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Sex Differences of Visceral Fat Area and Visceral-to-Subcutaneous Fat Ratio for the Risk of Incident Type 2 Diabetes Mellitus

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Background: This study aimed to determine the optimal cut-off values of visceral fat area (VFA) and visceral-to-subcutaneous fat ratio (VSR) for predicting incident type 2 diabetes mellitus (T2DM).
Methods: A total of 10,882 individuals (6,835 men; 4,047 women) free of T2DM at baseline aged between 30 and 79 years who underwent abdominal computed tomography scan between 2012 and 2013 as a part of routine health check-ups were included and followed. VFA, subcutaneous fat area, and VSR on L3 vertebral level were measured at baseline.
Results: During a median follow-up of 4.8 years, 730 (8.1% for men; 4.3% for women) incident cases of T2DM were identified. Receiver operating characteristic curve analysis showed that the optimal cut-off values of VFA and VSR for predicting incident T2DM were 130.03 cm^2 and 1.08 in men, respectively, and 85.7 cm^2 and 0.48 in women, respectively. Regardless of sex, higher VFA and VSR were significantly associated with a higher risk of incident T2DM. Compared with the lowest quartiles of VFA and VSR, the highest quartiles had adjusted odds ratios of 2.62 (95% confidence interval [CI], 1.73 to 3.97) and 1.55 (95% CI, 1.14 to 2.11) in men, respectively, and 32.49 (95% CI, 7.42 to 142.02) and 11.07 (95% CI, 3.89 to 31.50) in women, respectively.
Conclusion: Higher VFA and VSR at baseline were independent risk factors for the development of T2DM. Sex-specific reference values for visceral fat obesity (VFA ≥130 cm^2 or VSR ≥1.0 in men; VFA ≥85 cm^2 or VSR ≥0.5 in women) are proposed for the prediction of incident T2DM.

Keywords: Diabetes mellitus, type 2; Intra-abdominal fat; Subcutaneous fat; Tomography

INTRODUCTION

The prevalence of type 2 diabetes mellitus (T2DM) has increased significantly worldwide and has become a global health burden [1]. The growing trend of T2DM is largely attributed to the obesity epidemic [1,2]. Obesity, especially visceral obesity, is an independent risk factor for T2DM [3-5]. Previous studies demonstrated that visceral fat was more significantly associated with insulin resistance or T2DM than other indices of obesity such as body mass index (BMI) or waist circumference (WC) [6,7], and showed independent associations between visceral fat and T2DM after multivariable adjustment [4,5,8].

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Excessive visceral fat accumulation results in the dysfunction of the endocrine system and dysregulation of pro-inflammatory factors, which may contribute to insulin resistance and the risk of T2DM [9,10]. Thus, measurement of the amount of visceral fat is crucial for assessing the risk of T2DM and other obesity-related disorders. Among the various techniques of visceral fat measurement, computed tomography (CT) scan is considered a gold standard method that can readily distinguish fat from other tissues and allow independent measurement of visceral and subcutaneous abdominal fat mass with high reproducibility [11].

Previous studies have reported a very wide range of cut-off values for visceral fat area (VFA) assessed by CT scan for predicting metabolic syndrome or obesity-related disorders according to ethnicity, sex, and age [12-22]. Because there has been no consensus for the optimal cut-off values of VFA, an absolute value of 100 cm^2 has been clinically used as a reference value of visceral fat obesity, which was proposed by the Japan Society for the Study of Obesity. However, considering that the patterns of body fat distribution are different between men and women [23], it is necessary to separately establish the optimal cut-off values of VFA for each sex. In addition, although some longitudinal studies have reported the association between VFA and the development of T2DM [4,5,8], there has not been a longitudinal study that suggested the optimal cut-off values of VFA for predicting incident T2DM. Previously, we demonstrated the sex differences in the optimal cut-off values of VFA for predicting incident T2DM [24]; however, the study was limited in that the VFA values were derived from bioelectrical impedance analysis (BIA) and not from CT scans.

The visceral-to-subcutaneous fat ratio (VSR) can also be used to assess visceral obesity. A Japanese study suggested that a VSR of 0.4 or higher can be defined as visceral obesity, and the cut-off value showed a significant correlation with glucose intolerance [25]. Although some studies have examined the association between VSR and cardiometabolic risk factors [26,27], the association between VSR and incident T2DM as well as the corresponding optimal cut-off values of VSR have yet to be determined.

Thus, we aimed to determine the sex-specific optimal cut-off values of VFA and VSR for the prediction of incident T2DM in an Asian population. Also, we evaluated whether VFA and VSR are independent risk factors for the development of T2DM.

METHODS

Study population and definition of T2DM

The study population was composed of individuals aged 30 to 79 years who underwent abdominal CT scan as a part of routine health check-ups at the Health Screening and Promotion Center of Asan Medical Center (Seoul, Republic of Korea) between January 1, 2012 and December 31, 2013, and underwent at least one follow-up visit until December 31, 2018 (n=12,778). We excluded 1,896 individuals due to missing data (n=62) or the presence of any systemic disorders including T2DM (n=1,358), cancer (n=432), liver cirrhosis (n=3), chronic renal insufficiency (n=17), overt thyroid dysfunction (n=59), severe anemia or polycythemia (n=16), and those currently taking glucocorticoids (n=62). Some individuals met more than two exclusion criteria, and a total of 10,882 individuals were finally included in this study.

