Superior role of waist circumference to body-mass index in the prediction of cardiometabolic risk in dyslipidaemic patients

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Running title: Predictive role of waist circumference in dyslipidaemia.

Summary

Background: Coronary risk evaluation by conventional factors (age, gender, smoking, blood pressure and cholesterol) may further be specified by facets of the metabolic syndrome, namely insulin resistance, hypertriglyceridaemia and obesity. Although obesity is usually defined as elevated body mass index (BMI), recent data indicate a superior role of waist circumference or hypertriglyceridaemic waist (HTGW) over BMI in the assessment of cardiometabolic risk. In dyslipidaemic patients, the specific contributions of risky waist, HTGW or BMI have not been evaluated as yet.

Methods: 686 dyslipidaemic subjects (322 males and 364 females) were enrolled into a cross-sectional study. In each subject basic antropometry (i.e. waist circumference, HTGW, BMI) and laboratory parameters of lipid profile and insulin resistance were determined. Cardiometabolic risk was given by fulfilling the criteria (harmonized definition) of metabolic syndrome. The significance of risky waist, HTGW and BMI were assessed by comparing the respective predictive values for the presence of metabolic syndrome.

Results: Dyslipidaemic patients with risky waist, HTGW or high BMI have a more atherogenic lipid profile and higher insulin resistance compared to those without risky waist, HTGW or high BMI. Risky waist is stronger predictor of metabolic syndrome (PPV 66%, NPV 90%) and thus poses a greater cardiometabolic risk than higher BMI *per se* does (PPV 42%, NPV 97%). The contribution of triglycerides (*i.e.* HTGW) to these predictive values is marginal (PPV 66%, NPV 92%).

Conclusions: The present results highlight the superior role of waist circumference as a screening tool over BMI for the evaluation of cardiometabolic risk in dyslipidaemic subjects.

HTGW brings little additional benefit in risk stratification. Lower BMI proved to be optimal for identifying the subjects with inferior risk.

Key words: waist circumference, dyslipidemia, hypertriglyceridaemic waist, body mass index

Introduction

The metabolic syndrome (visceral obesity, dyslipidaemia, hyperglycaemia, and high normal blood pressure *i.e*. blood pressure over 130/85 mmHg) has become one of the major public-health challenges worldwide (Alberti *et al.* 2005). The ultimate importance of metabolic syndrome is that it helps identify individuals at high risk of both type 2 diabetes and cardiovascular disease. The relationship to cardiovascular diseases is important mainly because more than one half of patients who die suddenly of cardiovascular disease have no previously recognized symptoms (Tankó *et al.* 2005). In the primary care, fast and cost-effective screening indicators of cardiovascular risk are essential that could facilitate timely referral of those who would benefit the most from adequate preventive programmes.

Obesity is usually defined as elevated body mass index (BMI). Although being practical, the consideration of total body mass completely ignores possible variation in body composition. Waist circumference reflects the proportion of body fat more accurately than BMI does. Central (abdominal) obesity, as assessed by waist circumference, is a fundamental component of fully expressed metabolic syndrome and may play a major role in its early development (Alberti *et al.* 2005). Waist circumference *per se*, however, cannot discriminate low-risk subcutaneous fat from visceral adiposity associated with insulin resistance – the underlying cause of metabolic syndrome. When combined with at-risk triglycerides (TG), at-risk waist

circumference correlates with the atherogenic triad of hyperinsulinaemia, elevated concentrations of apolipoprotein B and small dense low-density lipoprotein cholesterol (LDL-C) particles. The concurrence of risky waist and hypertriglyceridaemia, known as hypertriglyceridaemic-waist (HTGW), has thus been proposed as a surrogate marker of visceral obesity and increased cardiovascular risk (Lemieux *et al.* 2000). Lemieux *et al.* were the first to recognize that hypertriglyceridemia together with HTGW is associated with increased cardiovascular disease risk and is the central component of metabolic syndrome (Lemieux *et al.* 2000). In particular, the HTGW is associated with the atherogenic triad of hyperinsulinemia, elevated concentrations of apolipoprotein B and small dense low-density lipoprotein cholesterol (LDL-C) particles. Therefore, the HTGW phenotype could be used as a simple and inexpensive screening tool to identify people at increased risk of metabolic syndrome – both adults (Chen *et al.* 2016) and adolescents (Conceicao-Machado *et al.* 2013) – and insulin resistance (Barreiro-Ribeiro *et al.* 2016).

