THE USE OF ANTHROPOMETRIC MEASUREMENTS OF OBESITY IN PREDICTION OF MICROVASCULAR COMPLICATIONS IN OBESE TYPE 2 DIABETIC PATIENTS

Tomislav Bulum¹,², Kristina Blaslov¹ and Lea Duvnjak¹,²

¹Vuk Vrhovac Clinic for Diabetes, Endocrinology and Metabolic Diseases, Merkur University Hospital; ²School of Medicine, University of Zagreb, Zagreb, Croatia

SUMMARY – Waist circumference (WC), waist-to-hip ratio (WHR), and waist-to-height ratio (WHtR) are superior to body mass index (BMI) in predicting type 2 diabetes mellitus (T2DM) development. The aim of this study was to investigate the predictive power of BMI, WC, WHR and WHtR for microvascular (chronic kidney disease (CKD), retinopathy and peripheral neuropathy) prevalence in obese (BMI ≥35 kg/m²) T2DM patients. This cross-sectional study included 125 T2DM patients of both genders. The validity of each test was assessed by Receiver Operating Characteristic (ROC) curves; the area under the curve (AUC) was calculated for each anthropometric parameter and microvascular complication. AUCs for WHtR were significantly higher than AUCs for WC with respect to CKD. Optimal cut-off for WHtR was >0.593 and WC >112 cm regarding CKD. The AUC for peripheral neuropathy was significant only for WHR and optimal cut-off for WHR was >1.409 with low sensitivity and high specificity. Our study demonstrated that WHtR, WC and WHR might be used as simple and noninvasive methods for detection of CKD and peripheral neuropathy in obese T2DM population.

Key words: Diabetes mellitus, type 2; Obesity – complications; Waist circumference; Waist-height ratio; Renal insufficiency, chronic; Diabetic neuropathy; Diabetic retinopathy

Introduction

Obesity is considered to be the major risk factor for type 2 diabetes mellitus (T2DM) development, the estimated prevalence of which was 8.5% in Europe in 2013, while this population continues to develop diabetic macro- and microvascular complications resulting in increased disability and enormous healthcare costs¹,². Several study reports suggest that fat distribution is important as a risk factor for T2DM development, i.e. anthropometric measurements that describe central or ‘android fat’ distribution are superior to general obesity measurements in predicting T2DM³⁻⁷.

Anthropometric measurements are commonly used to assess disease risk factors as they are easy to monitor at the community level, as well as in large epidemiologic studies in order to predict T2DM development⁴. Body mass index (BMI) relates weight to height and was most frequently used to estimate the prevalence of obesity within a population; while BMI ≥25 kg/m² is associated with increased T2DM morbidity, BMI ≥30 kg/m² is associated with an increased risk of morbidity and mortality from diabetes and its complications⁸. However, BMI reflects total body fat and does not distinguish different patterns of fat distribution¹¹. Waist circumference (WC) and waist-to-hip ratio (WHR) have been proposed as tools to detect central obesity but taking into consideration that WC might over- or under-evaluate the risk for tall or short individuals with similar WC and that WHR has a limitation in case of weight loss when both sizes decrease but
changes in the ratio remain rather small. Waist-to-height ratio (WHtR) is another anthropometric measurement of central obesity that corrects WC for height and is supported as an index that can be used in different ethnic, age and sex groups for central obesity screening.

The relationship between metabolic control and development of microvascular complications (retinopathy, neuropathy and nephropathy) is a primary concern of clinicians. Factors involved in the development of vascular complications in diabetes include duration of diabetes, poor glycemic control, smoking, hypertension and dyslipidemia, but the role of body weight/body fat distribution is unclear. There is a possible effect of BMI on retinopathy in diabetic patients, derived primarily from Diabetes Control and Complications Trial (DCCT), where BMI was observed to have a significant predictive value in developing retinopathy besides the traditional factors, as later confirmed by Henricsson et al. Only a few recent reports suggest a role of BMI in neuropathy development. However, there are several studies linking obesity to chronic kidney disease (CKD) in diabetic patients. Moreover, recent data suggest that central obesity might play a key role in associating obesity with the risk of microvascular complications, acting through several different pathophysiological pathways.

The aim of our study was to investigate the predictive power of BMI, WC, WHR and WHtR for the prevalence of microvascular complications (CKD, retinopathy and peripheral neuropathy) in obese (BMI ≥35 kg/m²) T2DM patients.

