Ratio of Waist-to-Calf Circumference and Carotid Atherosclerosis in Korean Patients With Type 2 Diabetes

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OBJECTIVE—To investigate whether waist circumference (WC), calf circumference (CC), and waist-to-calf ratio (WCR) are associated with carotid atherosclerosis in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS—This was an observational study performed in 3,694 Korean patients with type 2 diabetes. Anthropometric measures and carotid ultrasound were performed on each subject. Carotid atherosclerosis was defined as having a clearly isolated focal plaque or mean carotid intima-media thickness (CIMT) ≥1.1 mm.

RESULTS—CIMT and the frequency of carotid atherosclerosis were higher with increasing WC quartiles and decreasing CC quartiles. There was an augmentative effect of CC and WC on the frequency of carotid atherosclerosis, which was dramatically higher in both the highest WC quartile and lowest CC quartile. However, except for the relationship between the quartile of CC with the frequency of carotid atherosclerosis in men, those associations disappeared after adjusting for potential confounders. In contrast, WCR was significantly related to CIMT (only in women) and carotid atherosclerosis, even after adjustment (adjusted odds ratio for carotid atherosclerosis for the highest quartile of WCR compared with the lowest quartile being 1.178 [95% CI 1.026–1.353] and 1.276 [1.053–1.545] in men and women, respectively).

CONCLUSIONS—A low CC and high WC seems to be associated with a carotid atherosclerotic burden in Korean diabetic patients. In particular, compared with each circumference, WCR is independently associated with carotid atherosclerosis. However, the cross-sectional nature of the study limits conclusions regarding the direction or causality. Further longitudinal study is warranted in this and other ethnic groups.

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Obesity is an important risk factor for a broad spectrum of cardiometabolic disturbance, including hypertension, dyslipidemia, glucose intolerance, and even cardiovascular disease. In particular, abdominal obesity is more closely associated with risk of disease than general obesity. Waist circumference (WC) or waist-to-hip ratio (WHR), as indicators of abdominal obesity, may be better predictors of the risk of disease than the BMI, an indicator of general obesity (1,2). In contrast, leg muscle mass and peripheral adiposity might offer protection from cardiometabolic diseases. Larger hip or thigh circumferences seem to be associated with a lower risk of type 2 diabetes and a decreased risk of developing coronary artery disease and premature death (3–5). Recent evidence that calf circumference (CC) is also associated with mortality or cardiovascular risk is growing (6–8).

Considering that the effects of abdominal fat and leg lean mass on the risk of diseases are diametrically opposed, indices that assess both masses simultaneously may be better at evaluating the risk for cardiometabolic disease compared with indices that separately estimate either abdominal fat or leg lean mass. In that sense, the WHR or waist-to-thigh ratio (WTR) may be better than other simple anthropometric indices, and some studies have suggested that both indices are more sensitive than WC at estimating cardiometabolic risk (9–11). However, it is not practical to use those two indices in a busy clinical practice. In particular, the WHR may mask the accumulation of abdominal fat if the hip circumference is also increased (12).

In this study, we measured WC and CC to evaluate abdominal fat and leg lean mass and used the waist-to-calf ratio (WCR) as an index to assess the disproportion between abdominal fat and leg muscle mass. The aim of the current study was to investigate whether WC, CC, and WCR are associated with carotid atherosclerosis in a large cohort of patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

—As a part of the Seoul Metabolic Syndrome cohort, 9,532 diabetic patients were consecutively enrolled at the Huh's Diabetes Center in Seoul, Korea. We included the 2,116 men and 1,578 women who had no antiglutamic acid decarboxylase antibody and whose fasting C-peptide was >0.23 mmol/L, gave complete information on all covariates, and underwent both a short insulin tolerance test (SITT) and a carotid ultrasound. The positivity for antiglutamic acid decarboxylase antibody and low fasting C-peptide level might mean type 1 diabetes rather than type 2 diabetes. All participants signed consent forms, and the ethics committee of the Yonsei University College of Medicine approved the study.

