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Original Article

The association and interaction analysis of metabolic syndrome and chronic kidney disease on cardiovascular autonomic neuropathy in the general Chinese population

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Abstract: Background: The objective of this study was to evaluate associations of metabolic syndrome (MetS) and chronic kidney disease (CKD) with cardiovascular autonomic neuropathy (CAN), and to estimate the extent to which interaction of MetS and CKD affects the outcome in the Chinese population. Method: We conducted a large-scale, population-based study to analyze the association and interaction of the two factors for CAN in a sample of 2,092 Chinese people. Univariate and multiple linear regression (MLR) analysis were employed to detect these relationships. Interaction on an additive scale can be calculated by using the relative excess risk due to interaction (RERI), the proportion attributable to interaction (AP), and the synergy index (S). Results: MLR adjusted for confounding factors showed that MetS was independently associated with CAN ($P < 0.001$). A significant interaction effect was detected by MLR ($P = 0.042$). In addition, a positive interaction between MetS and CKD on CAN was estimated by using parameters of RETI = 0.119 (95% CI: 0.059-0.178), AP = 0.049 (95% CI: -0.039-0.138) and S = 1.091 (95% CI: 0.164-2.019). Conclusion: Our findings suggest that MetS is independently associated with CAN and offer evidence to support the hypothesis that MetS and CKD have positive interactions on CAN.

Keywords: Metabolic syndrome, chronic kidney disease, cardiovascular autonomic neuropathy, interaction analysis

Introduction

The prevalence of cardiovascular autonomic neuropathy (CAN) is rapidly growing in all populations worldwide, particularly in the developing world [1]. Individuals with previously undiagnosed CAN have an unfavorable cardiovascular risk profile, especially in terms of sudden death, indicating a higher risk of cardiovascular disease [1]. In general, this disease was a major factor in the cardiovascular complications of diabetes mellitus (DM) [2]. CAN is also associated with many other majority segments of the general population, such as the elderly and patients with hypertension (HTN) and metabolic syndrome (MetS) [1, 3, 4].

MetS refers to a constellation of the risk factors of cardiovascular disease, and increases the risk of developing cardiovascular disease [5]. Low Heart Rate Variability (HRV), or abnormal CAF, was found in patients with MetS [3, 6]. Studies provided evidence that CAN is common in persons with impaired glucose tolerance; and obesity seems to play an important role in the early pathogenesis of CAN [6, 7]. Our previous studies showed that MetS, or its severity, was associated with abnormal CA function or CAN in the Chinese population [8, 9]. Chronic kidney disease (CKD) is one of the most serious public health problems. CKD may also be identified when it leads to one of its recognized complications, such as cardiovascular disease, anemia, or pericarditis. CAN or abnormal CA function were independently associated with CKD, albuminuria, and eGFR in diabetic patients [10, 11]. In addition, HRV was an independent risk factor for cardiovascular mobility and mortality in type 1 patients with nephropathy [12].

In general, physicians pay more attention to the associations of risk factors and outcomes. However, we often neglect how the interaction of risk factors affect outcomes. It is essential for physicians to clarify the relationships of risk factors and how they affect diseases. A classic example is the interaction between smoking and asbestos in connection to the risk of lung cancer [13]. The term of interaction refers to the situation where the effect of one risk factor on a certain disease outcome is different across strata of another risk factor, or vice versa. In clinical practice, interaction should generally be assessed on an additive scale rather than a multiplicative scale [14-17]. Interaction on an additive scale can be calculated using relative risks and different measures quantifying this interaction, which have been described, such as the relative excess risk due to interaction (RERI), the proportion attributable to interaction (AP), and the synergy index (S) [18].

Previous studies had been conducted to evaluate associations of MetS and abnormal renal function with abnormal CAF, respectively [1, 3, 5-7, 9, 10, 12, 19]. However, there is little known about the interaction of MetS and the status of renal function as far as how they affect CAN. Our hypothesis is that MetS and CKD will have an interaction effect that influences progression of CAN. The objective of this study was to evaluate associations of MetS and CKD with CAN, and to estimate the extent to which interaction of MetS and CKD affect the outcome in the Chinese population.