Patients and Methods

This was a cross-sectional study including a sample of 125 T2DM consecutive patients of both genders presenting for complete annual check-up at our Clinic for Diabetes, Endocrinology and Metabolic Diseases. Patients with kidney (other than diabetic nephropathy) and liver disorders, psychiatric diseases, non-essential hypertension, or any chronic or acute infection were not included in the study. The study protocol complied with the Declaration of Helsinki, as well as with local institutional guidelines, and was approved by the local ethics committees. A written informed consent was obtained from all participants.

All subjects were studied in the morning between 07:00 and 08:30 AM after an overnight fast. Baseline anthropometric measurements were performed in 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) and height was measured using a wall-mounted stadiometer and expressed in centimeters (cm) according to the Third National Health and Nutrition Examination Survey (NHANES III) study. A steel tape measure was used to measure female WC, 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 standing position and to the nearest 0.5 cm. BMI was calculated as weight in kilograms divided by the square of height in meters (kg/m²). WHR and WHtR were calculated by dividing WC by hip circumference and 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 on 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 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula to determine the presence of diabetic nephropathy. CKD was defined as the presence of impaired eGFR (less than 60 mL/min·1.73m²) and/or macroalbuminuria (UAE ≥300 mg/24 h). Retinopathy was diagnosed by binocular indirect slit lamp funduscopy and fundus photography after mydriasis with eye drops containing 0.5% tropicamide and 5% phenylephrine. Color fundus photographs of two fields of both eyes were taken with a suitable 45° fundus camera (VISUCAM, Zeiss, Germany) according to the EURODIAB retinal photography methodology. In each patient, the ‘worse’ eye was graded for retinopathy using fundus photographs. Evaluation of peripheral neuropathy was based on clinical symptoms (neuropathy symptom score), signs (neuropathy disability score), quantitative sensory testing (vibration perception threshold), and electroneuromyography testing was performed to detect peripheral sensorimotor neuropathy.
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 10-min rest and expressed in mm Hg. Fasting venous blood samples were collected for determination of biochemistry panel, lipid profile status and HbA1c. Serum cholesterol and triglycerides were measured by an enzymatic colorimetric method. HbA1c was measured spectrophotometrically by turbidimetric immuno-inhibition (Olympus AU600, Beckman-Coulter, USA).

**Statistics**

Baseline data on all patients were reported using descriptive statistics. Normality of distribution for continuous variables was analyzed using Shapiro-Wilk test. Normally distributed variables were described with mean and standard deviation (SD), while variables that were not normally distributed were described with median, minimum and maximum. Nominal variables were reported with absolute numbers and/or percentages. The validity of each test was assessed by the receiver operating characteristic (ROC) curves; the area under the curves (AUC) was calculated for each anthropometric parameter (BMI, WC, WHR and WHtR) and microvascular complication. Individual cutoffs, sensitivity and specificity were estimated by Youden index. Differences between AUCs were tested with nonparametric test$^{10}$. AUC indicates a measure of degree of separation between affected and nonaffected subjects by a specific test and the value of 0.5 or lower indicates no discriminative value of the test used. Statistical interference is based on 95% confidence interval (CI) and 5% $P$ values. Statistical analysis was conducted using the Statistical Package for Social Sciences (SPSS) ver. 17.0 and MedCalc 12.0 for Windows.

**Results**

Out of 125 T2DM study patients, there were 65 (52%) male patients, median age 58 years with 11 years of disease duration. Table 1 summarizes descriptive anthropometric characteristics and biomedical data, as well as the prevalence of microvascular complications in all study subjects. The results of ROC analysis of the four anthropometric indices for three major microvascular complications (CKD, retinopathy and peripheral neuropathy) are shown in Table 2. The AUC for WHtR was significantly higher than the AUC for WC with respect to CKD. The AUC for peripheral neuropathy was significant only for WHR. With regard to retinopathy, there was no significant difference among the anthropometric parameters observed. Moreover, the AUCs suggested that these predictors should not be considered as validated tests. Table 3 shows optimal cutoffs and their sensitivity and specificity for the parameters that showed validity according to AUCs. Optimal cutoff for WHtR was >0.593

