 20.97	0.804
SBP (mm Hg)	137.68 ± 15.80	125.09 ± 10.85	137.37 ± 15.81*	138.16 ± 15.80*	0
DBP (mm Hg)	80.26 ± 11.45	74.30 ± 8.42	79.90 ± 11.28*	80.81 ± 11.69*	0
HR (beats/min)	72.37 ± 9.40	74.35 ± 11.96	72.26 ± 9.10	72.54 ± 9.87	0.398
TBIL (μmol/L)	14.75 ± 6.23	14.25 ± 5.98	15.14 ± 6.60	14.13 ± 5.56	0.116
CR (μmol/L)	71.52 ± 19.56	62.52 ± 11.51	69.89 ± 19.76*	74.08 ± 19.00*#	0
Glucose (mmol/l)	5.90 ± 1.46	5.52 ± 1.04	5.41 ± .63	6.68 ± 1.96*#	0
TC (mmol/l)	4.97 ± 1.17	5.11 ± 0.98	4.92 ± 1.05	5.03 ± 1.35	0.291
TG (mmol/l)	1.64 ± 1.13	1.46 ± 0.73	1.25 ± 0.60	2.24 ± 1.45*#	0
HDL (mmol/l)	1.44 ± 0.59	1.46 ± 0.39	1.47 ± 0.42	1.39 ± 0.79	0.168
WBC (10^9/l)	6.27 ± 1.72	5.53 ± 1.55	6.09 ± 1.62*	6.55 ± 1.84*#	0
UA (μmol/l)	368.11 ± 98.89	323.77 ± 104.49	353.63 ± 92.83*	390.90 ± 101.42*#	0
FMD (%)	8.70 ± 4.43	12.03 ± 4.51	8.98 ± 4.32*	8.23 ± 4.58*#	0
EID (%)	16.34 ± 7.19	18.42 ± 7.75	16.64 ± 7.49*	15.87 ± 6.67*	0.019
Medication (%)					
ACEI/ARB	242 (39.3%)		140 (37.2%)	102 (42.7%)	0.204
Beta-blocker	129 (21.0%)		77 (20.5%)	52 (21.8%)	0.761
CCB	218 (35.4%)		132 (35.1%)	86 (36.0%)	0.863
Statins	169 (27.5%)		98 (26.1%)	71 (29.7%)	0.354
Diabetes (%)	23 (3.7%)		12 (3.2%)*	61 (25.5%)*#	0.008
HUA%	240 (39.0%)	4 (4.6%)	120 (31.9%)*	120 (50.2%)*#	0

NC: Normal Control; NMS: Hypertensives without Metabolic Syndrome; MS: Hypertensives with Metabolic Syndrome; WC: Waist Circumference; BMI: Body Mass Index; EH: Essential Hypertension; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; HR: Heart Rate; TBIL: Total Bilirubin; CR: Creatinine; TC: Total Cholesterol; TG: Triglyceride; HDL: High-Density Lipoprotein; WBC: White Blood Cells; UA: Uric Acid; FMD: Flow Mediated Dilatation; EID: Endothelium-Independent Dilatation; ACEI: Angiotensin Converting Enzyme Inhibitors; ARB: Angiotensin Receptor Blockers; CCB: Calcium-Channel Blocker; MS: Metabolic Syndrome; HUA: Hyperuricemia; *P <0.05 compared to controls: #P <0.05 compared to NMS group.

Table 1: Demographic characteristics of hypertensives with and without MS.

Comparison of UA and endothelial function in hypertensives with and without MS

Gradually increased UA concentration was found among NC, NMS and MS group, as showed in (Figure 1). Correspondingly, higher prevalence of hyperuricemia was also found among the groups. In general, a trend of decreased FMD was showed among those groups. There was no significant difference of EID values between MS group and NMS group, although both of them were lower than NC group, as showed in (Figure 2).

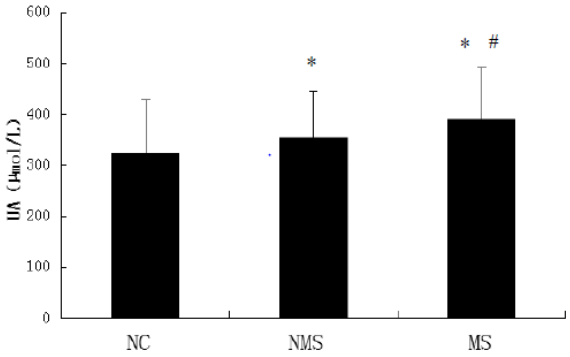

Figure 1: Relationship among UA in normotensives, hypertensives with and without MS. *indicates p value less than 0.05 versus controls; # indicates p value less than 0.05 versus NMS group.