Methods

Study population

We performed a CAN factor survey carried out in a random sample of the Chinese population. Participants were recruited from rural and urban communities in Shanghai. Survey participants with undiagnosed CAN, aged 30-80 years, were included in this study. A total of 3,012 subjects were invited to a screening visit between 2011 and 2012. Some subjects were excluded from the study to eliminate potential confounding factors that may have influenced their CA function. Briefly, the exclusion criteria were as follows: 1) history or findings of arrhythmia and hyperthyroidism or hypothyroidism; 2) pregnancy or lactation; and/or 3) serious hepatic or renal dysfunctions (GFR < 30 mL/min/1.73 m^2). Of these subjects, complete baseline data were obtained for 2,092 (69.46%) of the participants. Written consent was obtained from all patients before the study, which was performed in accordance with the ethical standards laid down in Declaration of Helsinki and approved by the Medicine Ethical Committee of Fudan University.

Measurement

The subjects were interviewed for the documentation of medical histories, medication, and history of smoking habits. Laboratory assessment of cardiovascular disease risk factors were completed, along with standardized examination for heart rate variability (HRV). All study subjects underwent a complete clinical baseline characteristics evaluation after an eight-hour fast, which included: 1) history and physical examination; 2) heart rate and blood pressure; 3) fasting serum glucose and insulin; and 4) fasting plasma lipids.

Systolic and diastolic blood pressure (BP) values were the means of two physician-obtained measurements taken from the left arm of the seated participant. Fasting plasma glucose (FPG) was quantified by the glucose oxidase procedure; HbA1c was measured by ion-exchange, high-performance liquid chromatography (HPLC; Bio-Rad, Hercules, CA, USA). Serum total cholesterol (TC), high-density lipoprotein (HDL) cholesterol, triglyceride (TG) levels, serum creatinine (SCr), and uric acid (UA) were measured by an enzymatic method with a chemical analyzer (Hitachi 7600-020, Tokyo, Japan). Low-density lipoprotein (LDL) cholesterol levels were calculated using the Friedewald formula, and creatinine clearance rate (Ccr) was calculated using the Cockcroft- Gault formula. An enzyme coupled method was used to measure urine creatinine concentration and to calculate the urinary albumin/urinary creatinine ratio (Alb/Cr). The most recently advocated formula for calculating the GFR is one developed by the Modification of Diet in Renal Disease Study Group [20]. For creatinine in μmol/L: eGFR = 32788 × serum creatinine$^{-1.154}$ × age$^{-0.203}$ × (0.742 if female). The day-to-day and inter-assay coefficients of variation at the central laboratory in our hospital for all analyses were between 1% and 3%.

Definition

HTN was defined as BP ≥ 140/90 mmHg, or a history of hypertension medication. Body mass index (BMI) was calculated with weight in kilograms divided by the square of height in meters. BMI was classified based on the Chinese criteria: normal BMI < 24.0 kg/m^2; overweight 24.0 kg/m^2 ≤ BMI < 28.0 kg/m^2; and obese BMI ≤ 28.0 kg/m^2. High FPG was defined as FPG ≥ 5.6 mmol/L. DM was defined by oral glucose tolerance test (OGTT) and either HbAlc ≥ 6.5% or the use of insulin or hypoglycemic medications.

MetS was diagnosed according to the updated National Cholesterol Education Program/Adult Treatment Panel III criteria (WHO Western Pacific Region obesity criteria) in individuals meeting three or more of the following [21]: 1) central obesity; 2) TG levels > 150 mg/dl (1.7 mmol/l) or specific treatment for this lipid abnormality; 3) HDL cholesterol < 40 mg/dl (1.03 mmol/l) in men and < 50 mg/dl (1.29 mmol/l) in women or specific treatment for this lipid abnormality; 4) raised BP, systolic BP > 130 mm Hg or diastolic BP > 85 mm Hg or treatment for previously diagnosed HT; and 5) raised FPG level, > 100 mg/dl (> 5.6 mmol/l) or previously diagnosed type 2 DM.

