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# Cystatin C in healthy middle-aged adults: A relationship with anthropometric and cardiometabolic parameters

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## ABSTRACT

**Introduction:** Data suggesting that cystatin C levels are linked to obesity, apart from renal pathology, are conflicting. The aim of the study was to explore the potential association between serum cystatin C levels, anthropometric, and cardiometabolic parameters in healthy middle-aged adults.

**Methods:** A total of 132 participants (mean age 56.2 ± 6.73 years, 69% females) were included in this cross-sectional study. Anthropometric and biochemical parameters, as well as blood pressure, were obtained.

**Results:** Obese participants displayed higher cystatin C levels than normal-weight participants ($p < 0.001$). Multiple linear regression analysis revealed that waist circumference (WC) (Beta = 0.376, $p < 0.001$) and estimated glomerular filtration rate (Beta = -0.484, $p < 0.001$) were independently associated with cystatin C levels ($R^2 = 0.447$; $p < 0.001$).

**Conclusions:** Cystatin C is associated with abdominal obesity independent of renal function. Its relationship with changes in other target organs should be determined.

**Keywords:** Cystatin C; glomerular filtration rate; inflammation; obesity

## INTRODUCTION

When first introduced, it was thought that serum cystatin C level was not influenced by pathologies other than renal disease (1). However, this assumption has been questioned recently, since some studies

have shown that serum cystatin C concentration is influenced by some other factors (2).

A recent discovery that cystatin C is expressed in human adipose tissue (3) has questioned its role in estimating glomerular filtration rate in obese individuals. Several previous studies have reported higher serum cystatin C levels in obese participants than in normal-weight subjects (3,4), and a significant positive correlation between cystatin C and anthropometric indices was observed (5-7). Cystatin C was also shown to be a reliable marker for metabolic syndrome (8). Moreover, a recent study reported

that increased cystatin C values are associated with increased risk of cardiovascular morbidity, even in severely obese pediatric population (9).

However, these data were not supported by sufficient evidence, both in children (10-12) and adults (13-15), thus indicating that cystatin C is not affected by body fat distribution.

Consequently, it is still questionable whether obesity contributes to higher cystatin C levels. Moreover, data regarding the association between cystatin C level and obesity-related co-morbidities, comprising insulin resistance, inflammation, dyslipidemia and hypertension, are not well elucidated, taking into account that obesity is an independent risk factor for diabetes mellitus (DM), cardiovascular disease (CVD), and chronic kidney disease (CKD). Therefore, the purpose of the current study was to determine serum cystatin C levels and to examine its potential associations with anthropometric and cardiometabolic parameters in healthy middle-aged adults.

## METHODS

### Study population
The study enrolled a total of 132 middle-aged adults (mean age 56.2 ± 6.73 years, 69% females) who volunteered to participate in the examination. The participants were recruited in the Primary Health Care Center in Podgorica, Montenegro during their regular check-up, in a period from March 2013 to October 2013. All the participants completed a questionnaire including demographic characteristics, somatic illnesses, smoking history, and current medication use. Medical history and clinical examinations were carried out on the same day.

The inclusion criteria were creatinine-based estimated glomerular filtration rate (eGFR) ≥ 60 mL/min/1.73 m² [calculated using the Chronic Kidney Disease Epidemiology Collaboration Equation (CKD-EPI)], and normoalbuminuria [urinary albumin excretion (UAE) < 30 mg/24 h], non-smokers, without signs and symptoms of acute inflammatory disease, urinary infection, CVD, with no history or the presence of malignancy, hypo- and hyperthyroidism, as well as those who did not use any medications in the previous 6 months. The inclusion

criterion was also fasting glucose < 7.0 mmol/L. In addition, all participants with fasting glucose ≥ 5.6 mmol/L, but ≤ 6.9 mmol/L, underwent a two-hour oral glucose tolerance test (OGTT) with 75 g anhydrous glucose dissolved in 250 mL of water in order to exclude DM. Participants with 2-hour postload glucose ≥ 11.1 mmol/L were excluded from the study (16). Participants who had DM (fasting glucose ≥ 7.0 mmol/L or 2-hour postload glucose ≥ 11.1 mmol/L), renal dysfunction (creatinine-based eGFR < 60 mL/min/1.73 m²), UAE ≥ 30 mg/24 h, type 1 DM, morbid obesity (body mass index [BMI] > 40 kg/m²), hepatic dysfunction, cardiovascular disorders, and high sensitivity C-reactive protein (hsCRP) > 10 mg/L (17) were excluded from the study, as well as those who used anti-inflammatory, lipid-lowering, hypoglycemic, antihypertensive, or any other medications that might influence the association between cystatin C and other variables.

