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Waist-to-height ratio is independently associated with chronic kidney disease in overweight type 2 diabetic patients

Running head: Waist-to-height ratio-a risk factor for CKD?

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Abstract

Objective: Chronic kidney disease (CKD) is one of the most serious complications in obesity induced type 2 diabetes mellitus (T2DM). Body mass index (BMI), waist to hip ratio (WHR), waist circumference (WC) and waist to height ratio (WHtR) are recognised as sensitive measures for obesity which is suggested as a risk factor of greater importance for T2DM. We aimed to investigate the association of BMI, WC, WHR and WHtR with CKD prevalence in overweight T2DM patients.

Design, Subjects and Methods: We subsequently obtained 125 overweight T2DM patients coming for their comprehensive in-patient annual visit. Metabolic profiles and anthropometric indices were measured and calculated, urine albumin excretion (UAE) was determined as the mean of 24-h urine from two consecutive days and serum creatinine was measured from fasting blood sample and used to calculate the estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. Patients were divided in two groups according to CKD prevalence. Results: Sixty-five patients (52%) were male, median age 58 years and 11 years disease duration. Thirty-six (28.8%) met diagnostic criteria for CKD. The WHtR and waist circumference were higher in the group with CKD. WHtR correlated positively with UAE (r=0.828, p<0.001) and negatively with eGFR (r=-0.262, p=0.015). No significant correlation was observed with waist circumference in relation to UAE (r=0.111, p=0.335) nor eGFR (r=-0.154, p=0.121). WHtR yielded the significant and great OR in association to nephropathy after adjustment for all confounding risk factors.

Conclusion: WHtR might be of a greater importance in association to CKD compared to other anthropometric parameters that indicate central obesity. Whether it is a best measure of central obesity and its exact role in CKD pathology is yet to be investigated.

Key words: chronic kidney disease, central obesity, type 2 diabetes mellitus, waist-to-height ratio
**Introduction**

The prevalence of type 2 diabetes mellitus (T2DM) is globally rising at an alarming rate. Micro- and macrovascular complications are the leading cause of morbidity and mortality in diabetic patients (1). Obesity is considered a major risk factor for T2DM development but not only total body fat is important but also its distribution (3). Several independent studies suggest that anthropometric measures of central obesity are superior in predicting T2DM than those of general obesity (4-7).

Anthropometric measures are commonly used to assess disease risk factors as they are easy to monitor at the community level (8). Body mass index (BMI) which relates weight to height is most frequently used to estimate the prevalence of obesity within a population. BMI ≥ 25 kg/m² is associated with increased morbidity, primarily T2DM, while BMI ≥ 30 kg/m² is associated with an increased risk of morbidity and mortality, mainly because of diabetes (9, 10). However, BMI does not distinguish fat from muscle weight nor can distinguish fat distribution (11). Waist circumference (WC) and waist-to-hip ratio (WHR) have been proposed as tools to detect central obesity, but WC might over- or under-evaluate central obesity prevalence for tall or short individuals with similar waist circumference while WHR has a limitation in case of weight loss when both sizes decrease and the changes in ratio remain rather small (12). Waist-to-height ratio (WHtR) is an anthropometric proxy of central obesity that corrects WC for height and is suggested as an index that can be used in different ethnic, age and sex groups for central obesity screening (13-15).

Chronic kidney disease (CKD) i.e. diabetic nephropathy is one of the most serious complications of central obesity-induced diabetes (T2DM) (16). Moreover, in the industrial nations T2DM is a single most frequent cause of end-stage renal disease (17). The data from the Framingham Heart study that included over 2,600 patients with no CKD at baseline showed an increased risk in developing stage 3 CKD in obese (BMI ≥ 30 kg/m²) compared to non-obese subjects (18). The precise mechanism by which central obesity contributes to the development and/or CKD progression is not completely understood. However, it is a well-recognized risk factor for T2DM and hypertension development which are leading causes of CKD (19). Elevated fasting blood glucose level, hypertriglyceridemia and low high-density lipoprotein cholesterol (HDL-C) are also proposed risk factors for CKD development.
All of those can be found in individuals with central obesity and/or T2DM. WHR shows an association with CKD in diabetic as well as non-diabetic population (21, 22). The association of WHtR with CKD in non-diabetic subjects was also recently described (23, 24). Consisted with this, the aim of our study to investigate the association of BMI, WC, WHR and WHtR with CKD prevalence in overweight T2DM patients which to the best of our knowledge it has not been investigated yet.

