Central Obesity, C-Reactive Protein and Chronic Kidney Disease: A Community-Based Cross-Sectional Study in Southern China

Shanying Chen a,b,f Hongmei Liu c,f Xinyu Liu a Yongqiang Li a Mi Li d Yan Liang a Xiaofei Shao a Harry Holthöfer e Hequn Zou a

Abstract

Objective: Previous studies have shown that central obesity is associated with chronic kidney disease (CKD). We hypothesized that the association of central obesity with CKD is modified by the presence of inflammation. To test this hypothesis, we performed this study.

Methods: This was a cross-sectional study in southern China. Waist-to-height ratio (WHtR) was used as a central obesity index and C-reactive protein (CRP) was used as an index for inflammation. CKD was defined as estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73m² or albumin-to-creatinine ratio (ACR) > 30mg/g. Multivariable logistic regressions were used and logistic regression models were adjusted for potential confounders and other components of metabolic syndrome.

Results: 1834 subjects were included in the current study. WHtR, body mass index and waist circumference were significantly associated with the level of CRP. When adjustment for potential confounders, only central obesity with a higher CRP level was associated with CKD (Relative-risk Ratio, 95% CI: 1.68, 1.03 – 2.75, P = 0.04). In multivariate logistic models, WHtR was associated with CKD. The odd ratio for WHtR (every SD increment), was 1.38 (95% CI 1.15, 1.66, P < 0.001). Further adjustment for log-transformed CRP had an impact on the odd ratios.

Conclusion: Central obesity is associated with CKD, independently of other MetS components. Central obesity is also associated with inflammation and the presence of inflammation modifies the associations of central obesity and CKD. This study is based on a community-based chinese population, and the results may only be applicable for Chinese population.
Introduction

Previous studies have shown that central obesity is associated with chronic kidney disease (CKD) [1-10]. Possible mechanisms of renal injury include 1. obesity –induced hypertension [11, 12] 2. adverse effects of adaptations to increase body mass/excretory load. 3. adverse effects of adaptations to obesity-induced sodium retention. 4. direct or indirect effects of hyperinsulinemia/insulin resistance and 5. renal lipotoxicity [13]. In central obesity state, excessive pro-inflammatory adipokins are produced, anti-inflammatory adipokins are reduced, and macrophage infiltration in adipose tissues is enhanced [13, 14].

It has been shown that inflammation is related with central obesity in general population and patients with CKD [15, 16]. Inflammation may be one of the potential causal pathways between central obesity and CKD. To our knowledge, there is a paucity of data on whether inflammation is one potential causal pathway between central obesity and CKD. We hypothesized that the association of central obesity with CKD is modified by the presence of inflammation. To test this hypothesis, we performed this study.

Patients and Methods

Participants

A community-based cross-sectional survey was conducted in Wanzhai county, Zhuhai city from June, 2012 to October, 2012. Zhuhai is a city located on the southern coast of China. Three communities in Wanzhai Town were randomly selected for this survey (There are six communities in Wanzhai Town). All adult residents (aged 18 years or older) living in the three communities were invited to participate in this survey. Participants were recruited by mail and home visiting. 2142 residents voluntarily participated in this survey. This study was approved by the Ethics Committee of the Third Affiliated Hospital of Southern Medical University. All participants gave their informed consent. We described the cross-sectional study in our previous paper [17].

Data collection

All physicians, medical students and nurses participating in this study had received intensive training. Data were collected in a local community clinic or during home interviews. All participants completed questionnaires including data about age, gender, education attainment, cigarette smoking, alcohol use, physical activity, personal history and family history [17].

Anthropometric indices (height, weight, waist, and hip measurements) were collected in a community clinic and measured according to the recommendations by the World Health Organization [18]. Body mass index was calculated as weight (in kilograms) divided by the square of the height (in meters). Waist-to-height ratio (WHtR) was calculated as the ratio of waist circumference to height. WHtR was selected as the index for central obesity [19-23].