The participants were instructed not to perform any vigorous physical activity the day before the blood samples were taken. All the participants provided written informed consent. The study protocol was approved by the Ethical Committee of Primary Health Care Center in Podgorica, Montenegro, and the research was carried out in compliance with the Declaration of Helsinki.

### Anthropometric measurements
Basic anthropometric measurements: Body height (cm), body weight (kg), and waist circumference (WC) (cm) were obtained in the morning. Weight was measured to the nearest 0.1 kg on a balance beam scale, with the subjects barefoot and with light clothes. Height was measured to the nearest 0.1 cm using a wall-mounted stadiometer, without shoes. WC was measured with a non-stretchable tape, over the unclothed abdomen at the midpoint between the lowest rib and the iliac crest. The tape was parallel to the floor and did not compress the skin. BMI was calculated as weight in kilograms divided by height in meters squared (kg/m²).

Blood pressure (BP) was measured with a sphygmomanometer after the subject had been seated for 15 minutes. Average of three measurements taken on the right arm was recorded. All measurements were taken by the same trained evaluator.

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The participants were divided into two groups: Normal weight (n = 53; 18.5 < BMI < 25 kg/m², WC < 80 cm and WC < 94 cm for females and males, respectively) and overweight/obese (n = 79; 25 ≤ BMI < 40 kg/m², WC ≥ 80 cm and WC ≥ 94 cm for females and males, respectively). Although our obese population consisted of slightly obese (overweight, n = 45; 25 ≤ BMI < 30 kg/m²) and moderately obese (n = 34; 30 ≤ BMI < 40 kg/m²), for simplicity reasons, we referred to them as the obese participants.

### Biochemical measurements

The blood samples were taken between 7-9 hours a.m., 12-14 hours after an overnight fast. Samples were allowed to clot for 30 minutes and then centrifuged at 3000 rpm for 10 minutes. Serum levels of glucose, creatinine, total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), and triglycerides (TG) were measured spectrophotometrically (Roche Cobas 400, Mannheim, Germany), using standardized enzymatic procedures. Urinary albumin excretion was measured with an immunoturbidimetric assay (Roche Cobas 400, Mannheim, Germany). Cystatin C and hsCRP levels were determined using an immunonephelometric assay (Behring Nephelometer Analyzer, BN II, Marburg, Germany). Insulin was measured by chemiluminescent immunometric assay (Immulite 2000, Siemens, Munich, Germany). Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated using the formula HOMA-IR = Fasting glucose (mmol/L) x fasting insulin (μIU/L)/22.5. Glomerular filtration rate was estimated using creatinine in the CKD-EPI (18).

### Statistical analysis

Statistical analysis was performed using SPSS statistical package (version 15.0 for Windows, SPSS, Chicago, IL, USA). Data are presented as mean ± standard deviation or median (interquartile range), or counts and percentages. Differences between groups were evaluated with the Student's t test for normally or Mann-Whitney test for non-normally distributed parameters, and $\chi^2$ test was used for categorical variables. A correlation analysis was performed to determine the relationships between cystatin C levels and other variables. Multiple linear regression analysis was performed to identify independent factors affecting cystatin C and to estimate the final predictors of its variability. A *p* value of <0.05 was considered as statistically significant.