Weight and height were measured for all subjects while they were wearing light clothing and not wearing shoes. WC was measured at the midpoint between the

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lower ribs and the iliac crest at the end of normal expiration. CC was measured at the point of the largest circumference of the calf. WCR was calculated as the ratio of the WC and CC. All the participants underwent measurements for fasting plasma glucose, HbA_{1c}, C-peptide, insulin, total cholesterol, LDL cholesterol, HDL cholesterol, and triglyceride and completed a questionnaire concerning smoking and drinking status and cardiovascular or other diseases.

Metabolic syndrome was defined according to the National Cholesterol Education Program Adult Treatment Panel III, with a modification for the cutoff of WC (13). Individuals having three or more of the following criteria were defined as having metabolic syndrome: *1*) abdominal obesity by WC (>90 cm in men; >80 cm in women), 2) elevated fasting blood glucose (≥5.6 mmol/L), 3) high blood pressure (≥130/85 mmHg) or the use of antihypertensive medications, *4*) hypertriglyceridemia (≥1.69 mmol/L) or specific treatment for lipid abnormality, and 5) low HDL cholesterol (<1.04 mmol/L in men; <1.29 mmol/L in women). All patients in the current study were defined to fulfill the criterion for hyperglycemia. Vascular disease was defined as having a history of stroke, including transient ischemic attack, or coronary artery disease, such as angina and myocardial infarction, or peripheral arterial disease.

SITT

Insulin sensitivity was assessed by SITT as a rate constant for plasma glucose disappearance (*Kitt*: %/min) (14). Briefly, the SITT was carried out at 8:00 A.M. after an overnight fast. Venous blood samples were collected at 0, 3, 6, 9, 12, and 15 min after an intravenous bolus injection of prediluted regular insulin (Humulin, Eli Lilly, Indianapolis, IN) at a dose of 0.1 units/kg. Plasma glucose concentrations were determined immediately after sampling using Beckman glucose analyzer II (Beckman Instruments, Fullerton, CA), and then the *Kitt* was calculated from the slope of the fall in log-transformed plasma glucose between 3 and 15 min. Immediately after the test, 100 mL of 20% dextrose solution was administered intravenously to avoid potential hypoglycemia.

Carotid ultrasound

The bilateral common carotid arteries were scanned using a high-resolution ultrasonographic system (LOGIQ 7, GE, Milwaukee, WI) with a 10 MHz linear transducer. Scanning was performed at the mid and distal common carotid artery by a lateral longitudinal projection. The carotid intima-media thickness (CIMT) was measured at three points on the far wall of the mid and distal common carotid artery, 1 cm proximal to the dilatation of the carotid bulb, and the mean value of six measurements from the right and left common carotid arteries were used. The CIMT was defined as the distance between the media-adventitia interface and the lumen-intima interface. Carotid plaque was defined as a distinct area of hyperechogenicity and/or protrusion into the lumen of the vessel with at least 50% greater thickness than the surrounding area. Carotid atherosclerosis was defined as having a focal plaque or diffuse thickening of the carotid wall (CIMT ≥1.1 mm).

Statistical analysis

Continuous variables were reported as mean ± SD, and categorical factors were reported as percentages. All the continuous variables were normally distributed with homogenous variances between groups except for triglyceride, which was log transformed before entering into the model. Quartiles of various anthropometric indices (WC, CC, or WCR) were determined after stratifying by sex. The intergroup comparisons were performed using a one-way ANOVA test followed by a Scheffé post hoc test. In particular, comparisons of the prevalence of carotid atherosclerosis were made by means of a χ^2 test. To estimate the odds ratio (OR) of carotid atherosclerosis in each quartile, logistic regression was performed, and the lowest quartile was used as the reference category. Multivariate-adjusted OR was presented with 95% CIs. For comparisons of CIMT, ANOVA and ANCOVA were used. Three models examining the association of anthropometric indices and CIMT and carotid atherosclerosis were used under different adjustment schemes. The first model adjusted only age. The second model additionally adjusted for duration of diabetes, smoking status, history of vascular diseases, hypoglycemic agents (insulin, sulfonylureas, metformin, α-glucosidase inhibitors, and thiazolidinediones), antihypertensive treatments (calcium channel blocker, angiotensin receptor blocker, ACE inhibitor, and β-blocker), lipid-lowering agents (statin and fenofibrate), systolic blood pressure, *Kitt*, HDL cholesterol, LDL cholesterol, and log-transformed triglyceride. The third model additionally adjusted for BMI. $P < 0.05$ was considered significant. All statistical analyses were performed using IBM SPSS Statistics (version 19.0; IBM Co., Somers, NY).