CKD was defined as the presence of kidney damage or reduced renal function for more than three months, regardless of the diagnosis. CKD is classified on the basis of the GFR, as recommended by the US National Kidney Foundation Kidney Disease Outcome Quality Initiative. CKD is classified into five stages: stage 1-kidney damage with normal or increased GFR ≥ 90 ml/min/1.73 m^2; stage 2-kidney damage with mildly decreased GFR of 60 to 89 ml/min/1.73 m^2; stage 3-moderately decreased GFR of 30 to 59 ml/min/1.73 m^2; stage 4-severely decreased GFR of 15 to 29 ml/min/1.73 m^2; stage 5-kidney failure with a GFR<15 ml/min/1.73 m^2. In this study, CKD patients with stages 1-3 were available for this association and interaction study. For this analysis, CKD was defined as the presence of albuminuria or an eGFR < 60 ml/min/1.73 m^2.

The study outcome

In this study, Short-term HRV test was applied to evaluate CA function [22]. HRV were measured non-invasively by power spectral analysis. Before CA function assessment, participants were to avoid alcohol, smoking, and coffee for 24-hours to influence their calm and quiet status. Subjects were studied while awake in the supine position after 20 minutes of rest. Testing times were from 8:00 to 11:00 in the morning. A type-I FDP-1 HRV non-invasive detecting system was used with software version 2.0 (Department of Biomedical Engineering of the Fudan University, Shanghai, China). Electrocardiography, respiratory signals, and beat-to-beat blood pressure were continually and simultaneously recorded for 15 minutes through an electrosphygmography transducer (HMX-3C placed on the radial artery of the dominant arm) and an instrument respiration sensor. Short-term HRV analysis was performed for all subjects using a computer-aided examination and evaluation system for spectral analysis to investigate changes in autonomic regulation. In this study, CAN was diagnosed based on at least two abnormal cardiovascular autonomic reflex test results based on short-term HRV tests [2, 22-24].

Statistical analysis

Continuous variables were detected whether followed normal distribution using Kolmogorov-Smirnov Test. Variables that were not normally distributed were log-transformed to approximate normal distribution for analysis. Results are described as mean ± SD or median, unless stated otherwise. Differences in variables between subjects with non-MetS and MetS were determined by unpaired *t*-test. Between groups, differences in properties were accessed by χ^2 analysis. Univariate logistic regression was performed to determine variables associated with CAN and to estimate confounding factors possibly disturbing the relation of MetS and/or CKD to CAN. Multivariable logistic regression (MLR) was carried out to control potential confounders for determining independent contribution of variables to CAN.

For interaction analysis, MLR was conducted to include two main variables and its interaction item to evaluate the interaction effect. Odds ratios (OR) with 95% confidence intervals (CI) were calculated for the relative risk of MetS and/or CKD with CAN. Three parameters of RERI, AP, and S were used to estimate measures of interaction on an additive scale. RERI calculated by formula: OR_{AB}-OR_{Ab}-OR_{aB} + 1,