The definition of metabolic syndrome, depending on the presence of at least three out of five markers, was proposed by many expert groups until a harmonized definition of metabolic syndrome was accepted (Alberti *et al*. 2009). This definition is also supported by the ESC/EAS guidelines for the management of dyslipidemias (Reiner *et al*. 2011).

In the present study we aimed at evaluating the specific contributions of elevated BMI, risky waist and HTGW to cardiometabolic risk prediction in a group of asymptomatic dyslipidaemic patients.

Methods

Study design and subjects

The study was carried out as a cross-sectional study on asymptomatic dyslipidemic subjects. 685 patients (319 men and 366 women) of the Lipid Center at the University Hospital Olomouc who came for their first visit because of hyperlipidemia (*i.e.* total cholesterol, TC ≥ 5 mmol/l and/or TG ≥ 1.7 mmol/l) between January 2005 and December 2016 were enrolled in the study. Detailed medical history was taken and physical examination performed. All subjects were tested for secondary hyperlipidaemia, particularly for the presence of diabetes mellitus, hypothyroidism and hepatic or renal failure. Exclusion criteria were as follows: lipid-lowering therapy within the previous six weeks, the presence of diabetes mellitus or other secondary hyperlipidaemia, acute infection or trauma, acute cardiovascular event within the last three months and chronic heart failure categorized as NYHA III or IV.

The study was reviewed and approved by the Institutional Ethics Committee of the Palacky University Medical Faculty (in accordance with the Helsinki Declaration as revised in 2013) and University Hospital in Olomouc and informed consent was obtained from all participants.

Anthropometric and laboratory measurements

BMI was determined as body weight / body height2 (kg/m2). Waist circumference was measured in the standing position, at the middle point between the anterior iliac crest and the lower border of the ribs. Waist circumference ≥ 90 cm in males and ≥ 85 cm in females was considered as risky waist. The HTGW phenotype was defined as risky waist and TG ≥ 2.0 mmol/l in males and risky waist and TG ≥ 1.5 mmol/l in females (Arsenault *et al*. 2010), the "risky waist" as waist ≥ 90 cm in men and waist ≥ 85 cm in women. The BMI, WC, systolic and diastolic blood pressure were determined. The auscultatory method of blood pressure measurement with a properly calibrated and validated mercury sphygmomanometer was used.

Patients treated with antihypertensive drugs or with systolic blood pressure ≥ 140 or diastolic blood pressure ≥ 90 mmHg were assumed to be hypertensive.

For a diagnosis of metabolic syndrome (MS) were used a harmonized definition published by Alberti et al with values of WC suggested by Adult Treatment Panel III. The presence of any three of five risk factors constitutes a diagnosis of MS: elevated WC (>102 cm in men and >88 cm in women), triglycerides 1.7 mmol/l (drug treatment for elevated TG is an alternative indicator – not present in our cohort), elevated blood pressure (systolic ≥ 130 and/or ≥ 85 mm Hg or antihypertensive drug treatment with a history of hypertension), low HDL-C (< 1 mmol/l in men and < 1,3 mmol/l in women), and elevated fasting glucose ≥ 5.6 mmol/l (antidiabetic pharmacotherapy, as an alternative indicator, was absent in our cohort) (Alberti *et al*. 2009).