Laboratory variables

Blood specimens were collected after a 10-hour overnight fast. Venous blood samples were collected by venipuncture in vacuum tubes. Urine specimens were collected early in the morning before breakfast and menstrual periods in females were avoided. All the samples were transported to the central laboratory in the third Affiliated Hospital of Southern Medical University. All the samples were disposed within 3 hours and stored at 2-8°C until analysis [17].

Urinary albumin was measured using a immune nephelometric method (Orion, Orion quick Read 101, Finland). High sensitivity C-reactive protein was measured by an enzymatic immunoassay turbidimetric method (Orion, Roche cobas6000, US). Samples were analyzed for serum creatinine, fasting blood glucose, serum total cholesterol, serum triglyceride and serum high density lipoprotein cholesterol and urinary creatinine using colorimetric methods (Roche, Roche cobas6000, US). Serum insulin was measured by an electrochemiluminescence immunoassay (Roche, Roche cobase601, BIORAD US) [17]. Urinary albumin to creatinine ratio (ACR) (mg/g) was calculated as the ratio of urinary albumin to urinary creatinine.
Estimated Glomerular Filtration Rate (eGFR). Estimated glomerular filtration rate (eGFR was calculated as 175× (Scr)$^{-1.234}$ × (Age)$^{-0.179}$ ×(if female, ×0.79) [24].

Definitions
Central obesity was defined as WHtR≥ 0.5 [22]. CKD was defined as eGFR less than 60 ml/min/1.73m$^2$ and/or ACR >30mg/g [25]. CRP was used to detect inflammation and a CRP level ≥ 3mg/L was considered to be inflammation.

After resting at least five minutes, blood pressure was measured in a sitting position, using calibrated mercury sphygmomanometers. Blood pressure measurement should be performed three times and a mean value was calculated [17]. Hypertension was defined as a self-reported history of hypertension and/or a systolic blood pressure ≥140 mm Hg and/or a diastolic blood pressure ≥90 mm Hg. Diabetes mellitus was defined as a self-reported history of diabetes or fasting serum glucose ≥7.0 mmol/l. Hyperuricemia was defined as serum uric acid≥ 416.4μmol/l (7mg/ldl) in men or ≥ 356.9μmol/l (6mg/ldl) in women. Insulin Resistance (IR) was defined as HOMA-IR > 2.69 [26, 27].

Statistical Analyses
Based on WHtR and serum levels of CRP, participants were divided into three subgroups for all analyses: non-obese participants (WHtR <0.5); centrally obese participants with a normal CRP level (WHtR ≥ 0.5 and CRP< 3mg/l); centrally obese participants with a high CRP level (WHtR ≥ 0.5 and CRP≥ 3mg/l).

Differences in clinical characteristics were analyzed for three subgroups. The Kruskal–Wallis test or one-way Analysis of variance was used for continuous variables. The chi-squared test or Fisher’s exact test was used to compare categorical variables.

The association of CRP with WHtR as a continuous variable was examined in a stepwise multiple linear regression model that included demographics (age and gender), comorbidity (hypertension, diabetes, stroke, coronary heart disease), physical inactivity, smoking, alcohol use, education attainment and other MetS components (fasting glucose, serum triglyceride, serum high density lipoprotein, systolic blood pressure and diastolic blood pressure). We also used a stepwise multiple linear regression model to examine the association of CRP with other anthropometric indices (BMI and waist circumference).

Multinomial logistic regression models were used to examine the association of WHtR and CKD. Non-obese subgroup was the reference category. The first model was unadjusted. The second model was adjusted for age and gender. Next this model was further adjusted by adding covariates that are likely potential confounders but unlikely to be in the causal pathway between central obesity and CKD. These variables include history of hypertension, diabetes, stroke, coronary heart disease, physical inactivity, smoking, alcohol use and education attainment. Finally, we examined whether the associations are independent of other MetS components. Fasting glucose, serum triglyceride, serum high density lipoprotein, systolic blood pressure, and diastolic blood pressure were added to the above covariates.

We also used logisiti regression models to examine whether the association of central obesity with CKD is modified by the presence of inflammation. Three anthropometric indices (WHtR, waist circumference and BMI) were used. Multivariate logistic models were adjusted for age, gender, history of hypertension, diabetes, stroke, coronary heart disease, physical inactivity, smoking, alcohol use and education attainment. Then, other MetS components (fasting glucose, serum triglyceride, serum high density lipoprotein, systolic blood pressure, and diastolic blood pressure) were added to the above covariates. Finally, log-transformed CRP was added to the models and the change in odds ratios was compared.