Subjects and Methods

This was a cross-sectional study of a sequential sample comprising T2DM 125 patients of both genders. BMI ≥29 kg/m² coming for their comprehensive annual review. Patients with thyroid, kidney (other than diabetic nephropathy and end stage renal disease), liver disorders, psychiatric diseases, non-essential hypertension or any chronic or acute infections were not included in the study. Data were collected from July 2012 to May 2013. The study protocol complies with the Declaration of Helsinki and local institutional guidelines. It was approved by the local ethics committee. Written informed consent was obtained from all participants.

All subjects were studied in the morning between 08:00 and 09:30 hours after an overnight fast. Basic anthropometric measurements were performed on all study subjects by the same physician. WC was measured on bare skin as the narrowest circumference between the 10th rib and the iliac crest with tailor meter. Weight was measured by the physician using a balanced-beam scale with light clothing without shoes and expressed in kilograms (kg). Height was measured using a wall-mounted stadiometer and expressed in centimetres (cm) according to the NHANES III study (25). A steel tape measure was used to measure the women's waist circumference, midway between the lower rib margin and the iliac crest, and hip circumference at the widest point between the iliac crest and buttock. The circumferences were measured in a standing position and to the nearest 0.5 cm (25). BMI was calculated as weight in kilograms divided by the square of height in meters (kg/m²). WHR and WHtR
were calculated by dividing the waist circumference by the hip circumference and the body height, respectively.

Urine albumin excretion (UAE) was measured from at least two 24-h urine samples and determined as the mean of 24-h urine from two consecutive days to minimize variability. Serum creatinine was measured in fasting blood sample. Data on serum creatinine levels, age, sex and race were used to calculate the estimated glomerular filtration rate (eGFR) using the ChronicKidneyDiseaseEpidemiologyCollaboration (CKD-EPI) formula, which was shown to be accurate in determining renal function in diabetic patients with normal renal function (26, 27) in order to determine the presence of diabetic nephropathy. Chronic kidney disease was defined as the presence of impaired eGFR (less than 60 ml/min/1.73m$^2$) and/or albuminuria $\geq$ 30 mg/24h in two measurements at least 3 months apart (28).

Blood pressure was measured in the sitting position with a mercury sphygmomanometer with a cuff appropriate to the length and circumference of the arm after a resting period of 10 minutes and expressed in mmHg. Patients taking blood pressure medications or with blood pressure $>140/90$ mmHg were considered to have hypertension. Fasting venous blood samples were collected for the determination of biochemistry panel, lipid profile status, HbA1c. Cholesterol and triglycerides in serum were measured by an enzymatic colorimetric method. Beside the lipid profile status, those patients with history of lipid-lowering agents consumption were considered to have dyslipidaemia. HbA1c was measured spectrophotometrically by turbidimetric immuno-inhibition (Olympus AU600, Beckman-Coulter, USA).

The data distribution was assessed by Shapiro-Wilk test. All the continuous variables are reported as mean ± standard deviation i.e. median and range, whereas categorical variables were reported as numbers and percentages. The differences between two study groups were tested by Student’s $t$-test while the categorical variables were analysed by the $\chi^2$ test. Correlations between WC, WHtR, UAE and eGFR were determined using Pearson’s correlation coefficient. All the tests were two-sided. The association between WHtR and CKD prevalence was further evaluated in multivariate logistic
regression. Adjustments were performed for gender, age, disease duration, HbA1c value, hypertension
(i.e. ACEI use), dyslipidaemia (i.e. the use of statins) and smoking status. Statistical inference is
based on 95% confidence intervals (CIs) and 5% P values. All statistical analysis was conducted using
the statistical package Statistical Package for the Social Sciences (SPSS) ver.17.0 and MedCalc 12.2.2
for Windows.

Results

Among the 125 T2DM patients, sixty five (52%) were male and 60 (48%) female. Median age 58 years
and 11 years disease duration. Table 1 summarizes the descriptive anthropometric characteristics and
biomedical data as well as CKD prevalence all study participants. One hundred and fourteen
patients (91.2%) had hypertension and 100% of them were on angiotensin-converting enzyme
inhibitors (ACEI). Thirty six (28.8%) met diagnostic criteria for CKD. The group of patients with
CKD compared to group without CKD showed no significant difference in age (56 vs 58 years,
p=0.166), gender (53.5% vs 50.5% males), disease duration (median 11 years for both groups; range
2-24 years vs 1-30 years, p=0.760), glycated hemoglobin (HbA1c) (8.64 vs 8.63%, p=0.946),
dyslipidemia (75 vs 74.16%, p=0.846) nor the ACEI (91.6 vs 91.02%, p=0.961) use. The WHtR and
waist circumference were higher in the group with CKD (Table 2.). WHtR correlated positively with
UAE (r=0.828, p<0.001) and negatively with eGFR (r=-0.262, p=0.015) while no significant
correlation was observed with waist circumference in relation to UAE (r=0.111, p=0.335) nor
eGFR(r=-0.154, p=0.121). In the logistic regression models WHtR remained significantly associated
with CKD presence after appropriate adjustments for all possible confounding risk factors (Table 3.).