Biochemical analyses

Venous blood samples were drawn in the morning after a 12-h fast. After centrifugation, the serum was used for other analyses. Total cholesterol (TC), TG and HDL-C were determined enzymatically on a COBAS c8000 analyzer (Roche, Basel, Switzerland). Total cholesterol (TC) concentrations were measured by enzymatic method CHOD-POD, standardized according to Abell-Kendall and ID/MS (set CHOL2, Roche Diagnostics GmbH, Mannheim, Germany). TG results were obtained by enzymatic method GPO-POD, standardized according to ID/MS (set TRIGL, Roche Diagnostics GmbH, Mannheim, Germany). HDLc was measured by enzymatic colorimetric test, standardized according to CDC reference method (set HDLC3, Diagnostics GmbH, Mannheim, Germany). LDL-C levels were calculated according to Friedewald formula. AIP (atherogenic index of plasma) was calculated as a log (TG/HDL-C) (Dobiášová and Frohlich 2001) and non-HDL-C as TC – HDL-C. Concentrations of apolipoprotein B (apoB) was determined

immunoturbidimetrically according to IFCC reference standards on COBASc8000 analyzer (sets APOBT and APOAT, all Roche Diagnostics GmbH, Mannheim, Germany). Glycaemia was determined using the enzyme-based Glucose hexokinase kit, standardized according to ID/MS (set GLUC3, Roche Diagnostics GmbH, Mannheim, Germany). All these assays were performed in a COBAS c8000 biochemical analyzer from Roche. Insulin was determined using Insulin IRMA kit (Beckman Coulter Inc, Indianapolis, USA) The result obtained were then used for calculation of HOMA-IR (homeostasis model assessment: fasting glycaemia*fasting insulin/22.5) (Matthews *et al*. 1985). C-peptide was determined using the commercially available C-peptide IRMA kit (Beckman Coulter Inc, Indianapolis, USA).

Statistical analyses

Independent t-test for two samples was used to compare patients with vs. without risky waist, HTGW or higher BMI. Chi square test and contingency tables were used to calculate the predictive values of risky waist, HTGW and BMI for the presence of metabolic syndrome. Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 23.0 (Armonk, NY: IBM Corp.). Probability values of $p < 0.05$ were considered statistically significant.

Results

To demonstrate the impact of risky waist, HTGW and obesity (i.e. elevated BMI > 25 kg/m2) on lipid profile and parameters of insulin resistance, the entire cohort was divided into the respective subgroups based on the presence or absence of given characteristics (Tab. 1-3). With the exception of LDL-C, the subgroups significantly differed in all studied laboratory indicators of cardiometabolic risk. All three phenotypes (i.e. risky waist, HTGW and elevated

BMI) were markedly associated with higher TC, TG, non-HDL, apo B, AIP, lower HDL-C and higher glucose, insulin, C-peptide and HOMA-IR, suggesting that risky waist, HTGW and elevated BMI are of comparably high prognostic value in dyslipidaemic patients. The sensitivities, specificities, and (negative and positive) predictive values of the three phenotypes for the prediction of metabolic syndrome are summarized in Tab. 4. The results indicate that waist-circumference-based phenotypes are better predictors of metabolic syndrome (i.e. have higher PPV) than elevated BMI per se. On the other hand, lower BMI proved to be optimal for identifying the subjects with low risk, since elevated BMI had the highest NPV.

Multivariable analysis was performed using the Logistic regression forward-stepwise method for prediction of Hypertriglyceridemic waist (HTGW). Independent predictors were: age, TC, HDL-C, Apo B, fasting glucose, insulin, HOMA-R, C peptide and BMI. The logistic regression revealed five statistical significant predictors: age, TC, HDL-C, C-peptide and BMI. An incraese of the age, TC, C-peptide and BMI means an increase of the odds of HTGW. An increase of the predictor HDL means an decrease of the odds of HTGW (Table 5).

Discussion

In our study, 67% of subjects with HTGW phenotype also met criteria of metabolic syndrome, whereas in a Canadian study 82,7 % of man having he HTGW also met the criteria of metabolic syndrome (Blackburn *et al*. 2009). The studied population in Canada had a higher incidence of metabolic syndrome (59,2 %) and HTGW (51,1 %) in comparison with our patients (prevalence of metabolic syndrome 25%, prevalence of HTGW 30%) and that is why more patients with HTGW in their study met also criteria of metabolic syndrome. Our

data are much closer to our previous study, where 69 % of men and 77,2 % of women also met criteria of metabolic syndrome (Vaverkova *et al*. 2015)[13]. Lower incidence of metabolic syndrome in our study in comparison to overall population of the Czech Republic can be explained by excluding patients with diabetes mellitus and including patients with familiar hyperlipidemia.