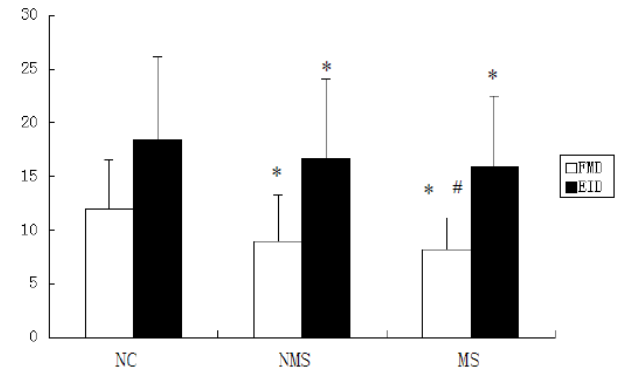

Figure 2: Trends of changes of FMD and EID in normotensives, hypertensives with and without MS. *indicates p value less than 0.05 versus controls; #indicates p value less than 0.05 versus NMS group.

Correlations between UA and endothelial function in hypertensives with MS aged less than 60 years old

Pearson correlation analysis showed that there was a weak negative correlation between UA and FMD in MS (r=-0.185, p <0.01) and NMS (r=-0.116, p <0.05). After stratification by gender and age, comparison of FMD between subjects with or without hyperuricemia was showed in Table 2. In MS group, after stratification, male hypertensives with hyperuricemia, especially those younger than 60 years old, had lower FMD values compared with those without hyperuricemia. Correlations between UA levels and FMD values were also shown in Table 4, in which significant relationship was found only in male MS patients, particularly for those younger than 60 years old (r=-0.314, p <0.01). So far as EID was concerned, there was no significant difference of EID values between hyperuricemic and non-hyperuricemic patients, as shown in Table 3.

	Normal UA	Hyperuricemia	p
MS (n=239)	8.91 ± 4.77	7.48 ± 4.27	0.017
Men (n=141)	9.31 ± 4.98	7.20 ± 4.54	0.009
<60 year (n=75)	9.98 ± 5.78	7.12 ± 4.49	0.019
≥ 60 year (n=66)	8.74 ± 4.19	7.30 ± 4.69	0.192
Women (n=98)	8.42 ± 4.57	8.29 ± 3.63	0.873
<60 year (n=42)	9.48 ± 4.43	8.53 ± 2.60	0.391
≥ 60 year (n=56)	7.36 ± 4.52	8.17 ± 4.07	0.485
NMS (n=376)	9.25 ± 4.34	8.44 ± 4.26	0.094
Men (n=190)	8.30 ± 4.73	7.87 ± 4.18	0.534
<60 year (n=92)	8.31 ± 5.07	7.92 ± 4.06	0.698
≥ 60 year (n=98)	8.30 ± 4.48	7.80 ± 4.42	0.621
Women (n=186)	10.16 ± 3.72	9.10 ± 4.29	0.091
<60 year (n=102)	10.59 ± 3.53	9.80 ± 4.88	0.376
≥ 60 year (n=84)	9.53 ± 3.92	8.54 ± 3.74	0.261
Controls (n=87)	12.12 ± 4.28	11.75 ± 5.28	0.747

NMS: Hypertensives without Metabolic Syndrome; MS: Hypertensives with Metabolic Syndrome.

Table 2: Comparison of FMD between hypertentives with hyperuricemia and without hyperuricemia.

	Normal UA	Hyperuricemia	p
MS (n=239)	15.88 ± 6.89	15.79 ± 6.35	0.914
Men (n=141)	15.89 ± 6.80	15.64 ± 5.44	0.804
<60 year (n=75)	17.88 ± 7.26	15.95 ± 3.99	0.197
≥ 60 year (n=66)	14.20 ± 5.98	15.19 ± 7.07	0.539
Women (n=98)	15.73 ± 7.00	16.47 ± 8.24	0.634
<60 year (n=42)	19.40 ± 6.03	17.43 ± 6.94	0.356
≥ 60 year (n=56)	12.05 ± 5.95	16.00 ± 8.88	0.059
NMS (n=376)	16.98 ± 7.71	15.91 ± 7.00	0.197
Men(n=190)	14.84 ± 6.49	14.61 ± 5.92	0.818
<60 year (n=92)	15.46 ± 6.45	15.74 ± 5.67	0.835
≥ 60 year (n=98)	14.35 ± 6.53	13.08 ± 6.01	0.379
Women (n=186)	10.07 ± 8.23	17.40 ± 7.86	0.2
<60 year (n=102)	20.00 ± 8.55	20.92 ± 8.87	0.644
≥ 60 year (n=84)	17.71 ± 7.61	14.88 ± 5.54	0.074
Controls (n=87)	18.82 ± 7.67	17.20 ± 8.09	0.41

NMS: Hypertensives without Metabolic Syndrome; MS: Hypertensives with Metabolic Syndrome

Table 3: Comparison of EID between subjects with hyperuricemia and those without hyperuricemia in groups.