RESULTS—Baseline characteristics are shown in Table 1. The mean age was 56.5 ± 10.5 years, and 57.3% of the participants were men. The mean duration of type 2 diabetes was 8.04 ± 7.35 years. Among all participants, 1.1 and 18.3% had a history of vascular disease and carotid atherosclerosis, respectively. In both sexes, participants with a higher quartile of WCR, as compared with those who had a lower quartile of WCR, were older and more obese (both generally and centrally), had longer duration of diabetes, needed more medications (except sulfonylurea in women), had a lower insulin sensitivity (*Kitt*), and were likely to have more adverse metabolic profiles (Supplementary Table 1).

Either the highest quartile of WC or the lowest quartile of CC was associated with the higher frequency of carotid atherosclerosis compared with the lowest quartile of WC or the highest quartile of CC in both sexes (Fig. 1). It is interesting that there was an opposite but augmentative association of CC and WC with carotid atherosclerosis, which was 0.0 and 5.3% in men and women, respectively, in the highest calf quartile and the lowest waist quartile, against 42.9 and 30.0% in the lowest calf quartile and the highest waist quartile.

In both unadjusted and age-adjusted models, there were significant linear associations of the WCR with the CIMT and the frequency of carotid atherosclerosis, with the lowest at a bottom quartile of the WCR (Table 2). After further multivariable adjustments for age, BMI, duration of diabetes, smoking status, history of vascular diseases, hypoglycemic agents, antihypertensive treatments, lipid-lowering agents, systolic blood pressure, *Kitt*, HDL cholesterol, LDL cholesterol, and log-transformed triglyceride, the association of the WCR quartiles with the CIMT remained significant only in women, but the relationship with carotid atherosclerosis remained significant in both sexes. Men and women in the highest quartile of the WCR were 1.178 times (95% CI 1.026–1.353) and 1.276 times (1.053–1.545), respectively, more likely to have carotid atherosclerosis than those in the lowest quartile.

Table 1—*Clinical characteristics of subjects*

	Total	Men	Women
n	3,694	2,116	1,578
Age (years)	56.6 ± 10.5	55.1 ± 10.9	58.6 ± 9.4
Duration of diabetes (years)	8.04 ± 7.35	7.89 ± 7.54	8.25 ± 7.08
Antihyperglycemic agents (%)			
Sulfonylureas	54.4	52.6	56.7
Metformin	40.0	37.7	43.0
α-Glucosidase inhibitors	11.6	11.8	11.3
Thiazolidinediones	10.2	9.9	10.5
Insulin	12.3	10.3	15.0
Hypertension (%)	73.3	72.5	74.3
Antihypertensive treatment (%)	30.8	27.7	35.0
Dyslipidemia (%)	59.4	54.7	65.5
Lipid-lowering treatment (%)	19.5	16.6	23.4
Active smoker (%)	19.9	33.1	2.2
Metabolic syndrome (%)	59.8	55.9	65.0
History of vascular disease (%)	1.1	1.2	0.8
BMI (kg/m^2)	24.5 ± 3.2	24.6 ± 3.0	24.4 ± 3.4
WC (cm)	83.5 ± 8.5	85.9 ± 8.0	80.4 ± 8.3
CC (cm)	34.7 ± 3.1	35.8 ± 2.9	33.2 ± 2.7
Systolic blood pressure (mmHg)	134.5 ± 18.1	132.6 ± 17.2	136.9 ± 18.9
Diastolic blood pressure (mmHg)	85.5 ± 11.4	86.3 ± 11.4	84.4 ± 11.3
Kitt (%/min)	2.04 ± 0.95	2.04 ± 0.96	2.04 ± 0.96
Glucose (mmol/L)	8.60 ± 3.21	8.71 ± 3.22	8.44 ± 3.20
HbA_{1c} (%)	8.24 ± 1.91	8.27 ± 1.97	8.20 ± 1.81
C-peptide (mmol/L)	0.66 ± 0.31	0.67 ± 0.30	0.65 ± 0.32
Total cholesterol (mmol/L)	4.98 ± 1.01	4.86 ± 0.98	5.15 ± 1.02
Triglyceride (mmol/L)	1.58 ± 0.86	1.59 ± 0.88	1.56 ± 0.82
HDL cholesterol (mmol/L)	1.30 ± 0.35	1.25 ± 0.33	1.38 ± 0.35
LDL cholesterol (mmol/L)	2.95 ± 0.88	2.89 ± 0.85	3.06 ± 0.90
CIMT (mm)	0.85 ± 0.18	0.86 ± 0.19	0.83 ± 0.17
Carotid atherosclerosis (%)	18.3	21.2	14.4

