Association of body mass index, waist circumference, and metabolic syndrome with serum cystatin C in a Chinese population

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Abstract

Background: The aim of the study was to evaluate the association of body mass index (BMI), waist circumference (WC), and metabolic syndrome (MetS) with serum cystatin C (CysC) in a Chinese population.

Methods: The population was composed of 5866 subjects. MetS was diagnosed using the American Heart Association/National Heart, Lung, and Blood Institute 2005 (NCEP-R) criteria. Covariates were analyzed using logistic regression and Spearman partial correlation.

Results: In this population, triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), fasting plasma glucose (FPG), high sensitivity C-reactive protein (hs-CRP), BMI, WC, systolic blood pressure (SBP), diastolic blood pressure (DBP), serum creatinine (Scr), and CysC were significantly higher, and HDL-C and the estimated glomerular filtration rate (Chronic Kidney Disease Epidemiology Collaboration) (eGFR\textsubscript{CKD-EPI}) were significantly lower in the MetS than in the non-MetS group. TG, LDL-C, FPG, hs-CRP, BMI, WC, SBP, DBP, and Scr were significantly higher, and HDL-C and eGFR\textsubscript{CKD-EPI} were significantly lower in the 4th quartile than in the 1st quartile of CysC. Logistic regression analysis showed that sex, age, hs-CRP, and CysC were independently associated with the presence of MetS (OR = 3.732, 1.028, 1.051, and 3.334, respectively; P < 0.05). No significant association between the presence of MetS and either Scr or eGFR\textsubscript{CKD-EPI} was observed. After adjustment for age and sex, BMI, WC, hs-CRP, and Scr were all positively correlated, whereas eGFR\textsubscript{CKD-EPI} was negatively correlated with CysC (r = 0.029, 0.061, 0.189, 0.227, and –0.210, respectively; P < 0.05).

Conclusion: The present study revealed that the CysC was more closely associated with the presence of MetS, as compared Scr or eGFR\textsubscript{CKD-EPI}. CysC was positively correlated with BMI, and more strongly, positively correlated with WC and inflammation.

Abbreviations: BMI = body mass index, CysC = cystatin C, DBP = diastolic blood pressure, eGFR\textsubscript{CKD-EPI} = estimated glomerular filtration rate (Chronic Kidney Disease Epidemiology Collaboration), hs-CRP = high sensitivity C-reactive protein, LDL-C = low-density lipoprotein cholesterol, MetS = metabolic syndrome, SBP = systolic blood pressure, Scr = serum creatinine, TG = triglyceride, WC = waist circumference.

Keywords: body mass index, cystatin C, metabolic syndrome, waist circumference

1. Introduction

Cystatin C (CysC) is an extracellular inhibitor of cysteine proteases and is produced in all nucleated cells. CysC is freely filtered at the level of the renal glomeruli, and almost all of it is reabsorbed and metabolized in the proximal tubule.\textsuperscript{[1,2]} CysC can be used as a measure of kidney function. In recent years, multiple studies have shown that CysC may be used as a more accurate indicator of glomerular filtration rate (GFR) than creatinine.\textsuperscript{[3–7]} CysC has also served as a predictive marker of cardiovascular disease.\textsuperscript{[8,9]}

Metabolic syndrome (MetS) is highly prevalent worldwide\textsuperscript{[10–12]} and is associated with an increased risk for cardiovascular disease and diabetes.\textsuperscript{[13–15]} Many studies on the treatment of MetS have recently been conducted, including studies examining complementary and alternative medicine (CAM) treatments and the use of berry fruits.\textsuperscript{[16,17]} Some researchers have found that low testosterone concentration and high serum ferritin level were risk factors for MetS.\textsuperscript{[18,19]} Others have demonstrated that CysC is associated with MetS\textsuperscript{[20–23]} and have reported a positive relationship between CysC, body mass index (BMI), and waist circumference (WC).\textsuperscript{[20,23]} To the best of our knowledge, research on the association between MetS and CysC is limited. In the present study, we assessed the association of BMI, WC, and MetS with serum CysC in a large Chinese population.
2. Methods

2.1. Study designs and population
A total of 6,306 subjects visited our health care center for their regular checkup between January and December 2013. The medical history, including medications, of each subject was obtained. Subjects with thyroid dysfunction, pregnancy, malignant disease, cirrhosis, infectious disease, acute liver disease, chronic kidney disease, missing a valid measurement for necessary indices, or less than 18 years old were excluded (n = 440). Of the total sample (N = 5,866), none had a history of corticosteroid or cyclosporine use, hyperhomocysteinemia, or rheumatic diseases.