CRP and triglycerides values were logarithmically transformed to normal conditions.

All statistical analyses were performed with STATA 11 (STATA 11, TX) for Window 2003. Continuous variables with the normal distribution were shown as the mean ± the standard deviation. Continuous variables with a skewed distribution were shown as median and interquartile range. Absolute and relative (%) values were used for showing the categorical variables. Significance was set at P<0.05 in all tests.

Results

Baseline Characteristics (see table 1)
Among 2142 study participants, 308 participants were excluded from the analysis due
to missing data. We included 1834 participants with mean age 52.8 ± 14.5 years in the current study. Over all, 37.0% were men and 63.0% were women. The proportion of men was less than women. A potential cause was that women had a higher unemployment rate than men and employees could receive free physical examination in the workplace. This could lead to a lower participation rate for men. 235 (12.81%) participants had CKD, but only 45 (2.45%) had an eGFR < 60 ml/min/1.73 m².

685 (37.35%) participants were non-obese and 1149 (62.65%) participants had central obesity. Among 1149 centrally obese participants, 852 participants had normal CRP levels and 297 participants had high CRP levels. Characteristics of three subgroups are shown in table-1. In general, centrally obese participants were older than non-obese subgroup. Centrally obese participants had a higher proportion of history of hypertension, diabetes, as well as higher systolic blood pressure, diastolic blood pressure, BMI, waist circumference, WHtR, fasting glucose, serum C-reactive protein, serum triglyceride and serum uric acid (P<0.05). Centrally obese participants had a lower eGFR and a higher ACR.

Table 1: Baseline characteristics of non-obese and centrally obese participants according to C-reactive Protein