Data are means ± SD or %.

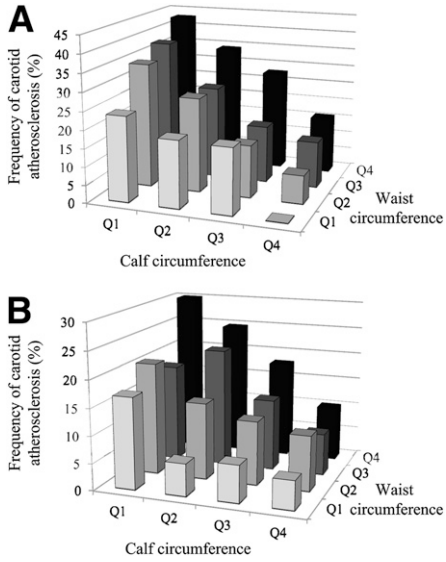

Figure 1—*Multiplicative effect of CC and WC on the frequency of carotid atherosclerosis in men* (A) *and women* (B). *Q, quartile.*

In contrast, quartiles of WC were associated with increasing CIMT, but not with the frequency of carotid atherosclerosis, in both sexes (Supplementary Table 2). There were significant trends with greater CIMT and higher frequency of carotid atherosclerosis associated with decreasing CC quartile in both sexes (Supplementary Table 3). With multivariable adjustments, however, only the association of quartiles of CC with carotid atherosclerosis in men remained significant.

CONCLUSIONS—It is well known that abdominal fat is a causal factor of cardiometabolic diseases, whereas muscle mass plays a protective role in those diseases (1–5). Muscle mass is gradually decreased with age, even if body weight or body fat mass is unchanged or slightly increased. That phenomenon, so-called sarcopenia or sarcopenic obesity, is frequently observed in the elderly as well as young or middle-aged adults with chronic disease. Subjects with a particular phenotype may be more prone to developing metabolic and cardiovascular diseases than those with the opposite phenotype or those with high abdominal fat mass alone (15,16). Therefore, both body fat (especially abdominal) and muscle mass need to be considered when assessing the risk for those diseases. The current study compared WC, CC, and WCR to carotid atherosclerotic burden. We demonstrated that CC was negatively and WC was positively associated with carotid atherosclerotic burden. Furthermore, the WCR had the strongest association with carotid atherosclerosis compared with each circumference, and that association was independent of multiple potential confounders.

Computed tomography and magnetic resonance imaging have been considered to be the gold standards for assessing visceral fat and skeletal muscle distributions. Previous studies reported that the ratio of visceral fat to thigh muscle area is a good parameter that reflects insulin resistance and is an indicator for the risk of metabolic syndrome (17,18). However, the clinical application of those imaging devices is limited because of the time required, cost, accessibility, and risk of radiation exposure. The simplest and most widely used method for assessing visceral fat accumulation and assuming the disproportion between abdominal fat and lean mass is measuring WC and WHR, which are well known as anthropometric parameters to reflect cardiovascular risks (1,2,19,20). However, recent studies demonstrate that measuring WC alone may be insufficient to assess the visceral fat amount or predict the cardiometabolic risk (21). Indeed, even subjects with a normal WC are more prone to having carotid atherosclerosis if they have centrally located body fat (22). Also, in the case of WHR, there are a number of problems inherent in the use of a ratio indicator. Because of the equation used to determine that value, both lean and massively obese individuals may end up having the same WHR.