	Correlation coefficient	p
MS (n=239)	-0.185	0.005
Men (n=141)	-0.248	0.003
<60 year (n=75)	-0.314	0.006
≥ 60 year (n=66)	-0.176	0.157
Women (n=98)	-0.045	0.661
<60 year (n=42)	-0.302	0.152
≥ 60 year (n=56)	0.164	0.226
NMS (n=376)	-0.116	0.025
Men (n=190)	-0.03	0.682
<60 year (n=92)	0.067	0.525
≥ 60 year (n=98)	-0.127	0.213
Women (n=186)	-0.067	0.367
<60 year (n=102)	0.016	0.877
≥ 60 year (n=84)	-0.107	0.33

NMS: Hypertensives without Metabolic Syndrome; MS: Hypertensives with Metabolic Syndrome.

Table 4: Pearson correlations between UA and FMD in hypertensives with and without MS.

Multivariate linear regression analysis

After adjustment for age, gender, Scr, WBC, SBP, DBP, GLU, TC, LDL, HDL, TG and BMI, association between UA and FMD (entered as a continuous variable) were evaluated by multivariate linear regression analysis. Significant correlation was found only in male MS patients as well, especially those with age less than 60 years old (beta=-0.37, p <0.01).

Multivariate logistic regression

The study population was stratified by FMD value at the cut-point of 8% as reported by Tatsuaki [23]. Endothelial dysfunction was defined as FMD value less than 8%, while FMD value greater than or equal to 8% was considered as normal. In this case, after adjustment for SBP, DBP, GLU, HDL, TG BMI and WBC, a 50 μmol/L increase in the concentration of UA carried a 21.9% (Table 5) higher risk for endothelial dysfunction in male MS patients, and this risk could increase to 41.1% (Table 5) for those younger than 60 years old.

	OR	95% CI	p
Model 1			
SBP	1.43	0.654-3.079	0.361
DBP	1.267	0.497-3.323	0.621
GLU	1.31	0.599-2.862	0.499
HDL	1.566	0.656-3.736	0.312
TG	1.214	0.551-2.674	0.63
BMI	1.46	0.704-3.027	0.309
WBC	1.572	0.258-9.568	0.623
UA	1.219	1.004-1.480	0.045
Model 2			
SBP	1.499	0.407-5.516	0.543
DBP	1.753	0.484-6.342	0.393
GLU	1.356	0.441-4.173	0.596
HDL	0.964	0.216-4.308	0.962
TG	2.535	0.678-9.469	0.167
BMI	1.937	0.649-5.777	0.236
WBC	4.04	0.355-46.014	0.261
UA	1.411	1.036-1.922	0.029

Model 1, in male hypertensives with MS; Model 2, in male hypertensives with MS aged less than 60 years old; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; GLU: Glucose; HDL: High-density Lipoprotein; TG: Triglyceride; BMI: Body Mass Index; WBC: White Blood Cells; UA: Uric Acid.

Table 5: Multivariate logistic analyses of the association between uric acid and endothelial function in male hypertensives with MS.

Discussion

In this study, it was showed that hypertensives with MS had poorer FMD and higher levels of UA compared with those hypertensives without MS. UA was an independent risk factor for endothelial dysfunction in male hypertensives with MS in Chinese, especially for those younger than 60 years old.