<table>
<thead>
<tr>
<th></th>
<th>Group 1 waist-to-height ratio &lt;0.5</th>
<th>Group 2 waist-to-height ratio ≥0.5 and CRP&lt;3mg/l</th>
<th>Group 3 waist-to-height ratio ≥0.5 and CRP≥3mg/l</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N= 685</td>
<td>N= 852</td>
<td>N= 297</td>
<td></td>
</tr>
<tr>
<td>Demographics</td>
<td>Age (Years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>47.37 ± 15.09</td>
<td>55.47 ± 13.02</td>
<td>57.48 ± 13.39</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male (%)</td>
<td>241 (35.18)</td>
<td>325 (38.15)</td>
<td>113 (38.05)</td>
<td>0.45</td>
</tr>
<tr>
<td>Clinical Characteristics</td>
<td>History of diabetes mellitus (%)</td>
<td>23 (3.36)</td>
<td>63 (7.39)</td>
<td>9 (9.76)</td>
</tr>
<tr>
<td></td>
<td>History of hypertension (%)</td>
<td>67 (9.78)</td>
<td>215 (25.23)</td>
<td>90 (30.3)</td>
</tr>
<tr>
<td></td>
<td>History of stroke (%)</td>
<td>2 (0.29)</td>
<td>3 (0.35)</td>
<td>2 (0.67)</td>
</tr>
<tr>
<td></td>
<td>History of coronary heart disease (%)</td>
<td>12 (1.75)</td>
<td>21 (2.35)</td>
<td>9 (3.03)</td>
</tr>
<tr>
<td>Smoke-status</td>
<td>Non-smoke (%)</td>
<td>567 (82.77)</td>
<td>721 (85.80)</td>
<td>248 (83.50)</td>
</tr>
<tr>
<td></td>
<td>Past-smoker (%)</td>
<td>31 (4.52)</td>
<td>31 (3.63)</td>
<td>13 (4.38)</td>
</tr>
<tr>
<td></td>
<td>Current smoker (%)</td>
<td>85 (12.41)</td>
<td>96 (11.27)</td>
<td>42 (14.14)</td>
</tr>
<tr>
<td></td>
<td>Current alcohol use (%)</td>
<td>33 (4.81)</td>
<td>56 (6.57)</td>
<td>17 (5.72)</td>
</tr>
<tr>
<td>School above (%)</td>
<td>335 (48.91)</td>
<td>317 (37.21)</td>
<td>89 (29.97)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Physical inactivity (%)</td>
<td>393 (57.37)</td>
<td>459 (53.87)</td>
<td>161 (54.21)</td>
<td>0.36</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>120.19 ± 18.23</td>
<td>132.48 ± 19.22</td>
<td>136.68 ± 20.93</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>74.32 ± 9.99</td>
<td>79.78 ± 10.89</td>
<td>81.48 ± 10.60</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anthropometric indices</td>
<td>Body Mass Index (kg/m²)</td>
<td>20.69 ± 2.54</td>
<td>24.51 ± 2.74</td>
<td>25.84 ± 3.32</td>
</tr>
<tr>
<td></td>
<td>Waist circumference (cm)</td>
<td>73.44 ± 5.79</td>
<td>87.91 ± 7.05</td>
<td>90.93 ± 7.75</td>
</tr>
<tr>
<td></td>
<td>Waist-to-height ratio</td>
<td>0.46 ± 0.03</td>
<td>0.55 ± 0.04</td>
<td>0.57 ± 0.05</td>
</tr>
<tr>
<td>Laboratory values</td>
<td>Serum Creatinine (umol/l)</td>
<td>71.72 ± 15.78</td>
<td>73.84 ± 16.05</td>
<td>74.40 ± 19.02</td>
</tr>
<tr>
<td></td>
<td>Serum uric acid (umol/l)</td>
<td>326.89 ± 87.97</td>
<td>358.10 ± 93.67</td>
<td>387.31 ± 105.49</td>
</tr>
<tr>
<td></td>
<td>eGFR (ml/min/1.73m²)</td>
<td>103.63 ± 22.19</td>
<td>97.32 ± 20.83</td>
<td>97.55 ± 24.38</td>
</tr>
<tr>
<td></td>
<td>Urine albumin-to-creatinine ratio (mg/g)</td>
<td>7.51 (5.30 - 11.40)</td>
<td>8.66 (5.92 - 15.56)</td>
<td>11.14 (6.98 - 24.13)</td>
</tr>
<tr>
<td></td>
<td>Fasting glucose (mmol/l)</td>
<td>4.74 ± 0.91</td>
<td>5.10 ± 1.21</td>
<td>5.39 ± 1.51</td>
</tr>
<tr>
<td></td>
<td>Serum C-reactive protein (mg/l)</td>
<td>0.53 (0.28 - 1.10)</td>
<td>0.99 (0.58 - 1.73)</td>
<td>5.14 (3.73 - 8.09)</td>
</tr>
<tr>
<td></td>
<td>Serum triglyceride (mmol/l)</td>
<td>0.97 (0.74 - 1.28)</td>
<td>1.41 (0.99 - 2.09)</td>
<td>1.52 (1.13 - 2.37)</td>
</tr>
<tr>
<td></td>
<td>Serum low density lipoprotein (mmol/l)</td>
<td>2.98 ± 0.86</td>
<td>3.26 ± 0.90</td>
<td>3.39 ± 0.93</td>
</tr>
<tr>
<td></td>
<td>Serum high density lipoprotein (mmol/l)</td>
<td>1.63 ± 0.33</td>
<td>1.50 ± 0.32</td>
<td>1.45 ± 0.32</td>
</tr>
<tr>
<td></td>
<td>HOMA – index (ui/ml)</td>
<td>1.32 (0.94 - 1.83)</td>
<td>2.10 (1.47 - 3.03)</td>
<td>2.57 (1.60 - 4.13)</td>
</tr>
</tbody>
</table>

Mean ± SD or median (25th to 75th percentiles) for continuous variables and proportion (95% confidence interval) for category variables are presented.
level (P<0.05). Centrally obese participants also had higher prevalences of hypertension, diabetes, hyperuricemia and IR (P<0.05). In centrally obese participants, 297 (25.85%) had high CRP levels, and only 8.47% (58/685) non-obese participants had high CRP levels. Even centrally obese participants with normal CRP levels had a higher CRP level than non-obese participants, and the difference was statistically significant (not shown in the table).