WTR has been proposed as an new alternative index for abdominal obesity and is more strongly associated with cardiovascular and metabolic risk factors than WHR (11,23). However, thigh circumference, a component of WTR, may also be as confounded anatomically as hip circumference. Two different anatomical landmarks have been used to determine the exact location for measuring

Table 2—*Association of CIMT and carotid atherosclerosis with quartiles of WCR*

	Q1	Q2	Q3	Q4	*P* for trend
Men					
n	520	534	536	526	
CIMT (mean ± SE)					
Unadjusted (mm)	0.796 ± 0.007	0.852 ± 0.008*	0.878 ± 0.008*	0.921 ± 0.008*†‡	<0.001
Adjusted (mm)§	0.838 ± 0.008	0.863 ± 0.007*	0.871 ± 0.007*	0.875 ± 0.008*	0.002
Adjusted (mm)‖	0.847 ± 0.008	0.865 ± 0.007	0.869 ± 0.007*	0.865 ± 0.008	0.182
Adjusted (mm)¶	0.849 ± 0.008	0.865 ± 0.007	0.869 ± 0.007	0.863 ± 0.008	0.295
Carotid atherosclerosis					
Unadjusted (%)	12.3	18.4*	22.2*	31.9*†‡	<0.001
Adjusted OR (95% CI)§	1.000	1.240 (0.863–1.782)	1.217 (1.023–1.448)	1.194 (1.061–1.344)	0.002
Adjusted OR (95% CI)‖	1.000	1.144 (0.773–1.691)	1.135 (0.940–1.371)	1.137 (0.994–1.300)	0.082
Adjusted OR (95% CI)¶	1.000	1.181 (0.795–1.753)	1.146 (0.945–1.388)	1.178 (1.026–1.353)	0.028
Women					
n	393	398	390	397	
CIMT (mean ± SE)					
Unadjusted (mm)	0.768 ± 0.008	0.823 ± 0.008*	0.845 ± 0.009*	0.886 ± 0.008*†‡	<0.001
Adjusted (mm)§	0.803 ± 0.008	0.827 ± 0.008	0.841 ± 0.008*	0.852 ± 0.008*†	<0.001
Adjusted (mm)‖	0.812 ± 0.008	0.826 ± 0.008	0.841 ± 0.008*	0.844 ± 0.008*	0.037
Adjusted (mm)¶	0.811 ± 0.009	0.826 ± 0.008	0.841 ± 0.008*	0.844 ± 0.008*	0.045
Carotid atherosclerosis					
Unadjusted (%)	7.9	12.3*	17.4*†	20.2*†	<0.001
Adjusted OR (95% CI)§	1.000	1.378 (0.848–2.237)	1.352 (1.070–1.709)	1.267 (1.078–1.489)	0.002
Adjusted OR (95% CI)‖	1.000	1.135 (0.675–1.908)	1.300 (1.006–1.681)	1.198 (1.002–1.433)	0.048
Adjusted OR (95% CI)¶	1.000	1.251 (0.729–2.147)	1.433 (1.090–1.884)	1.276 (1.053–1.545)	0.003

Q, quartile. Q1 was the lowest quartile. *$P < 0.05$ vs. Q1, †$P < 0.05$ vs. Q2, ‡$P < 0.05$ vs. Q3. §Adjusted for age. ‖Like § and additionally adjusted for duration of diabetes, smoking status, history of vascular diseases, hypoglycemic agents (insulin, sulfonylurea, metformin, α-glucosidase inhibitors, and thiazolidinediones), antihypertensive treatments (calcium channel blocker, angiotensin receptor blocker, ACE inhibitor, and β-blocker), lipid-lowering drugs (statin and fenofibrate), systolic blood pressure, *Kitt*, HDL cholesterol, LDL cholesterol, and triglyceride (log transformed). ¶Like ‖ and additionally adjusted for BMI.