Table 1. Baseline characteristics of subjects

Variable	Total sample	non-MetS	MetS	*P* value*
Demographical information				
N	2092	1259	833	-
Age year	60.42 ± 8.68	59.7 ± 8.82	61.51 ± 8.36	< 0.001
Gender male (%)	705 (33.7%)	434 (34.47%)	271 (32.53%)	0.358
Height	161.46 ± 7.82	161.51 ± 7.87	161.38 ± 7.75	0.694
Weight kg	63.26 ± 10.65	60.34 ± 9.74	67.63 ± 10.47	< 0.001
WC cm	85.07 ± 9.77	81.38 ± 8.75	90.56 ± 8.54	< 0.001
SBP mmHg	127.62 ± 18.77	122.5 ± 17.25	135.38 ± 18.33	< 0.001
DBP mmHg	79.83 ± 9.74	77.83 ± 9.36	82.86 ± 9.53	< 0.001
Glucose profiles				
FPG mmol/L	5.53 ± 1.82	5.06 ± 1.32	6.24 ± 2.19	< 0.001
PBG mmol/L	7.67 ± 3.63	6.68 ± 2.91	9.16 ± 4.07	< 0.001
FINS pmol/L	49.96 ± 82.36	41.75 ± 71.53	62.25 ± 95.05	< 0.001
Lipids profiles				
TC mmol/L	5.32 ± 1	5.31 ± 0.95	5.34 ± 1.06	0.416
TG mmol/L	1.71 ± 0.98	1.35 ± 0.65	2.25 ± 1.13	< 0.001
HDL mmol/L	1.36 ± 0.32	1.46 ± 0.32	1.2 ± 0.26	< 0.001
LDL mmol/L	3.19 ± 0.77	3.17 ± 0.75	3.21 ± 0.79	0.216
Renal function				
SCr μmol/L	77.81 ± 26.11	76.93 ± 28.27	79.14 ± 22.44	0.058
UA μmol/L	281.21 ± 84.01	267.05 ± 78.27	302.47 ± 87.8	< 0.001
GFR mL/min/1.73 m^2	84.1 ± 30.03	85.67 ± 30.42	81.75 ± 29.29	0.003
Ccr ml/min	82.01 ± 31.02	83.27 ± 31.56	80.1 ± 30.09	0.023
HRV indices				
HR bpm	72.42 ± 10.13	71.43 ± 9.9	73.91 ± 10.29	< 0.001
TP ms^2	873.95 ± 702.47	937.08 ± 722.16	778.55 ± 660.67	< 0.001
LF ms^2	190.98 ± 207.88	210.35 ± 219.31	161.7 ± 185.61	< 0.001
HF ms^2	183.05 ± 219.43	203.39 ± 239.63	152.31 ± 180.61	< 0.001
LF/HF	1.7 ± 1.98	1.68 ± 2.05	1.75 ± 1.87	0.409
Medical history				
Smoking (%)	306 (14.63%)	182 (14.46%)	124 (14.89%)	0.785
HTN (%)	976 (46.65%)	389 (30.9%)	587 (70.47%)	< 0.001
DM (%)	446 (21.33%)	120 (9.54%)	326 (39.14%)	< 0.001
CKD %	175 (8.41%)	86 (6.89%)	89 (10.7%)	0.002
CAN (%)	387 (18.5%)	183 (14.54%)	204 (24.49%)	< 0.001

Note: *present the difference between subjects with MetS and non-MetS. WC- waist circumference, SBP- systolic blood pressure, DBP- diastolic blood pressure, FPG- fasting plasma glucose, PBG- plasma blood glucose, FINS- fasting blood insulin, TC- serum total cholesterol, TG- triglyceride, UA- uric acid, HDL- high-density lipoprotein cholesterol, LDL- low density lipoprotein cholesterol, SCR- serum creatinine, CCR- Creatinine clearance rate, GFR- Glomerular filtration rate, HR- heart rate, TP- total power of variance, LF- low frequency, HF- high frequency, MetS- metabolic syndrome, HTN- Hypertension, DM- Diabetes, CAN- Cardiovascular autonomic neuropathy.

means part of the total effect is due to interaction, where Ab is exposed to one factor, aB is exposed to the other factor, and AB is exposed to both factors. AP refers to proportion of the combined effect due to interaction, which is calculated by RERI/OR_{AB}. S is defined as the ratio between combined effect and individual effects, and derived from the formula: (OR_{AB}-1)/(OR_{Ab}-1 + OR_{aB}-1). The three parameters of RERI, AP, and S were then estimated in each of these new samples and the 95% CI for the three parameters were estimated as the 2.5th and 97.5th percentiles of the resulting bootstrap sampling distribution.