We obtained information on medication, previous medical or surgical diseases, history of T2DM in first-degree relatives, and habits on drinking, smoking, and exercise using a standard questionnaire. Drinking habits were estimated as grams of alcohol consumed per day, and smoking habits were categorized as never, previous, or current. Regular aerobic exercise was defined as engaging in moderate-intensity aerobic activity for a minimum of 30 minutes for 5 days per week or vigorous-intensity aerobic activity for a minimum of 20 minutes for 3 days per week. Regular resistance exercise was defined as engaging in resistance training sessions for at least 3 days per week. Pre-existing diabetes was determined as fasting plasma glucose (FPG) ≥126 mg/dL, glycosylated hemoglobin (HbA1c) level ≥6.5%, or the use of antidiabetic medications as indicated on a questionnaire at baseline examinations. Incident T2DM was defined as FPG ≥126 mg/dL, HbA1c level ≥6.5%, or the initiation of antidiabetic medications during the follow-up period. The study protocol was approved with exemption of written informed consent by the Institutional Review Board of Asan Medical Center (IRB No. 2018-0917) because this is a retrospective analysis of pre-existing clinical data that were de-identified before the analysis and had therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Anthropometric, body composition, and laboratory measurements

Trained nurses measured the height and weight of the individ-

uals wearing light clothing without shoes. BMI was calculated as the weight in kilograms divided by the square of the height in meters. WC was measured in a horizontal plane at the midway point between the inferior margin of the last rib and the superior iliac crest. Blood pressure was measured using an automatic manometer on the right arm with an appropriate cuff size after a resting period of ≥5 minutes.

Body composition was measured with a direct segmental multifrequency BIA using the InBody 720 (InBody Co. Ltd., Seoul, Korea). Body composition measurements were performed with the individuals in a standing position grasping the handles of the analyzer, thereby providing contact with a total of eight electrodes (two per each foot and hand). The system separately measured the impedance of the right arm, left arm, trunk, right leg, and left leg at six different frequencies (1, 5, 50, 250, 500, and 1,000 kHz). Appendicular skeletal muscle mass was calculated as the sum of the lean muscle mass in the bilateral arms and legs.

After overnight fasting, blood samples were drawn early in the morning from the antecubital vein into vacuum tubes and analyzed at a certified central laboratory at Asan Medical Center. Glucose was measured using the hexokinase method with an autoanalyzer (Toshiba 200 FR Neo autoanalyzer, Toshiba Medical System Co., Tokyo, Japan), and HbA1c level was measured by ion-exchange high-performance liquid chromatography using an automated system (BioRad Laboratories Inc., Hercules, CA, USA) certified by the National Glycohemoglobin Standardization Program and aligned to the Diabetes Control and Complications Trial reference method. The levels of fasting total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol, and triglyceride were measured using the autoanalyzer (Toshiba). Serum insulin concentrations were calculated using an immunoradiometric assay (TFB, Tokyo, Japan). The homeostasis model assessment of insulin resistance (HOMA-IR), an index of insulin resistance, was calculated as the FPG (mg/dL) multiplied by the fasting insulin (μIU/mL) divided by 405.

CT image acquisition and assessment of the visceral and subcutaneous fat area

We used a standardized CT acquisition protocol for health check-ups and assessed the VFA and subcutaneous fat area (SFA) as previously described [28]. VSR was calculated as VFA divided by SFA. VFA was adjusted by the square of the height (VFA/height^2), weight (VFA/weight), and BMI (VFA/BMI), which were collectively referred to as the visceral fat indices (VFIs).

Statistical analysis

Continuous variables with normal distributions are expressed as mean±standard deviation, and those with skewed distributions are expressed as median and interquartile range. Categorical variables are expressed as percent (%). Continuous variables were analyzed with Student's *t*-test or Mann-Whitney *U* test, and categorical variables were analyzed with chi-square test. A receiver operating characteristic (ROC) curve analysis was used to estimate the cut-off values for VFA and VSR, and the Youden's index was used to identify the best cut-off values.

VFA and VSR were categorized into sex-specific quartiles (Q1–Q4). The ranges of the quartiles of VFA were Q1 <95.6, 95.6≤ Q2 <133.9, 133.9≤ Q3 <174.8, Q4 ≥174.8 for men and Q1 <38.6, 38.6≤ Q2 <63.7, 63.7≤ Q3 <94.8, Q4≥ 94.8 for women. The ranges of the quartiles of VSR were Q1 <0.80, 0.80≤ Q2 <1.07, 1.07≤ Q3 <1.39, Q4 ≥1.39 for men and Q1 <0.30, 0.30≤ Q2 <0.42, 0.42≤ Q3 <0.59, Q4 ≥0.59 for women.