## RESULTS

Table 1 shows the general clinical and biochemical characteristics of the study participants divided into normal weight and obese groups. As expected, compared with the normal-weight, the obese participants had higher fasting glucose (*p* = 0.006), fasting insulin and HOMA-IR (*p* < 0.001, respectively), TG (*p* = 0.015), systolic blood pressure (SBP), diastolic blood pressure (DBP) and hsCRP levels (*p* < 0.001, respectively), but lower HDL-C levels (*p* < 0.001). Moreover, the obese participants displayed higher serum cystatin C level (*p* < 0.001). No significant difference was found with respect to the age, sex, TC, and LDL-C levels between these two groups. Furthermore, there was no difference in the serum creatinine, eGFR, and UAE levels.

The relationships between cystatin C and clinical and biochemical characteristics are presented in Table 2. As shown, the serum cystatin C level correlated positively with the age (*p* = 0.021), BMI and WC (*p* < 0.001, respectively), fasting glucose (*p* = 0.002), TG (*p* = 0.028), fasting insulin, HOMA-IR, creatinine, SBP, DBP, hsCRP (*p* < 0.001, respectively), and negatively with HDL-C (*p* = 0.034) and eGFR (*p* < 0.001) in all participants. No significant association between the serum cystatin C level and TC, LDL-C and UAE was found (Table 2).

In order to find out if the examined anthropometric parameters were significantly associated with the serum cystatin C level independently of renal function, linear regression models were performed in the whole group of participants (Table 3). Due to stronger association between WC and cystatin C compared to the association between BMI and cystatin C, the associations of WC (rather than BMI) and eGFR with cystatin C were analyzed independently. Significant positive correlations between cystatin C and WC were observed even after adjustment for age and sex (Beta = 0.502, *p* < 0.001, R² = 0.278), for age, sex and HOMA-IR (Beta = 0.307, *p* = 0.002,

**TABLE 1.** General characteristics of studied participants

| Characteristics | Normal-weight (n=53) | Obese (n=79) | *p* |
|---|---|---|---|
| Age (years) | 56.1±6.57 | 56.3±6.88 | 0.823 |
| Sex (females) % (n) | 66.0 (35) | 69.6 (55) | 0.807 |
| BMI (kg/m²) | 23.0±1.43 | 30.1±3.10 | <0.001 |
| WC (cm) | 81.5±7.43 | 101.5±9.99 | <0.001 |
| Fasting glucose (mmol/L) | 5.34±0.36 | 5.52±0.40 | 0.006 |
| Fasting insulin (µIU/L) | 4.10 (3.10-5.92) | 9.24 (5.85-15.85) | <0.001 |
| HOMA-IR | 0.99 (0.73-1.50) | 2.34 (1.45-4.04) | <0.001 |
| TC (mmol/L) | 6.09±1.43 | 6.14±1.12 | 0.845 |
| HDL-C (mmol/L) | 1.67±0.46 | 1.39±0.45 | <0.001 |
| LDL-C (mmol/L) | 3.95±1.41 | 4.05±1.19 | 0.649 |
| TG (mmol/L) | 1.21 (1.00-1.46) | 1.51 (1.02-2.28) | 0.015 |
| SBP (mm Hg) | 128±14.9 | 141±15.0 | <0.001 |
| DBP (mm Hg) | 79.3±9.62 | 89.5±9.68 | <0.001 |
| hsCRP (mg/L) | 0.55 (0.24-1.22) | 1.65 (1.00-3.21) | <0.001 |
| Creatinine (µmol/L) | 61.9±13.76 | 65.1±13.45 | 0.190 |
| eGFR (mL/min/1.73 m²) | 98.1±11.08 | 95.3±11.14 | 0.156 |
| UAE (mg/24 h) | 5.92 (4.96-7.90) | 6.65 (4.99-8.90) | 0.257 |
| Cystatin C (mg/L) | 0.75 (0.68-0.80) | 0.81 (0.73-0.87) | <0.001 |

Data are presented as mean±standard deviation or median (interquartile range), or counts and percentages, BMI: Body mass index, WC: Waist circumference, HOMA-IR: Homeostasis model assessment of insulin resistance, TC: Total cholesterol, HDL-C: High density lipoprotein cholesterol, LDL-C: Low density lipoprotein cholesterol, TG: Triglycerides, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, hsCRP: High sensitivity C reactive protein, eGFR: Estimated glomerular filtration rate, UAE: Urinary albumin excretion

$R^2 = 0.336$), for age, sex and hsCRP (Beta = 0.474, $p < 0.001$, $R^2 = 0.281$), for age, sex and HDL-C (Beta = 0.493, $p < 0.001$, $R^2 = 0.279$), as well as after the adjustment for age, sex, and SBP (Beta = 0.437, $p < 0.001$, $R^2 = 0.293$).