Discussion

This cross-sectional study was designed in order to examine the association of several most frequently
used obesity anthropometric parameters with CKD in overweight T2DM patients. It revealed that those
individuals with CKD have higher WC and WHtR which is in support to the hypothesis that central
obesity is associated with CKD in this patient population (19-22). However, only WHtR correlated both with eGFR and UAE. This is particularly important since it is not an uncommon finding that elderly patients with T2DM, especially those with recent onset of the disease, have mildly impaired renal function in setting of normal UAE. Our finding suggests that WHtR might be associated with diabetic glomerulosclerosis. Additionally, WHtR remained positively associated with CKD when calculating ORs adjusted for further influencing parameters proven to affect CKD in T2DM population (29). This finding is partially in support to Tseng (2005) (30) who demonstrated that WC and WHtR are the best indicators of microalbuminuria in Chinese T2DM woman but not man.

Although there are several studies have linking microalbuminuria and variable proteinuria degrees to obesity (31, 32) the exact mechanisms linking central obesity as a causal factor of renal injury is still largely speculated. Diabetes related abnormalities: insulin resistance (IR), hyperglycaemia, dyslipidaemia along with oxidative stress and low grade inflammation are attenuated by hormonally active visceral adipose tissue (24, 33). This metabolic milieu represents a cluster of atherosclerosis risk factors in general population (34, 35) but it might cause renal injury as well. Several studies indicate that central adipose tissue contributes to the renin-angiotensin-system (RAS) hormones disruption i.e. increase in circulating levels of renin, angiotensinogen, angiotensin-converting enzyme (ACE), aldosterone and angiotensin II (AngII) (36). AngII is widely known to adversely affect the progression of renal disease by a sum of mechanisms that leads to induction of intrarenal inflammation and cell apoptosis which is why ACEI found their place in CKD prevention and treatment (37). We did not find the difference in the use of ACE inhibitors (ACEI) between two study groups. Moreover, in the regression analysis after adjustment for the ACEI use, WHtR remained positively associated to CKD. Dyslipidaemia, defined as high total cholesterol, high low-density lipoprotein cholesterol and low high-density cholesterol with race cut-off’s may cause renal mesangial and epithelial cell injury and promote renal disease progression (38-40). We did not observe the difference in dyslipidaemia prevalence between our two study groups, probably because its high prevalence rate in both study groups. Therefore, there is practically no doubt that central obesity plays an important role in CKD development and progression. Both total and visceral/central fat can be precisely measured by double
energy X-ray densitometry (DXA), computerised tomography magnetic resonance imaging (41). Due to high costs and complex procedures these methods are not likely to be used in large epidemiological studies or individual physician assessment, thus there is a need for a simple to perform and accurate anthropometric test in order to indicate body fat distribution and their accuracy in CKD development and progression risk. In support to this study, Barreto Silva et al (2013) (24) evaluated the precision of different anthropometric measures of abdominal adiposity in non-diabetic non-dialysed patients with CKD. They studied the accuracy of the following anthropometric indices: WC, WHR, conicity index and WHtR to assess abdominal adiposity and compared them using trunk fat by dual x-ray absorptiometry (DXA) as a reference method but they also explored their association with insulin resistance using HOMA-IR. Among studied indices, WHtR was the only one to show correlation with DXA trunk fat after adjusting for confounders and also indicated high HOMA-IR.

Our study results indicate that WHtR is strongly associated with CKD and that it might be of a great importance in its development compared to other anthropometric parameters that indicate central obesity. However, it is important to emphasise the study limitations: first, this study was cross-sectional which clearly diminishes its power any general conclusions cannot be made. Second, we did not perform the body composition analysis so we cannot strongly claim that WHtR is the best indicator of central obesity. However, the relationship between WHtR and CKD progression in the prospective analysis would be of great interest.
References:


30. Tseng CH. Waist-to-Height Ratio Is Independently and Better Associated With Urinary Albumin Excretion Rate Than Waist Circumference or Waist-to-Hip Ratio in Chinese Adult Type 2 Diabetic Women but Not Men. Diabetes Care September 2005; vol. 28 no. 9 2249-2251.