Table 2. Univariate logistic regression analysis for cardiovascular autonomic neuropathy

Variable	*β*	S.E.	*P* value	*OR*	95% CI
Age	0.042	0.007	< 0.001	1.043	1.029-1.103
BMI	0.066	0.016	< 0.001	1.068	1.034-1.046
WC	0.034	0.006	< 0.001	1.034	1.023-1.024
SBP	0.018	0.003	< 0.001	1.018	1.012-1.030
DBP	0.019	0.006	0.001	1.019	1.007-1.261
FPG	0.178	0.027	< 0.001	1.195	1.133-1.149
PBG	0.111	0.014	< 0.001	1.117	1.087-1.722
FINS	0.014	0.006	0.015	1.014	1.003-1.159
IR	0.091	0.029	0.001	1.095	1.036-1.212
GFR	0.001	0.001	0.559	0.999	0.997-1.002
Ccr	0.001	0.002	0.623	0.999	0.995-1.003
HR	0.090	0.006	< 0.001	1.094	1.081-1.108
HTN	0.779	0.116	< 0.001	2.178	1.736-3.248
DM	0.936	0.123	< 0.001	2.550	2.003-3.156
MetS	0.646	0.114	< 0.001	1.907	1.527-1.307
CKD	0.329	0.188	0.081	1.389	0.961-2.009

Note: MetS- metabolic syndrome, HR- heart rate, BMI- Body mass index, WC- waist circumference, SBP- systolic blood pressure, DBP- diastolic blood pressure, FPG- fasting plasma glucose, PBG- plasma blood glucose, FINS- fasting blood insulin, IR- insulin resistance, CCR -Creatinine clearance rate, GFR- Glomerular filtration rate, HTN- Hypertension, DM- Diabetes. CKD- chronic kidney disease.

Results were analyzed using the Statistical Package for Social Sciences for Windows version 16.0 (SPSS, Chicago, IL, USA). Tests were two-sided and a *p*-value of < 0.05 was considered significant. For interaction analysis, a *p*-value of < 0.05 was also considered to be significant.

Results

Clinical characteristics of subjects

The baseline clinical characteristics of the 2,092 subjects are listed in **Table 1**. There were 443 males and 835 females (mean age, 59.7 ± 8.82 years) in the non-MetS group and 271 males and 562 females (mean age, 61.51 ± 8.36 years) in the MetS group. Subjects with MetS were significantly older than subjects free from MetS (P < 0.001). There was no significant difference in the ratio of male to female between the two groups (P = 0.358). There were worse glucose profiles in subjects with MetS as compared with subjects free from MetS (P < 0.05 for all). There was no significant difference in Scr levels between the two groups (P < 0.05). On the contrary, the UA, GFR, and Ccr levels were significantly different between the two groups (P < 0.05 for all). Most of the HRV indices (TP, HF, and LF) were significantly lower in subjects with MetS as compared to subjects without MetS (P < 0.001 for all). The prevalence of HTN, DM, CKD, and CAN was frequent in subjects with MetS as compared to subjects without MetS (P < 0.01 for all).

Univariate and multiple logistic regression analysis for CAN

To estimate the association of various clinical factors and CAN, univariate logistic regression models were developed to include demographical information, glucose profiles, lipid profiles, parameters of renal function, HRV indices, and medical history (**Table 2**). The univariate logistic analyses indicated that age, BMI, WC, SBP, DBP, FPG, PBG, FINS, IR, HR, HTM, DM, and MetS were significantly associated with CAN (*P* < 0.05 for all). However, the variables of CKD were not significantly associated with the outcome (*P* = 0.081). The proportion of CAN was 14.54% and 24.49% in the non-MetS group and MetS group, respectively. In subjects with MetS, the OR for CAN was 1.907 (95% CI: 1.527-2.307, *P* < 0.001). MLR demonstrated that MetS remained significantly different between the two groups after adjustment for potential confounders (*P* < 0.001, OR = 1.847, 95% CI: 1.463-2.331, **Table 3**). There were no significant associations between CKD and CAN by using MLR (*P* = 0.937, **Table 3**).