All variables found to have a significant predictive value in the linear regression model (e.g., WC, HOMA-IR, HDL-C, hsCRP, SBP, and eGFR), were further analyzed in multiple linear regression analysis for cystatin C prediction. In multiple linear regression analysis, WC (Beta = 0.376; $p < 0.001$) and eGFR (Beta = -0.484; $p < 0.001$) remained significant independent predictors of serum cystatin C level among all participants ($R^2 = 0.447$; $p < 0.001$) (Table 4).

## DISCUSSION

When initially mentioned, serum cystatin C was assumed to be related only to renal pathology (1). In the current study, obese (otherwise healthy participants) displayed significantly higher cystatin C levels as compared with normal-weight participants.

These findings are in accordance with the results reported by Naour et al. (3,4), who also found higher serum cystatin C levels in obese versus normal-weight counterparts. Moreover, they reported that cystatin C was highly expressed in human adipose tissue, equally in subcutaneous and omental fat depots (3), suggesting that cystatin C may play a role in preventing inflammation and controlling adipose tissue mass through cathepsins inhibition.

The observed association between serum cystatin C levels and anthropometric indices (e.g., BMI and WC) was also shown by some previous reports (5-7). However, in the current study the association between WC and cystatin C was stronger than reported for BMI and cystatin C, indicating that visceral, rather than overall adiposity, is more closely related to higher cystatin C levels (5). This association between cystatin C and WC remained significant even after the adjustment for confounding factors. On the other hand, some other studies (10-15) failed to find the association between cystatin C and obesity-related parameters, thus rejecting the

hypothesis that body composition affects cystatin C levels.

Sledziński et al. (19) also reported significantly higher serum cystatin C concentrations in obese patients compared to non-obese subjects. However,

decrease of body and fat mass after bariatric surgery resulted in improvement of cardiometabolic parameters (e.g., serum lipids, blood pressure, and insulin sensitivity), but surprisingly the mean post-operative serum cystatin C concentration was not significantly different from that before the surgery, suggesting that serum cystatin C concentration is not tightly associated with body and fat mass loss in obese patients.

Obesity is an independent risk factor for renal impairment, as showed by Chen et al. (20) who reported that the risk for CKD was more than twice as high in patients with increased WC than in those without increased WC. Furthermore, Young et al. (21) found that visceral and subcutaneous adipose tissue (as measured by computed tomography) were associated with CKD defined only with cystatin C estimating equations, but not when using a creatinine-based estimating equations.

Obesity is an independent risk factor for kidney dysfunction, even in pediatric age groups (9). Furthermore, Codoñer-Franch et al. (9) showed that obese children at the highest tertile of cystatin C levels had the cluster of several cardiometabolic risk factors, and cystatin C levels were correlated with cardiometabolic risk factors independently of renal function.

In our study, serum cystatin C correlated with blood pressure, both SBP and DBP, which is similar to other findings (8). Namely, Salgado et al. (22) reported the association of SBP, but not DBP, with serum cystatin C levels. On the other hand, Mena et al. (23) found that DBP negatively correlated

**TABLE 2.** Correlations of serum cystatin C level and studied parameters in all participants

| Variable | r | p |
|---|---|---|
| Age (years) | 0.201 | 0.021 |
| BMI (kg/m²) | 0.330 | <0.001 |
| WC (cm) | 0.472 | <0.001 |
| Glucose (mmol/L) | 0.270 | 0.002 |
| Fasting insulin (µIU/L) | 0.439 | <0.001 |
| HOMA-IR | 0.447 | <0.001 |
| TC (mmol/L) | 0.052 | NS |
| HDL-C (mmol/L) | -0.185 | 0.034 |
| LDL-C (mmol/L) | 0.094 | NS |
| TG (mmol/L) | 0.192 | 0.028 |
| SBP (mm Hg) | 0.378 | <0.001 |
| DBP (mm Hg) | 0.362 | <0.001 |
| hsCRP (mg/L) | 0.320 | <0.001 |
| Creatinine (µmol/L) | 0.443 | <0.001 |
| eGFR (mL/min/1.73 m²) | -0.558 | <0.001 |
| UAE (mg/24 h) | 0.121 | NS |