2.2. Clinical indices and anthropometric measurements
Venous blood samples were drawn after a 10-hour fast for serum index measurements. Triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), fasting plasma glucose (FPG), high-sensitivity C-reactive protein (hs-CRP), and serum creatinine (Scr) concentrations were measured using glycerol phosphate oxidase and peroxidase (GPO-POD), surfactant elution, selected inhibition, hexokinase, turbidimetric immunoassay, and sarcosine oxidase methods, respectively, using a Beckman Coulter AU 5400 machine. CysC concentrations were measured using the turbidimetric immunoassay method, specifically with a Beckman Coulter AU 5400 machine, at a reference range of less than 1.03 mg/L. Both the intra- and interassay coefficients of CysC were less than 10%. CysC levels were between 0.33 and 1.81 mg/L. Estimated glomerular filtration rate (Chronic Kidney Disease Epidemiology Collaboration) (eGFRCKD-EPI) equation (24) was used. Blood pressure (BP) was measured after at least 5 minutes of rest. WC was measured on standing subjects with a measuring tape midway between the lowest rib and the iliac crest. Body weight was measured in kilograms (with light clothing), and height was measured in meters (without shoes). BMI was calculated by using the formula: Weight (kg)/[Height (m)]².

MetS was diagnosed according to the American Heart Association/National Heart, Lung, and Blood Institute 2005 (NCEP-ATP III),(25) which requires at least 3 of the following criteria to be met: WC ≥90 cm in males and ≥80 cm in females; TG ≥1.7 mmol/L (150 mg/dL) or a specific treatment for TG; HDL-C < 1.03 mmol/L (40 mg/dL) in males and < 1.29 mmol/L (50 mg/dL) in females or a specific treatment for reduced HDL-C; systolic blood pressure (SBP) ≥130 mmHg, diastolic blood pressure (DBP) ≥85 mmHg, or antihypertensive treatment; and FPG ≥5.6 mmol/L (100 mg/dL) or drug treatment for elevated glucose.

2.3. Ethical issues
The ethical committee of the Second Affiliated Hospital, School of Medicine, Zhejiang University approved the study. All subjects provided informed consent.

2.4. Statistical analyses
SPSS software (version 13.0; SPSS Inc., Chicago, IL) was used for statistical analysis. Normal distribution data were expressed as the mean ± standard deviation. Skewed distribution data were expressed as the median with 25th and 75th percentiles (P25–P75). The Mann–Whitney U test was used to compare relevant data between non-MetS and MetS groups. The non-MetS group was defined as those subjects without MetS (2 or less MetS criteria). The Mann–Whitney U test was used to compare the data between the 1st and 4th quartiles of CysC. Logistic regression was performed to identify independent factors of MetS, and estimate odds ratios (ORs) and 95% confidence intervals (95% CIs) for the factors. The following were considered covariates in the logistic regression analysis: age, sex, hs-CRP, Scr, eGFRCKD-EPI, and CysC. SAS software (Version 9.2; SAS Institute Inc., Cay, NC) was used to perform a Spearman partial correlation analysis, adjusting for age and sex, to determine the association of BMI, WC, hs-CRP, Scr, and eGFRCKD-EPI with CysC. P < 0.05 was considered statistically significant.

3. Results

3.1. Clinical characteristics
The clinical data on this cohort are shown in Table 1. A total of 5,866 subjects were included in the study (females: 2,081, males: 3,785; age range: 18–84 years). Compared to the non-MetS group, the MetS group exhibited significantly higher levels of TG, LDL-C, FPG, hs-CRP, BMI, WC, SBP, DBP, Scr, and CysC, and lower levels of HDL-C and eGFRCKD-EPI.

3.2. CysC and other indices
The data were divided into 4 groups according to the quartiles of serum CysC concentration (Table 2). Comparisons between the indices in the 1st and 4th quartiles showed significantly higher values for TG, LDL-C, FPG, hs-CRP, BMI, WC, SBP, DBP, and Scr, whereas both HDL-C and eGFRCKD-EPI were significantly lower in the 4th quartile.

3.3. Logistic regression analysis
Logistic regression analysis revealed that sex, age, hs-CRP, and CysC were independently associated with the presence of MetS (OR = 3.732, 1.028, 1.051, and 3.334; 95% CI: 2.396–5.812, 1.004–1.053, 1.027–1.075, and 2.259–4.919; P < 0.001, 0.021, <0.001, and <0.001, respectively). No significant association was observed for presence of MetS and either Scr (P = 0.089) or eGFRCKD-EPI (P = 0.253) (Table 3).