Tankó et al. studied a population of postmenopausal women and compared the significance of HTGW and criteria of metabolic syndrome in ability to predict fatal cardiovascular events. They came to conclusion that the combined presence of an enlarged waist and elevated triglycerides may be the best indicator of cardiovascular risk in postmenopausal women. Other components of metabolic syndrome add little medical value (Tankó *et al*. 2005). In concordance with this study, we have proved, that both HTGW and just larger waist circumference (risky waist) can predict the presence of metabolic syndrome and are better for prediction than higher BMI.

Although multiple risk factors are included in the definition of metabolic syndrome, the concept of metabolic syndrome stems from insulin resistance and abdominal obesity. However, obesity is remarkably heterogeneous. Some very obese patients have a fairly normal metabolic risk profile, despite their obesity. On the other hand, some moderately overweight individuals have a whole cluster of atherogenic and diabetogenic metabolic abnormalities. The recent concept of "metabolically healthy obesity" refers to the subgroup of obese subjects who lack high-risk laboratory pattern such as dyslipidaemia and insulin resistance. These individuals demonstrate less visceral adipose tissue and smaller adipocytes conferring them a certain of level of cardiovascular protection relative to their "metabolically unhealthy" counterparts. That is why patients with HTGW show higher risk of incident diabetes than subjects with normal waist circumference and normal TAG level (Han *et al*. 2014). Therefore, it is necessarily to distinguish "metabolically healthy obese" from those at

high risk of developing cardiovascular and metabolic complications. According to above mentioned studies, measuring waist circumference alone, does not help enough to do this differentiation. The combination of waist circumference together with elevated triglycerides (HTGW phenotype) can help to identify men at risk better than waist circumference alone. Yu et al. suggested that the identification of subjects with the HTGW phenotype improves the selection of subjects at high risk of metabolic disturbances, insulin resistance and subsequent cardiovascular disease (Yu *et al*. 2010).

In agreement with these studies, our subjects with HTGW had an atherogenic lipid profile with increased TG, non-HDL, apo B, AIP and lower HDL-C, but without significant changes in LDL-C. It is also in conformity with our previous study (Vaverkova *et al*. 2015) and other studies (Conceição-Machado *et al*. 2013). Moreover, patients with HTGW have increased markers of insulin resistance, elevated blood pressure, proinflammatory markers and prothrombotic changes with impaired fibrinolysis in comparison with those without HTGW as confirmed in our previous study (Vaverkova *et al*. 2015). In our study, HTGW had a higher positive predictive value (66 %) in predicting metabolic syndrome than BMI itself (42 %). Our results also demonstrate that HTGW is associated with a proatherogenic lipid profile and presence of insulin resistance, similarly to individuals meeting the harmonized definition of metabolic syndrome. Thus, is not surprising that in multiple prospective studies HTGW has been shown to be associated with an increased risk of developing cardiovascular disease, e.g. assessed by Framingham score (Poirier *et al*. 2015), type 2 diabetes (Han *et al*. 2014) and insulin resistance (Barreiro-Ribbeiro *et al*. 2016).

On the other hand, this concept has been questioned in our study and also in studies questioning the concept of "metabolically healthy obesity" (Eckel *et al.* 2018). According to our study, the contribution of triglycerides (*i.e.* HTGW) to predictive values of metabolic syndrome is marginal (PPV 66%, NPV 92%). Our study favors measuring of WC and shows

its superior role to body-mass index. We did not confirm significant supplementary value of measuring TG together with WC (*i.e.* HTGW) in prediction of metabolic syndrome. Also Eckel showed, that obesity remains a risk factor for cardiovascular disease and large proportion of metabolically healthy participants (without dyslipidaemia) converted to and unhealthy phenotype over time (Eckel *et al*. 2018)

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Conclusions

Our results stress the importance of measuring waist circumference to identify patients in danger of metabolic syndrome. We suggest that waist circumference may be as discriminant as the harmonised definition of metabolic syndrome and could be used as an initial screening approach to identify individuals with deteriorated cardiometabolic risk markers. This might also offer advantages in terms of estimating future risk of manifest cardiovascular diseases.