BMI: Body mass index; WC: Waist circumference, HOMA-IR: Homeostasis model assessment of insulin resistance, TC: Total cholesterol, HDL-C: High density lipoprotein cholesterol, LDL-C: Low density lipoprotein cholesterol, TG: Triglycerides, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, hsCRP: High sensitivity C-reactive protein, eGFR: Estimated glomerular filtration rate, UAE: Urinary albumin excretion, NS: Nonsignificant

**TABLE 3.** Linear regression models with association between cystatin C and WC, and association between cystatin C and eGFR, independently in all participants

| | WC | | | eGFR | | |
|---|---|---|---|---|---|---|
| | R² | Std Beta | p | R² | Std Beta | p |
| No adjustment | 0.222 | 0.472 | <0.001 | 0.311 | -0.558 | <0.001 |
| Age, sex* | 0.278 | 0.502 | <0.001 | 0.319 | -0.558 | <0.001 |
| Age, sex, HOMA-IR* | 0.336 | 0.307 | 0.002 | 0.449 | -0.460 | <0.001 |
| Age, sex, hsCRP* | 0.281 | 0.474 | <0.001 | 0.371 | -0.539 | <0.001 |
| Age, sex, HDL-C* | 0.279 | 0.493 | <0.001 | 0.340 | -0.541 | <0.001 |
| Age, sex, SBP* | 0.293 | 0.437 | <0.001 | 0.383 | -0.521 | <0.001 |

*After adjustment, WC: Waist circumference, eGFR: Estimated glomerular filtration rate, HOMA-IR: Homeostasis model assessment of insulin resistance, hsCRP: High sensitivity C-reactive protein, HDL-C: High density lipoprotein cholesterol, SBP: Systolic blood pressure

**TABLE 4.** Multiple linear regression analysis with cystatin C as dependent variable in all participants

| Independent variable | Std Beta | p |
|---|---|---|
| eGFR | -0.484 | <0.001 |
| WC | 0.376 | <0.001 |

WC: Waist circumference, eGFR: Estimated glomerular filtration rate

with cystatin C, while Shankar et al. (24) confirmed that mild reductions in kidney function as measured by serum cystatin C levels among subjects without clinically recognized chronic kidney disease were associated with hypertension in women, but not in men.

Previous studies have also shown that higher cystatin C levels were closely related to insulin resistance and inflammation (8,25). Although we observed significant association of cystatin C with inflammation (as measured by hsCRP), dyslipidemia, insulin resistance and hypertension in all participants, these associations were rejected after the multiple linear regression analysis, while only the association with WC and eGFR remained significant. Adipose tissue dysfunction has been shown to be a mediator in the development of obesity-associated complications (26). The results of the current study suggest that the relationship between serum cystatin C and inflammation, insulin resistance, endothelial dysfunction and activation of the renin-angiotensin-aldosterone system, all of which may be interrelated, could be secondary to the underlying association between serum cystatin C and obesity.

Despite the fact that we did not measure GFR directly and despite the cross-sectional nature of this study which makes the interpretation of the results limited, it is important to emphasize that we included only participants who were not under any medicament therapy which might influence the associations between cystatin C and other variables. Moreover, we excluded participants with eGFR < 60 mL/min/1.73 m² and albuminuria, CVD, DM, thyroid dysfunction, and acute inflammation and smoking, all of which may be strong determinants of cystatin C. As our study was not based on general population, selection bias might have affected the outcome of the study. The current study, however, suggests that serum cystatin C level can be used as a potential indicator of obesity and metabolic abnormalities associated with obesity, independent of renal function.

## CONCLUSION

Cystatin C is independently associated with abdominal obesity and its relationship with changes in other target organs should be evaluated.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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