3.4. Partial correlation analysis
Spearman partial correlation coefficients of BMI, WC, hs-CRP, Scr, and eGFRCKD-EPI with CysC are summarized in Table 4. After adjustment for age and sex, the results indicated that BMI, WC, hs-CRP, and Scr were positively correlated with CysC, whereas eGFRCKD-EPI was negatively correlated with CysC (r = 0.029, 0.061, 0.189, 0.227, and −0.210; P = 0.0260, <0.0001, <0.0001, <0.0001, and <0.0001, respectively).

4. Discussion
MetS is characterized by high fasting blood glucose, TG, BP levels, elevated WC, and low HDL-C levels. The worldwide prevalence of MetS has recently been acknowledged as an important public health challenge. MetS was present in 26.1% of the current study subjects, identical to that found in the literature. Furthermore, CysC concentrations were significantly higher in the MetS group than in the non-MetS group. Similar to our findings, Liu et al. demonstrated higher...
Table 1

| Relevant data according to the presence or the absence (non-MetS) of MetS. | Non-MetS | MetS | P
|---|---|---|---|
| N (all: 5866) | 4334 | 1532 | <0.001 |
| Sex ratio (MF), % | 2538/1706 (68/41.4) | 2247/295 (78.1/18.6) | <0.001 |
| Age, years | 41 (34–48) | 47 (40–53) | <0.001 |
| TG, mmol/L | 1.12 (0.80–1.57) | 2.34 (1.83–3.30) | <0.001 |
| LDL-C, mmol/L | 2.70 (2.27–3.20) | 3.12 (2.64–3.62) | <0.001 |
| HDL-C, mmol/L | 1.35 (1.16–1.57) | 1.02 (0.90–1.20) | <0.001 |
| FPG, mmol/L | 4.78 (4.48–5.07) | 5.25 (4.79–5.91) | <0.001 |
| hsCRP, mg/L | 0.4 (0.2–0.8) | 0.8 (0.4–1.6) | <0.001 |
| BMI, kg/m² | 22.77 (20.91–24.76) | 26.62 (24.2.76) | <0.001 |
| WC, cm | 81 (75–87) | 93 (89–97) | <0.001 |
| SBP, mm Hg | 117 (106–129) | 138 (125–149) | <0.001 |
| DBP, mm Hg | 71 (64–79) | 76 (71–83) | <0.001 |
| Scr, μmol/L | 67 (66–77) | 71 (63–69) | <0.001 |
| eGFRCKD-EPI, mL/min/1.73m² | 110 (101–117) | 105 (98–111) | <0.001 |
| CysC, mg/L | 0.72 (0.61–0.86) | 0.81 (0.69–0.96) | <0.001 |

The normal-distribution data were expressed as the mean ± SD. Skewed distribution data were expressed as the median with 25th and 75th percentiles (P25–P75). BMI = body mass index, CysC = cystatin C, DBP = diastolic blood pressure, eGFRCKD-EPI = estimated glomerular filtration rate (Chronic Kidney Disease Epidemiology Collaboration), FPG = fasting plasma glucose, HDL-C = high-density lipoprotein cholesterol, hsCRP = high sensitivity C-reactive protein, LDL-C = low-density lipoprotein cholesterol, SBP = systolic blood pressure, Scr = serum creatinine, SD = standard deviation, TG = triglyceride, WC = waist circumference.

Table 2

| Comparison of data among the different quartiles of CysC. | Q1 (0.33–0.63) | Q2 (0.64–0.75) | Q3 (0.76–0.89) | Q4 (0.90–1.81) | P
|---|---|---|---|---|---|
| n (all: 5866) | 1543 | 1491 | 1404 | 1428 | <0.001 |
| Sex ratio (MF), % | 600/943 (30.9/61.1) | 981/510 (65.8/34.2) | 1247/295 (78.1/18.6) | 1210/218 (84.7/15.3) | <0.001 |
| Age, years | 39 (33–45) | 42 (34–49) | 43 (36–51) | 47 (39–54) | <0.001 |
| TG, mmol/L | 1.09 (0.74–1.70) | 1.36 (0.90–2.14) | 1.44 (0.93–2.22) | 1.59 (1.09–2.29) | <0.001 |
| LDL-C, mmol/L | 2.60 (2.11–3.11) | 2.80 (2.33–3.32) | 2.87 (2.40–3.39) | 2.98 (2.52–3.53) | <0.001 |
| HDL-C, mmol/L | 1.44 (1.23–1.68) | 1.28 (1.10–1.50) | 1.22 (1.04–1.44) | 1.11 (0.95–1.31) | <0.001 |
| FPG, mmol/L | 4.86 (4.54–5.16) | 4.84 (4.53–5.20) | 4.85 (4.52–5.21) | 4.92 (4.58–5.35) | <0.001 |
| hsCRP, mg/L | 0.4 (0.2–0.7) | 0.5 (0.2–0.9) | 0.5 (0.3–1.1) | 0.7 (0.4–1.5) | <0.001 |
| BMI, kg/m² | 22.68 (20.62–24.68) | 23.78 (22.3–24.0) | 24.01 (23.0–24.7) | 24.72 ± 3.16 | <0.001 |
| WC, cm | 83 (73–96) | 84 (76–90) | 86 (78–90) | 88 (82–94) | <0.001 |
| SBP, mm Hg | 117 (106–129) | 122 (111–133) | 125 (113–137) | 130 (118–143) | <0.001 |
| DBP, mm Hg | 70 (62–79) | 74 (66–82) | 75 (67–84) | 80 ± 12 | <0.001 |
| Scr, μmol/L | 58 (51–69) | 69 (58–77) | 70 ± 15 | 75 (68–83) | <0.001 |
| eGFRCKD-EPI, mL/min/1.73m² | 114 (107–120) | 108 (101–116) | 106 ± 12 | 102 (93–110) | <0.001 |