Association of anthropometric indices with CRP in the entire cohort (see table 2)
In the unadjusted regression model, WHtR was associated with log-transformed CRP in the entire cohort (P<0.001). After adjusted for demographics (age and gender), comorbidity (hypertension, diabetes mellitus, stroke, coronary heart disease, smoking status, alcohol use, physical inactivity, education attainment; Adjusted for above + systolic blood pressure, diastolic blood pressure, serum high density lipoprotein, fasting glucose, log serum triglyceride, serum high density lipoprotein), BMI and waist circumference were also significantly associated with log-transformed CRP (P<0.001).

Association of WHtR and CKD (see table 3)
In the unadjusted model, both central obesity with a normal CRP level and central obesity with a high CRP level were associated with CKD (P<0.01). But after adjustment for age and gender, only central obesity with a high CRP level was associated with CKD. After adjusting for other potential confounders (history of hypertension, diabetes mellitus, stroke, coronary heart disease, smoking status, alcohol use, physical inactivity, education attainment) and other components of MetS (blood pressure, triglyceride, high density lipoprotein and fasting glucose), the association was still significant with relative-risk ratio 1.68 (95% CI 1.03 – 2.75, P=0.04).

Association of anthropometric indices, CRP and CKD in entire cohort (see table 4)
In multivariate logistic models, all of three anthropometric indices were associated with CKD (P<0.05). The respective odd ratios for WHtR (every SD increment), waist circumference
(every SD increment) and BMI (every SD increment) were 1.38 (95% CI 1.15, 1.66, P < 0.001), 1.31 (95% CI 1.09, 1.57, P=0.003), and 1.24 (95% CI 1.05, 1.47, P=0.01).

Further adjustment for log-transformed CRP had an impact on the odd ratios, and the odd ratios were reduced. The association of BMI with CKD was abolished after adjusted for log-transformed CRP. The association of WHR or waist circumference with CKD was still significant. Log-transformed CRP is associated with CKD in the three multivariate logistic models (p<0.05, not shown in the table).

Discussion

The results of the current study suggest that central obesity is associated with CKD. The associations of central obesity with CKD are independent of other MetS components. Central obesity is associated with inflammation and the presence of inflammation modifies the associations of central obesity with CKD.

According to several cross-sectional and prospective cohort studies, central obesity was associated with the incidence of CKD and the progression of CKD [1, 3-9]. But the mechanism is not fully understood. Current knowledge suggests that central obesity may promote kidney injury by direct and indirect mechanisms [28]. Central obesity is a risk factor for developing type 2 diabetes and hypertension [11, 29-32], which are well known risk factors for CKD and cardiovascular mortality.

With regards to hemodynamic changes, obesity leads to glomerular hyperperfusion, hyperfiltration, and hypertension which would increase urinary albumin excretion and eventually lead to glomerulosclerotic damage [14, 28]. Further, a common pathologic finding of renal involvement in obese patients is focal and segmental glomerulosclerosis and glomerulomegaly [14]. Activation of sympathetic nervous system and renin–angiotensin system in central obesity may contribute to hemodynamic changes [14, 33]. An additional mechanism explaining the associations between obesity and CKD is lipotoxicity resulting from increased free fatty acid (FFA) levels [13].

Adipose tissue is currently considered as an endocrine organ that produces diverse adipocytokines including tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), resistin, leptin, adiponectin, plasminogen activator inhibitor-1, angiotensigen and so on. These adipocytokines play a role in energy homeostasis, insulin sensitivity, and vascular disease [13, 14, 32-34]. Among these adipocytokines, leptin and adiponectin could have beneficial effects.