Our data demonstrated that hypertensives with MS had higher levels of UA compared with those without MS. This result was consistent with previous studies that the presence of MS conferred an increased UA [24,25]. Recently, several researchers have identified high levels of UA as an independent risk factor for the cardiovascular events [1,2], and one of our previous study demonstrated that serum uric acid correlated with left ventricular mass index independent of blood pressure [26]. Theoretically, several possible pathological mechanisms linking UA to cardiovascular disease have been proposed, including negative correlation with endothelial function while the relationship between uric acid and micro vascular dysfunction has been doubted [27]. Endothelial dysfunction is considered to play an important role in the pathogenesis of cardiovascular diseases [**1**]. However, the underling mechanism between UA and endothelial function is still unknown. In animal experiments, Nakagawa T [28] demonstrated that UA dose-dependently inhibited Ach-induced relaxation responses in fructose-fed rats and suggested that UA might impair endothelial function. Sánchez-Lozada LG [29] showed that mild hyperuricemia induced by uricase inhibition in Sprague-Dawley rats might provoke an increased intrarenal oxidative stress, which contributed to low plasma NO and the development of the systemic hypertension as well as the renal abnormalities. Several clinical studies also indicated an inverse circadian relationship between UA levels and NO [4,14,30], supporting the hypothesis that UA may lead to impaired endothelial function, even if this relationship did not necessarily suggest a causal and unidirectional relationship between UA and NO bioavailability. In our study, UA was shown to correlate with FMD in hypertensives with MS.

The mechanism underlying the relationship between high UA level and endothelial dysfunction has not been deeply looked into in this study. Yet, the increased WBC count in hyperuricemic patients with MS may be a possible explanation. WBC, as one subtype of immune cells, could interact with the endothelial cells by producing and releasing reactive oxygen species and cytokines, which could influence gene and protein expression, intracellular signaling, and vasodilation in response to vascular-active substances [31]. Simultaneously, neutrophils and monocytes, as parts of WBC, were independently related with UA [32]. Taken together, hypertensives with MS might accompany with increased UA and WBC count, which played an important role in inflammation, finally caused endothelial dysfunction. Although EID was also a marker of vascular injury, we did not found any relationship between UA and EID in all groups. However, alteration of EID was not commonly considered as an indicator representing vascular smooth muscle cell vasoreactivity in the early phases of cardiovascular disease.

Interestingly, a significant association between UA and FMD was only found in male hypertensives with MS. A possible explanation for this gender differences may be the influence of sex hormones [33]. Several protective effects of estrogen on the cardiovascular system have been reported [34]. Microvascular reactivity was improved by estrogens and improvement of FMD was found in postmenopausal women with hormone replacement therapy [35]. However, results from Renate B. Schnabel [36] indicated that correlations between estradiol and FMD were present in female only. Accordingly, correlations between UA and FMD may become relatively weak in women, for the protection of estrogens to vascular function, which is totally different in men. Despite a series of major risk factors, gender differences in cardiovascular disease (CVD) susceptibility remain obvious. Our results revealed that sex-specific differences in relationship between UA and FMD might account for part of this phenomenon. As the nature of vascular function is multifactorial, the influence of sex hormones on the relationship between UA and FMD need to be further studied.

Importantly, we also found that the relationship between UA and FMD was affected by age in male hypertensives with MS. To our

knowledge, there was no report showing that higher level of UA was related to worse endothelial function differently by age. However, it is well known that the capacity of vascular endothelium to generate nitric oxide (NO) declines with aging, even in healthy individuals. Thus, endothelial function was persistently impaired with increasing age, through accelerated nitric oxide (NO) degradation [37], reduced endothelial nitric oxide synthase (eNOS) expression/action [38], increased production of reactive oxygen species [39], inhibition of NOS activity by endogenous NOS inhibitors, inflammatory reactions [39], and increased phosphodiesterase activity [40], decreased endothelial progenitor cells [41]. Anyway, UA was produced by a series of enzymatic waterfall-like reaction by which NADPH was a main intermediate by-product. So far as we know, one of the most important effects of NADPH is oxidation stress [42]. Therefore, it is believed that the process of UA metabolism is accompanied with oxidative stress [43]. Taken together, existing data support that the role of UA and gender to endothelial function is secondary to age. With increasing age, endothelial function will decrease gradually in both male and female, at this stage, the age related effects on endothelial function may be too prominent to show the effect of UA on endothelial function, and as a result, the effects of UA on FMD may become weak. Based on our data, the close relationship between UA and FMD was mainly reflected in those less than 60-year-old male hypertensives with MS.

In conclusion, our findings indicated that hypertensives with MS had blunted FMD and higher levels of UA compared with those without MS. UA was an important risk factor for endothelial dysfunction in male hypertensives with MS, especially those younger than 60 years. The risk of endothelial dysfunction would soar up 41.1% accompanied with every 50 μmol/L increase in UA concentration in this cohort. Increased UA can be used as an alternative indicator for monitoring endothelial function and preventing vascular damage in male hypertensives with MS aged less than 60 years old.

Conflict of Interest

The authors declare no conflict of interest.

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