The normal-distribution data were expressed as the mean ± SD. Skewed distribution data were expressed as the median with 25th and 75th percentiles (P25–P75). BMI = body mass index, CysC = cystatin C, DBP = diastolic blood pressure, eGFRCKD-EPI = estimated glomerular filtration rate (Chronic Kidney Disease Epidemiology Collaboration), FPG = fasting plasma glucose, HDL-C = high-density lipoprotein cholesterol, hsCRP = high sensitivity C-reactive protein, LDL-C = low-density lipoprotein cholesterol, SBP = systolic blood pressure, SD = standard deviation, TG = triglyceride, WC = waist circumference.

A limitation of our study is that it only included subjects who visited our center for a checkup. The analysis was also limited by the cross-sectional design.

In conclusion, we found the CysC was more closely associated with the presence of MetS, as compared Scr or eGFRCKD-EPI. CysC was positively correlated with BMI and more strongly, positively correlated with WC and inflammation.
Table 3
Association of CysC, hsCRP and the presence of MetS in logistic regression models.

| Variable (n=5866) | B | S.E. | Wald | P | OR | Lower | Upper |
|-------------------|---|------|------|---|----|-------|-------|
| Sex               | 1.317 | 0.226 | 33.934 | <0.001 | 3.732 | 2.196 | 5.812 |
| Age, years        | 0.028 | 0.012 | 5.319 | 0.021 | 1.028 | 1.004 | 1.053 |
| hsCRP, mg/L       | 0.050 | 0.012 | 18.244 | <0.001 | 1.051 | 1.027 | 1.075 |
| CysC, mg/L        | 1.204 | 0.198 | 36.803 | <0.001 | 3.334 | 2.259 | 4.919 |
| Scr, μmol/L       | -0.024 | 0.014 | 2.895 | 0.089 | 0.976 | 0.949 | 1.004 |
| eGFR<sub>CKD-EPI</sub>, mL/min/1.73m<sup>2</sup> | -0.018 | 0.016 | 1.306 | 0.253 | 0.982 | 0.952 | 1.013 |

Variable (s) entered on step 1: sex, age, hsCRP, CysC, Scr, and eGFR. 95% CI=95% confidence interval. CysC=cystatin C, eGFR<sub>CKD-EPI</sub>=estimated glomerular filtration rate Chronic Kidney Disease Epidemiology Collaboration, hsCRP=high sensitivity C-reactive protein, MetS=metabolic syndrome, OR=odds ratio, Scr=serum creatinine.

Table 4
Further partial correlation analysis between BMI, WC, hsCRP, Scr, and eGFR with CysC.

| Variable (n=5866) | r | P |
|-------------------|---|---|
| BMI, kg/m<sup>2</sup> | 0.029 | 0.0260 |
| WC, cm | 0.061 | <0.0001 |
| hsCRP, mg/L | 0.189 | <0.0001 |
| Scr, μmol/L | 0.227 | <0.0001 |
| eGFR<sub>CKD-EPI</sub>, mL/min/1.73m<sup>2</sup> | -0.210 | <0.0001 |

r: Spearman partial correlation coefficient after adjustment for age and sex. BMI=body mass index, CysC=cystatin C, eGFR<sub>CKD-EPI</sub>=estimated glomerular filtration rate (Chronic Kidney Disease Epidemiology Collaboration), hsCRP=high sensitivity C-reactive protein, Scr=serum creatinine, WC=waist circumference.

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