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Table 1: Physical characteristics, lipid profile and markers of insulin resistance. Comparison between groups with/without HTGW using independent t-test for two samples.

Parameter (unit)	Hypertriglyceridemic waist (HTGW)										p-value for trend
	Group 1, with HTGW (n = 202)					Group 2, without HTGW (n = 483)					
	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	
Age (years)	49.4	11.8	51.0	20.0	79.0	43.5	15.1	43.0	11.0	82.0	<0.0001
TC (mmol/l)	7.32	2.44	6.85	3.67	27.9	6.10	1.62	6.00	2.19	23.6	<0.0001
TG (mmol/l)	5.31	5.27	3.51	2.01	39.6	1.65	1.93	1.35	0.29	27.2	<0.0001
AIP	0.57	0.34	0.50	-0.01	1.74	-0.05	0.30	-0.06	-0.88	1.70	<0.0001
nonHDL-C (mmol/l)	6.14	2.32	5.72	2.63	23.7	4.51	1.63	4.39	0.81	22.1	<0.0001
HDL-C (mmol/l)	1.18	0.41	1.11	0.46	4.18	1.59	0.44	1.53	0.35	3.51	<0.0001
LDL-C (mmol/l)	4.07	2.06	3.79	0.94	20.5	3.78	1.35	3.69	0.50	11.1	0.08
Apo B (g/l)	1.33	0.39	1.29	0.01	3.20	1.12	0.32	1.11	0.22	2.46	<0.0001
Fasting glucose (mmol/l)	5.50	1.07	5.40	3.80	12.6	5.00	0.69	4.90	3.10	9.00	<0.0001
Insulin (mIU/l)	12.1	7.37	10.9	1.50	71.2	7.59	4.23	6.90	0.70	41.4	<0.0001
HOMA-R	2.98	2.56	2.58	0.00	29.8	1.71	1.06	1.52	0.16	9.20	<0.0001
C-peptide (pmol/l)	1027	413	969	139	3042	685	291	629	136	1938	<0.0001
BMI (kg/m^2)	29.6	3.50	29.0	22.8	43.6	24.8	3.90	24.2	16.6	48.0	<0.0001

Table 2: Physical characteristics, lipid profile and markers of insulin resistance. Comparison between groups with/without risky waist using independent t-test for two samples.

Parameter (unit)	Risky waist										p-value for trend
	Group 3, risky waist present (n = 185)					Group 4, risky waist not present (n = 501)					
	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	
Age (years)	51.5	11.5	54.0	20.0	81.0	43.0	14.7	42.0	11.0	82.0	<0.0001
TC (mmol/l)	6.97	2.42	6.62	3.51	27.9	6.27	1.76	6.15	2.19	23.6	0.0004
TG (mmol/l)	4.04	5.21	2.46	0.52	39.6	2.24	2.79	1.52	0.29	27.2	<0.0001
AIP	0.35	0.41	0.29	-0.52	1.74	0.05	0.40	0.00	-0.88	1.70	<0.0001
nonHDL-C (mmol/l)	5.66	2.27	5.28	2.14	23.7	4.75	1.83	4.53	0.81	22.1	<0.0001
HDL-C (mmol/l)	1.32	0.45	1.26	0.46	4.18	1.52	0.47	1.47	0.35	3.51	<0.0001
LDL-C (mmol/l)	4.05	1.89	3.94	0.94	20.5	3.79	1.46	3.64	0.50	13.8	0.055
Apo B (g/l)	1.28	0.36	1.26	0.51	2.97	1.15	0.35	1.12	0.01	3.20	<0.0001
Fasting glucose (mmol/l)	5.50	1.00	5.39	3.70	12.2	5.02	0.75	4.90	3.10	12.6	<0.0001
Insulin (mIU/l)	12.2	7.86	10.6	2.70	71.2	7.73	4.15	7.00	0.70	26.7	<0.0001
HOMA-R	3.04	2.72	2.47	0.00	29.8	1.75	1.04	1.57	0.16	7.59	<0.0001
C-peptide (pmol/l)	1024	438	936	139	3042	701	295	642	136	2059	<0.0001

Table 3: Physical characteristics, lipid profile and markers of insulin resistance. Comparison between groups with/without body mass index exceeding 25 kg/m^2 using independent t-test for two samples.