| Table 1. Baseline characteristics of study subjects |
|-----------------|-----------------|
| N=125            |                  |
| Age (years)      | 58 (31-76)      |
| Disease duration (years) | 11 (1-30) |
| HbA1c (%)        | 8.63±1.48       |
| Weight (kg)      | 110 (78-187)    |
| Body mass index (kg/m²) | 35.57±5.36  |
| Waist circumference (cm) | 119 (88-192) |
| Hip circumference (cm) | 116.5 (92-165) |
| Waist to hip ratio|                  |
| Waist to height ratio|              |
| Systolic blood pressure (mm Hg) | 140 (100-220) |
| Diastolic blood pressure (mm Hg) | 90 (60-150) |
| Hypertension, n (%) | 114 (91.2) |
| Total plasma cholesterol (mmol/L) | 5.07 (3.02-7.41) |
| HDL cholesterol (mmol/L) | 1.24 (0.70-2.49) |
| LDL cholesterol (mmol/L) | 2.95 (1.03-5.81) |
| Triglycerides (mmol/L) | 2.47 (0.76-10.83) |
| Dyslipidemia, n (%) | 93 (74.4) |
| Serum creatinine (μmol/L) | 74 (46-182) |
| Urinary albumin excretion rate (mg/dU) | 223.29 (2.80-4773.27) |
| Estimated GFR (mL/min/1.73 m²) | 83 (41-118) |
| Current smoker, n (%) | 105 (84) |
| Retinopathy prevalence, n (%) | 45 (36) |
| Chronic kidney disease prevalence, n (%) | 36 (28.8) |
| Peripheral neuropathy prevalence, n (%) | 188 (94.4) |

HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; LDL = low-density lipoprotein; GFR = glomerular filtration rate
and for WC >112 cm regarding CKD. Both tests showed high to moderate sensitivity but low specificity. Optimal cutoff for WHR regarding peripheral neuropathy was >1.409 with low sensitivity and high specificity.

**Discussion**

In this study on a representative sample of obese T2DM adults, we demonstrated that WC and WHtR were superior to BMI and WHR, and that WHtR was better than WC in discriminatory power for identifying CKD, while WHR was superior to other estimates for identification of peripheral neuropathy. Our study definitely supported the inconclusiveness of data on the relationship of BMI and microvascular complications. It is known that anthropometric measurements of BMI, WHR and WC do not correlate entirely and are indices of different aspects of obesity. For instance, adults with normal BMI may have markedly high anthropometric parameters of metabolic syndrome such as WC, sometimes referred to as metabolically obese normal-weight adults. As discussed in the Introduction section, other anthropometric measurements of obesity also have limitations but have been proven to correlate more accurately with the amount of visceral adipose tissue. Although the exact pathophysiological pathway by which visceral adipose tissue acts in the development of microvascular complications remains to be exactly defined, there are several hypotheses that link it with hypertension and dyslipidemia, which are confirmed to be among the major risk factors that cause vascular injury and some other homeostasis disorders which might enhance the effect of these two.

First, the hallmark of central obesity is insulin resistance and because insulin is considered to be an anti-inflammatory hormone, insulin resistance might be considered as a proinflammatory state and visceral adipocytes and macrophages are also a source of proinflammatory cytokines. The common knowledge suggests that they cause damage to endothelial cells and

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**Table 2. AUC estimated by ROC analysis**