thigh circumference, directly below the gluteal fold and at the midthigh (4,10). Wherever measured, there are substantial errors in every measurement. Moreover, thigh circumference is not convenient to measure in practice because of disrobing and, in particular, measurement of proximal thigh circumference may be uncomfortable for some individuals. In contrast, the measure of CC has several advantages over thigh circumference. It requires only rolling the pants up to the knees. It is more culturally acceptable in many cases and less susceptible to measurement and calculation errors than a measure of thigh circumference. Also, CC is a potential marker of leg muscle mass (24). For this reason, we selected CC as an anthropometric index representing leg lean mass and WCR as an index for assessing the disproportion between abdominal fat and leg muscle mass. Of course, WCR might also be susceptible to measurement and calculation errors by requiring the ratio of two measures as opposed to a single measurement. However, simultaneously measuring both WC and CC could provide more specific information for sarcopenic phenotype compared with either a WC or CC measurement. In our study, WCR had a better correlation with CIMT than WC or CC ($r = 0.242$, $P < 0.001$ vs. $r = 0.079$, $P < 0.001$ or $r = -0.143$, $P < 0.001$ in men; $r = 0.255$, $P < 0.001$ vs. $r = 0.144$, $P < 0.001$ or $r = -0.111$, $P < 0.001$ in women, respectively).

Our analysis demonstrated an opposite and multiplicative relationship of WC and CC with the frequency of carotid atherosclerosis in both sexes, the highest frequency being found in subjects with the highest quartile of WC and the lowest quartile of CC. The independent association with carotid atherosclerosis across quartiles of each index was observed only in the WCR in both sexes and in CC in men. The CIMT was larger with increasing WCR and WC and decreasing CC in both sexes, but except for WCR in women, the association disappeared after adjusting for multiple confounders. The associations with CIMT and atherosclerosis across WHR quartiles were not observed in both sexes, and in the case of WTR, the odds of carotid atherosclerosis across WTR quartiles were lower than WCR quartiles (data not shown). This indicates that WCR may be a better indicator for carotid atherosclerotic burden than other anthropometric indices.

Several limitations of this study should be noted. First, the cross-sectional study design limited conclusions regarding the direction or causality between the anthropometric indices and cardiometabolic risk. Second, our study showed an independent association of WCR with carotid atherosclerosis but did not observe the cardiovascular events and mortality. Also, we could not investigate a degree of physical activity, which could largely affect leg lean mass. Third, the contribution of fat or lean mass distribution to metabolic and cardiovascular diseases may vary among different populations. Accordingly, our results may differ from those in other ethnic groups. Fourth, we did not suggest a definite cutoff value of WCR or CC to screen subjects at higher risk for carotid atherosclerosis. Finally, CC is a surrogate marker of lean mass or peripheral subcutaneous fat. We cannot understand whether the inverse association between carotid atherosclerosis and increasing CC or decreasing WCR is due to a protective effect of either a large amount of lean mass or peripheral subcutaneous fat or both. Thus,

it may warrant further investigation using a longitudinal study design and implementing computed tomography or magnetic resonance imaging to measure the muscle and fat distribution within the calf separately.

This study also has several strengths. This study was performed using a relatively large cohort of type 2 diabetes performed in one institute. In particular, carotid Doppler was performed, and all data collection procedures including anthropometric indices were obtained by one trained study staff. This is the first study investigating the association of WCR, a relatively new measure of abdominal adiposity, and carotid atherosclerosis. It also adds to the growing discussion with regards to the characterization of high-risk phenotypes and the value of anthropometric measurements for clinical risk stratification.

The results of our study suggest that WCR may be superior to each single measure of WC or CC in association with prevalent carotid atherosclerosis. It is speculated that putting on abdominal fat and losing leg muscle might act synergistically, causing carotid atherosclerosis. WCR may be a useful and practical anthropometric index that facilitates the early identification of diabetic subjects with high risk for cardiovascular disease.

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S.-K.K. performed the study design and statistical analysis and wrote the manuscript. Y.J.C. and B.W.H. performed data collection and researched data. C.-S.K. reviewed the manuscript. S.W.P. contributed to the design, performed statistical analysis, and edited the manuscript. E.J.L. and Y.-W.C. provided significant expertise and reviewed the manuscript. K.B.H. provided the conception for the study, contributed to the conduct of the study, and critically reviewed the manuscript.

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