Parameter (unit)	Body mass index (BMI)										p-value for trend
	Group 5, BMI > 25 kg/m^2 (n = 382)					Group 6, BMI < 25 kg/m^2 (n = 303)					
	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	
Age (years)	48.6	12.4	49.0	12.0	81.0	41.0	15.7	39.0	11.0	82.0	<0.0001
TC (mmol/l)	6.73	2.26	6.40	2.23	27.9	6.13	1.50	6.08	2.19	10.7	0.0001
TG (mmol/l)	3.57	4.47	2.20	0.50	39.6	1.67	1.90	1.29	0.29	19.6	<0.0001
AIP	0.30	0.42	0.23	-0.57	1.74	-0.08	0.33	-0.11	-0.88	1.70	<0.0001
nonHDL-C (mmol/l)	5.42	2.22	5.04	0.89	23.7	4.46	1.53	4.33	0.81	9.45	<0.0001
HDL-C (mmol/l)	1.31	0.41	1.26	0.46	4.18	1.67	0.47	1.62	0.35	3.51	<0.0001
LDL-C (mmol/l)	3.97	1.72	3.78	0.62	20.5	3.73	1.40	3.64	0.50	11.1	0.049
Apo B (g/l)	1.24	0.37	1.20	0.01	3.20	1.12	0.33	1.10	0.25	2.46	<0.0001
Fasting glucose (mmol/l)	5.35	0.97	5.20	3.40	12.6	4.89	0.59	4.87	3.10	7.80	<0.0001
Insulin (mIU/l)	10.6	6.65	9.20	0.70	71.2	6.84	3.27	6.40	0.80	19.4	<0.0001
HOMA-R	2.55	2.12	2.18	0.00	29.8	1.50	0.77	1.38	0.19	4.74	<0.0001
C-peptide (pmol/l)	919	390	861	139	3042	616	246	556	136	1609	<0,0001

Table 4: Prediction of metabolic syndrome in the entire cohort using HTGW, BMI > 25 kg/m^2 and risky waist

HTGW			
parameter	males	females	both sexes
sensitivity, % (95% CI)	83 (74 - 90)	72 (61 - 82)	78 (71 - 84)
specificity, % (95% CI)	79 (73 - 84)	93 (90 - 96)	87 (84 - 90)
PPV, % (95% CI)	62 (54 - 70)	72 (61 - 82)	66 (59 - 72)
NPV, % (95% CI)	92 (87 - 95)	93 (89 - 95)	92 (90 - 95)
OR (95% CI)	18 (10 - 34)	33 (17 - 65)	23 (15 - 36)
BMI > 25 kg/m^2			
parameter	males	females	both sexes
sensitivity, % (95% CI)	97 (91-99)	93 (85-97)	95 (91-98)
specificity, % (95% CI)	45 (38-52)	67 (62-73)	58 (53-62)
PPV, % (95% CI)	42 (36-49)	43 (35-51)	42 (38-48)
NPV, % (95% CI)	97 (92-99)	98 (94-99)	97 (95-99)
OR (95% CI)	25 (8-81)	29 (11-75)	28 (13-57)
risky waist			
parameter	males	females	both sexes
sensitivity, % (95% CI)	59 (48-69)	87 (77-94)	71 (64-78)
specificity, % (95% CI)	92 (88-95)	84 (80-88)	88 (85-90)
PPV, % (95% CI)	76 (64-85)	60 (50-69)	66 (59-73)
NPV, % (95% CI)	84 (79-89)	96 (93-98)	90 (87-93)
OR (95% CI)	17 (9-31)	36 (17-74)	18 (12-27)

Table 5: Multivariate logistic regression for prediction of HTGW

Predictors	OR	95% CI for OR		p-value
Age (y.)	1,021	1,003	1,040	0,023
TC (mmol/l)	1,582	1,360	1,840	<0,0001
HDL-C (mmol/l)	0,057	0,027	0,120	<0,0001
C-peptide (pmol/l)	1,001	1,000	1,002	0,009
BMI (kg/m^2)	1,304	1,208	1,407	<0,0001

OR – odds ratio