MetS and CKD interaction analysis for CAN

MLR models were developed to include the two main effect variables of MetS and CKD, and the interaction item among them was detected in the MLR model after adjustment for relevant potential confounders (*P* = 0.042, OR_{inter} = 0.912, **Table 4** and **Figure 1**). In subjects free from MetS, the CAN prevalence was similar between subjects with CKD and subjects without CKD (14.39% vs. 16.60%, P > 0.05). On the contrary, in subjects with MetS, the CAN preva-

Table 3. Multiple logistic regression analysis for cardiovascular autonomic neuropathy

Variable	*β*	S.E.	*P* value	*OR*	95% CI
MetS	0.613	0.119	< 0.001	1.847	1.463-2.331
CKD	-0.065	0.202	0.746	0.937	0.631-1.391

Note: MetS- metabolism syndrome, CKD- chronic kidney disease. MLR with adjustment for age, gender, smoking, height and weight.

Table 4. Interaction analysis of MetS and CKD on CAN

Variable	β	S.E.	*P* value	OR	95% CI
MetS	0.652	0.12	< 0.001	1.920	1.517-2.429
CKD	0.324	0.29	0.263	1.383	0.784-2.439
MetS by CKD	-0.092	0.081	0.042	0.912	0.778-0.989
RERI				0.119	0.059-0.178
AP				0.049	-0.039-0.138
S				1.091	0.564-1.419

Note: MetS- metabolism syndrome, CKD- chronic kidney disease, RERI- relative excess risk due to interaction, AP- the proportion attributable to interaction, S- the synergy index. MLR with adjustment for age, gender, smoking, height and weight.

lence was frequent in subjects with CKD as compared without CKD (22.09% vs. 31.59% P < 0.05). The interaction on an additive scale was also estimated (RERI = 0.119 (95% CI: 0.059-0.178), AP = 0.049 (95% CI: -0.039-0.138), S = 1.091 (95% CI: 0.164-2.019).

Discussion

A large-scale, population-based study was conducted to evaluate the association and interaction of MetS and CKD on CAN in the general Chinese population. This sample was an adequate representation of the Chinese population, and the reference values may work similarly well outside the areas studied in China [25, 26]. Importantly, in the general Chinese population, we first performed an interaction analysis of the two risk factors for CAN. Physicians must understand the effect of interaction risk factors on outcomes. This is partly because most patients have more than two risk factors for a disease, and we should focus on controlling a modifiable risk factor interacting with other factors to efficiently reduce overall risks for the outcome.

In this study, our finding was that MetS was strongly and independently associated with CAN in the Chinese population. Univariate and multiple variable analysis provided evidence to support the finding (P < 0.001 for the two analyses). These results were consistent with our previous reports and others' studies where MetS was linked to lower HRV and impaired CAF [19, 27-29]. This finding is of particular importance given the direct relationship between MetS and CAN. The clustering of cardiovascular risk factors in MetS indicates the multiple complex metabolic reactions involved in glucotoxicity, lipotoxicity, altered insulin signaling, increased cytokine activity, and interstitial deposition of triacylglycerol may directly or indirectly impact cardiovascular autonomic nerves. In this study, we did not take into account, that diabetes status makes a greater contribution to impaired CAF than some other factors. A large-scale, case-controlled study or cohort study incorporating a more rigorous method of scoring MetS severity will be conducted in the future to develop a highly sensitive and specific model that uses MetS information to predict CAN.

Our important finding was that a significant positive interaction of MetS and CKD is associated with CAN in the Chinese population. MLR includes two main factors, and its interaction term was conducted to demonstrate a significant interaction of the two factors that affect CAN (P = 0.042). In addition, a positive interaction effect was estimated by using parameters of RETI > 0, AP > 0 and S > 1, suggesting that the combined effect of MetS and CKD on CAN is greater by 11.9% than the sum of the individual effects of the two factors. MLR analysis showed that CKD was not associated with CAN in our study sample, indicating that MetS modifies CKD to associate with CAN. These findings offered evidence that MetS patients with CKD were more susceptible to the influence of the progression of CAN. Smulders et al. estimated whether impaired CA function was independently associated with albuminuria in subjects with metabolic dysfunction. The study suggested that impaired CA function *was* independently associated with the presence of albuminuria in subjects with impaired glucose tolerance or diabetes [11]. Interestingly, Tahrani et al. per-