<table>
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<tr>
<th></th>
<th>Waist circumference (cm)</th>
<th>Waist to hip ratio</th>
<th>Waist to height ratio</th>
<th>Body mass index (kg/m²)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>AUC (95% CI)</td>
<td>AUC (95% CI)</td>
<td>AUC (95% CI)</td>
<td>AUC (95% CI)</td>
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<tr>
<td>Chronic kidney disease</td>
<td>0.621 (0.508-0.735)*</td>
<td>0.568 (0.446-0.690)</td>
<td>0.668 (0.569-0.789)*</td>
<td>0.554 (0.432-0.617)</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>0.456 (0.344-0.568)</td>
<td>0.520 (0.404-0.645)</td>
<td>0.436 (0.333-0.539)</td>
<td>0.380 (0.280-0.479)</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>0.437 (0.204-0.742)</td>
<td>0.672 (0.452-0.892)*</td>
<td>0.271 (0.104-0.437)</td>
<td>0.337 (0.144-0.530)</td>
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*Cut-off was estimated by Youden index with equal weighted sensitivity and specificity in ROC analysis (non validated tests were not included in analysis)
the process of atherogenesis in microcirculation begins. Second, several studies have indicated that central adipose tissue contributes to renin-angiotensin-aldosterone system (RAAS) hormone disruption, i.e. increment in circulating levels of renin, angiotensinogen, angiotensin-converting enzyme, aldosterone, and angiotensin II\(^{26}\). Angiotensin II has been recognized as an important factor in raising intraglomerular pressure in the kidney and induction of intrarenal inflammatory cytokines and growth factors which contribute to development and progression of hypertension. There also are data indicating that angiotensin II contributes to cytokine production in visceral adipocytes, thus creating a *circulus vitiosus* in microvascular endothelial damage\(^{24}\). Dyslipidemia, defined as high total and low-density lipoprotein cholesterol and low high-density lipoprotein cholesterol with race and gender defined cut-offs, is a well-documented phenomenon in visceral obesity, the role of which is unavoidable in vascular atherogenesis and development of microvascular complications\(^{41}\). As discussed above, visceral fat is definitely involved in the pathogenesis of cardiometabolic risk factors and thus search for the best noninvasive measurements of visceral fat and their ability to predict cardiometabolic risk factors, development of diabetes and its chronic complications has recently come in the focus of interest worldwide. The majority of studies performed in healthy subjects and diabetic population have found that WC, WHR and WHtR in particular are correlated with the mentioned outcomes\(^3,6,7,13,15,39,42-45\). We did not find any significance in retinopathy prediction among analyzed indices, and the possible explanation is that it is a complication that involves more factors than others, since the data published so far are most controversial of all\(^{17,18}\). The possibility of anthropometric measurements to predict peripheral neuropathy has been poorly investigated, but the data published to date might be in concordance with our results, although they only indicate that these aspects of central obesity are associated with diabetic neuropathy\(^{49}\). Interestingly, similarly to our study results, Silva *et al.*\(^{41}\) evaluated the precision of different anthropometric measures of abdominal adiposity in non-diabetic non-dialyzed patients with CKD. They assessed 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; they also explored their association with insulin resistance (IR) using homeostasis model assessment for IR index (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.

In conclusion, our study demonstrated that WHtR and WC might be used as simple and noninvasive methods for detection of CKD in obese T2DM population and we even may suggest using these indices as simple and inexpensive methods in epidemiological studies. On the other hand, WHR could correctly identify all patients without peripheral neuropathy with 100% specificity. However, there is a limitation regarding this result considering the high prevalence of the disease in our study population. It is important to emphasize that our study had several other limitations, i.e. we did not make adjustments of the analyzed indices for the possible confounding factors that might contribute to development of microvascular complications, such as age, gender, diabetes duration or glycemic control, and we strongly suggest additional studies to determine whether there is true association between obesity indices and microvascular complications in T2DM patients and which of them could be used as a simple method for detection of a particular microvascular complication.

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Obesity and microvascular complications in diabetes


Sažetak
UPOTREBA ANTROPOMETRIJSKIH OBLJEŽJA DEBLJINE U PROCJени MIKROVASKULARNIH KOMPLIKACIJA U PRETILIH BOLESNIKA S TIPOM 2 ŠEĆERNE BOLESTI

T. Bulum, K. Blaslov i L. Duvnjak

Opseg struka (OS), omjer opsega struka i bokova (OSB) i omjer opsega struka i visine (OSV) su bolji predskazatelji razvoja šećerne bolesti tipa 2 (ŠB2) nego široko upotrebljavani indeks tjelesne mase (ITM). Svrha ovoga istraživanja je bila istražiti učinkovitost ITM, OS, OSB i OSV u procjeni učestalosti mikrovaskularnih komplikacija (kronična bubrežna bolest (KBB), retinopatija i periferna neuropatija) u pretilih (ITM ≥35 kg/m2) bolesnika sa ŠB2. Ova presječna studija je uključila 125 bolesnika oba spola sa ŠB2. Dijagnostička vrijednost testova je procijenjena krivuljama ROC (engl. Receiver Operator Characteristic); područje ispod krivulje (AUC) je izračunato za svaki antropometrijski parametar i rizični čimbenik (mikrovaskularne komplikacije). AUC za OSV je bio značajno viši nego AUC za OS za KBB. Optimalna granična vrijednost za OSV je bila >0,593, a za OS >112 cm za KBB. AUC za perifernu neuropatiju je bio značajan samo za OSB i optimalna granična vrijednost za OSB je bila >1,409, uz nisku osjetljivost i visoku specifičnost. Rezultati našega istraživanja ukazuju na to da OSV, OS i OSB mogu biti jednostavna i neinvazivna metoda procjene učestalosti KBB i perifernih neuropatija u pretilih bolesnika sa ŠB2.

Ključne riječi: Diabetes mellitus, tip 2; Pretelost – komplikacije; Struk, opseg; Struk-visina, odnos; Renalna insuficijencija, kronična; Dijabetička neuropatija; Dijabetička retinopatija