The other potential pathway between obesity and kidney injure is chronic inflammation [14, 32, 34]. In central obesity state, excessive pro-inflammatory adipokins are produced, anti-inflammatory adipokins (such as adiponectin) are reduced, and macrophage infiltration in adipose tissues is enhanced [13, 14]. Visceral adipose tissue contains more free fat acid and produces more IL-6. Infiltrated macrophages produce excessive TNF-α [13, 14]. All
of these changes will lead to a chronic low-grade inflammatory state in centrally obese individuals. A cross-sectional study has shown that obesity is associated with inflammation in general population and CKD patients [36]. An epidemiological study based on the Third National Health and Nutrition Examination Survey showed that MetS was associated with inflammation in patients with CKD [16]. The current data also suggest that central obesity indices (WHtR and waist circumference) and BMI are associated with the level of CRP in regression analysis. The associations of central obesity and the level of CRP are independent of other potential confounders. Subsequent studies also showed that MetS and an elevated CRP level were independently associated with an increased prevalence of CKD. Compared with a low CRP level/without metabolic syndrome, the odds of CKD increased in the setting of high CRP and metabolic syndrome [37].

Central obesity is at the core of MetS. A prior study suggested that inflammation may be the pathogenic mechanism of obesity-related CKD [38]. But in the cross-sectional study, only 110 obese subjects and 50 non-obese subjects were included, and only 19 obese patients had CKD. The sample size was small. Whether inflammation modifies the associations of obesity with CKD is unclear. The current study suggests that central obesity with a high CRP level is associated with CKD, independently of other potential confounders and other MetS components. Compared with central obesity with normal CRP levels, the odds of CKD increased in the setting of central obesity and a high CRP level. When log-transformed CRP was added to the logistic model, BMI was not associated with CKD and the odd ratios for WHtR and waist circumference were reduced.

The current study indicates that central obesity is associated with inflammation. Inflammation modifies the associations of central obesity with CKD. Inflammation is a potential causal pathway between central obesity and CKD. Anti-inflammatory may be potential benefits in the reduction of the incidence of CKD in centrally obese subjects.

There were some limitations of the current study which should be considered. First, this is only a cross-sectional survey and we could not infer casual pathways. The associations of inflammation with CKD may be a chicken-and-egg question. But according to the previous study, early CKD was not associated with high CRP levels [39]. In the current study, only 2.45% participants had an eGFR< 60 ml/min/1.73 m². It is unlikely that CKD leads to inflammation in the population. High CRP levels are likely produced by central obesity. Second, despite indices of central obesity were recommended to use to diagnose of MetS [40, 41], there are no enough reliable data to ascertain the best cut-off point of waist circumference for Chinese population [42]. We selected WHtR as the index of central obesity based on previous studies [19-23]. The best index of central obesity and the best cut-off for Chinese population need to be further explored. Third, only 45 (2.45%) subjects have an eGFR< 60 ml/min/1.73 m² and the majority of the CKD subjects have normal GFR. Forth, we did not use the gold standard method to measure GFR. However, previous studies supported using MDRD equation to estimate GFR for Chinese people [24]. Fifth, all the indicators of CKD (eGFR and ACR) were obtained on the basis of a single measurement without repeating tests. According to the NHANAS III data in the United States, only 63.2% individuals with microalbuminuria still had albuminuria in the second visit [43]. Finally, the sample size is relatively small and only 37% of the participants are men. The sample is biased, but gender has been added to the adjusted models.

**Conclusion**

The results of the current study suggest that central obesity is associated with CKD. The associations of central obesity with CKD are independent of other MetS components. Central obesity is also associated with inflammation and the presence of inflammation modifies the associations of central obesity and CKD. This study is based on a community-based chinese population, and the results may only be applicable for Chinese population.
Conflict of Interests

The authors declare that they have nothing to disclose.

Abbreviations

Metabolic syndrome (MetS); High-density lipoprotein cholesterol (HDL-C); Chronic kidney disease (CKD); Body mass index (BMI); Waist circumference (WC); Waist to height ratio (WHtR); Urinary albumin to creatinine ratio (ACR); Estimated glomerular filtration rate (eGFR); Standard deviation (SD); C-reactive protein (CRP).

Acknowledgements

This study was supported by the following Science Foundation: 1. EU FP7 Program, UroSense, 2011; 2. ISN Research Committee grant, 2007; 3. ISN Research Committee grant, 2004; 4. Guangdong Provincial Science and Technique Program (No. 2011B031800386), 2011.

Reference