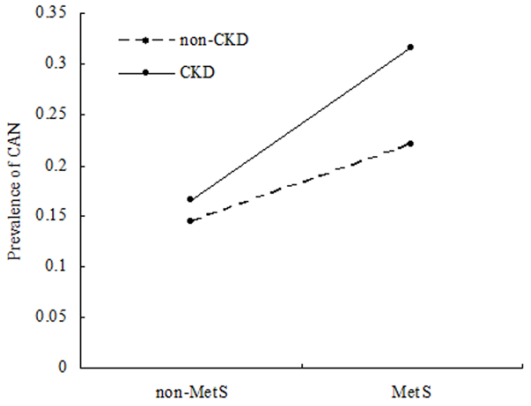

Figure 1. Interaction analysis of metabolism syndrome (MetS) and chronic kidney disease (CKD) on cardiovascular autonomic neuropathy (CAN). In subjects with non-MetS, the prevalence of CAN was 14.38% and 16.60% in those subjects with non-CKD and with CKD, respectively. In subjects with MetS, the prevalence of CAN was 22.09% and 31.59% in the subjects with non-CKD and with CKD, respectively. CKD was defined as the presence of albuminuria or an eGFR < 60 ml/min/1.73 m^2.

formed a cohort study in adults with type 2 diabetes to assess the impact of CAN on the development and progression of CKD, indicating that CAN was independently associated with CKD, albuminuria, and eGFR in diabetic patients [10]. Our findings were similar to those studies reporting that CKD was associated with CAN in a special subgroup of subjects with metabolism dysfunction. These results provided strong evidence that MetS modifies association between CKD and the development and progression of CAN. It is biologically plausible that the relationship between CAN and CKD could be mutually influenced in metabolism disorders. CKD may contribute to the progression of CAN through the lack of clearance of leptin, which can stimulate the sympathetic nervous system [30, 31]. The development and progression of CKD might attribute to CAN's impact on BP and cause haemodynamic changes, which can affect the intraglomerular pressure and the microvasculature surrounding the renal tubules [32, 33].

Several limitations of this study warrant comment. This study does not cover age groups other than 30-90 years. Additionally, the study data based on a cross-sectional study for interaction analysis requires a larger sample size and more geographic representations. The interaction results in this study need to be verified by future follow-up studies. Finally, it is important to mention that our study was performed on Chinese individuals, and our findings may not be relevant to people of other ethnicities.

Conclusion

In conclusion, our findings suggest that MetS is independently associated with CAN and offer evidence to support the hypothesis that MetS and CKD have positive interactions on CAN. Abnormal metabolic status may modify CKD to associate with the progression of this disease. The observations from this study constitute evidence that CKD patient-improved metabolic control may be an extra benefit in the goal of inhibiting progression of CA nerves.

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Disclosure of conflict of interest

None.

Abbreviations

ACEI, Angiotensin-converting enzyme inhibitor; Alb/Cr, Albumin/urinary creatinine ratio; AP, proportion attributable to interaction; BMI, Body mass index; CAN, Cardiovascular autonomic neuropathy; Ccr, Creatinine clearance rate; CKD, Chronic kidney disease; CI, Confidence intervals; Cr, Creatinine rate; DBP, Diastolic blood pressure; DM, Diabetes; FPG, Fasting plasma glucose; GFR, Glomerular filtration rate; HbAlc, Glycosylated hemoglobin; HDL, High-density lipoprotein cholesterol; HOMA-IR, Homeostasis model assessment insulin resistance estimate; IDF, International Diabetes Federation; LDL, Low-density lipoprotein cholesterol; MetS, Metabolic syndrome; MLR, Multivariable logistic linear regression; OGTT, Oral glucose tolerance test; OR, Odds ratios; PBG, Postprandial blood glucose; RERI, relative excess risk due to interaction; S, synergy index; SBP, Systolic blood pressure; TC, Serum total cholesterol; TG, Triglyceride; WC, Waist circumference; UA, Uric acid.

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