Table 1. Baseline characteristics of the study participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension, i.e. the use of ACEI in therapy n (%)</td>
<td>114 (91.2)</td>
</tr>
<tr>
<td>Total plasma cholesterol (mmol/L)</td>
<td>5.07 (3.02-7.41)</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1.24 (0.70-2.49)</td>
</tr>
<tr>
<td>LDL cholesterol (mmHg)</td>
<td>2.95 (1.03-5.81)</td>
</tr>
<tr>
<td>Tryglicerides (mmol/L)</td>
<td>2.47 (0.76-10.83)</td>
</tr>
<tr>
<td>Dyslipidemia , n (%)</td>
<td>93 (74.4)</td>
</tr>
<tr>
<td>Creatinine (µmol/L)</td>
<td>74 (46-182)</td>
</tr>
<tr>
<td>UAE (mg/dU)</td>
<td>223.29 (2.80-4773.27)</td>
</tr>
<tr>
<td>eGFR ( mL/min/1.73 m²)</td>
<td>83 (41-118)</td>
</tr>
<tr>
<td>Current smoker, n( %)</td>
<td>105 (84)</td>
</tr>
<tr>
<td>Chronic kidney disease prevalence, n(%)</td>
<td>36 (28.8)</td>
</tr>
<tr>
<td>- Based only on eGFR &lt;60 ml/min/1.73 m², n(%)</td>
<td>3 (2.4)</td>
</tr>
<tr>
<td>- Based only on UAE&gt;30 mg/24h, n(%)</td>
<td>26 (20.8)</td>
</tr>
<tr>
<td>- Based on eGFR &lt;60 ml/min/1.73 m²+ UAE&gt;30 mg/24h</td>
<td>7 (5.6)</td>
</tr>
</tbody>
</table>

*Legend: ACEI- angiotensin converting enzyme inhibitors; BMI-body mass index, eGFR-estimated glomerulal filtration rate, UAE-urin albumin excretion rate
Table 2. Differences in anthropometric indices of central obesity according to the CKD prevalence in obese T2DM patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>T2DM patients without CKD</th>
<th>T2DM patients with CKD</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist circumference (cm)</td>
<td>117 (92-148)</td>
<td>119 (88-192)</td>
<td>0.069</td>
</tr>
<tr>
<td>WHR</td>
<td>0.987 (0.795-1.243)</td>
<td>1.011 (0.842-1.401)</td>
<td>0.056</td>
</tr>
<tr>
<td>WHtR</td>
<td>0.666 (0.321-0.887)</td>
<td>0.710 (0.531-1.191)</td>
<td>0.031</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>37.58±4.12</td>
<td>38.93±5.80</td>
<td>0.033</td>
</tr>
</tbody>
</table>

*Legend: WHR-waist-to-hip ratio; WHtR-waist-to-height ratio; BMI-body mass index
Table 3. Odds ratio for nephropathy for one standard deviation increase in weight-to-height ratio adjusted by other risk factors: gender, age, disease duration, HbA1c value, hypertension (i.e. the use of ACEI), dyslipidaemia (i.e. the use of statins) and smoking status

<table>
<thead>
<tr>
<th>CHRONIC KIDNEY DISEASE PRESENCE</th>
<th>Crude</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
<th>Model 4</th>
<th>Model 5</th>
<th>Model 6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.625(1.103-1.865)</td>
<td>1.680(1.147-1.880)</td>
<td>1.705(1.174-1.895)</td>
<td>1.700(1.135-1.896)</td>
<td>1.700(1.134-1.896)</td>
<td>1.699(1.130-1.896)</td>
<td>1.697 (1.122-1.895)</td>
</tr>
<tr>
<td></td>
<td>p&lt;0.001</td>
<td>p=0.013</td>
<td>p=0.011</td>
<td>p=0.023</td>
<td>p=0.023</td>
<td>p=0.024</td>
<td>p=0.030</td>
</tr>
</tbody>
</table>

*Model 1: adjusted by age and gender; Model 2: adjusted by age, gender and disease duration; Model 3: adjusted by age, gender, disease duration and HbA1c; Model 4: adjusted by age, gender, disease duration, HbA1c and dyslipidaemia; Model 5: adjusted by age, gender, disease duration, HbA1c, dyslipidaemia and arterial hypertension; Model 6: adjusted by age, gender, disease duration, HbA1c, dyslipidaemia, arterial hypertension and smoking status