Demographic and biochemical characteristics of the study population sorted according to the quartiles of the VFA were compared using one-way analysis of variance (ANOVA) or Kruskal-Wallis test for continuous variables and chi-square test for categorical variables. Multivariate logistic regression analyses were carried out to determine the odds ratios (ORs) and 95% confidence intervals (CIs) for predicting incident T2DM. Analysis of ROC curves was performed by MedCalc version 14.8.1.0 for Windows (MedCalc Software, Mariakerke, Belgium) according to the method described DeLong et al. [29]. All statistical analyses were performed using IBM SPSS Statistics version 20.0 (IBM Corp., Armonk, NY, USA). *P* values <0.05 were considered statistically significant.

RESULTS

Baseline characteristics of the study population according to sex

During a median follow-up of 4.8 years (interquartile range, 3.2 to 5.5), 554 (8.1%) and 176 (4.3%) incident cases of T2DM were identified in men and women, respectively. The mean age was 52.8±7.8 years in men and 52.3±7.6 years in women. The baseline characteristics of the study population are presented in Table 1. Men and women showed significant differences in most baseline variables including anthropometric measure-

Table 1. Baseline characteristics of the study population according to sex

Variable	Men (n=6,835)	Women (n=4,047)	P value
Age, yr	52.8±7.8	52.3±7.6	0.001
BMI, kg/m^2	24.6±2.6	22.5±2.8	<0.001
WC, cm	87.4±7.3	78.0±7.8	<0.001
ASM, kg	23.9±2.8	16.2±1.9	<0.001
Body fat mass, kg	15.9±5.0	16.6±5.2	<0.001
Body fat, %	21.7±4.8	28.8±6.1	<0.001
SBP, mm Hg	124.0±12.8	116.0±13.7	<0.001
DBP, mm Hg	80.1±10.1	72.5±10.3	<0.001
Glucose, mg/dL	97.3±9.8	93.7±9.0	<0.001
Cholesterol, mg/dL	194.0±33.4	199.0±32.7	<0.001
HDL-C, mg/dL	52.3±12.9	62.8±14.9	<0.001
LDL-C, mg/dL	123.4±29.8	122.7±29.7	0.250
Triglyceride, mg/dL	113.0 (82.0–158.0)	84.0 (63.0–115.0)	<0.001
HbA1c, %	5.48±0.34	5.46±0.33	0.001
Insulin, μIU/mL	4.9 (2.9–7.0)	4.2 (2.5–6.4)	<0.001
HOMA-IR	1.17 (0.67–1.73)	0.96 (0.57–1.51)	<0.001
hsCRP, mg/dL	0.05 (0.03–0.11)	0.04 (0.02–0.07)	<0.001
Current smoker	2,084 (30.5)	98 (2.4)	<0.001
Alcohol consumption, g/day	15.0 (4.3–43.5)	0.4 (0.0–2.3)	<0.001
Regular aerobic exercise	654 (9.6)	349 (8.6)	0.101
Regular resistance exercise	1,207 (17.7)	428 (10.6)	<0.001
Menopause			
Natural menopause	-	1,951 (48.2)	-
Surgical menopause	-	487 (12.0)	-
Hypertension	2,624 (38.4)	806 (19.9)	<0.001
Taking lipid-lowering drugs	900 (13.2)	410 (10.1)	<0.001
Family history of T2DM	1,378 (20.2)	942 (23.3)	<0.001
Incident T2DM	554 (8.1)	176 (4.3)	<0.001
VFA, cm^2	133.9 (95.6–174.8)	63.7 (38.6–94.8)	<0.001
SFA, cm^2	119.7 (96.1–147.4)	144.0 (115.8–176.8)	<0.001
VSR	1.07 (0.80–1.39)	0.42 (0.30–0.59)	<0.001
VFA/height^2, cm^2/m^2	45.5 (32.6–59.7)	25.2 (15.1–37.9)	<0.001
VFA/weight, cm^2/kg	1.8 (1.4–2.3)	1.1 (0.7–1.6)	<0.001
VFA/BMI	5.4 (4.1–6.8)	2.8 (1.8–4.0)	<0.001

Values are presented as mean±standard deviation, median (range), or number (%).
BMI, body mass index; WC, waist circumference; ASM, appendicular skeletal muscle mass; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HbA1c, glycosylated hemoglobin; HOMA-IR, homeostasis model assessment of insulin resistance; hsCRP, high-sensitivity C-reactive protein; T2DM, type 2 diabetes mellitus; CT, computed tomography; VFA, visceral fat area; SFA, subcutaneous fat area; VSR, visceral-to-subcutaneous fat ratio.

Table 2. Baseline characteristics of the study population according to the presence of incident T2DM

Variable	Men			Women		
	No diabetes (n=6,281)	Incident diabetes (n=554)	P value	No diabetes (n=3,871)	Incident diabetes (n=176)	P value
Age, yr	52.8±7.9	53.8±6.9	0.001	52.1±7.6	55.8±7.1	<0.001
BMI, kg/m^2	24.5±2.6	25.7±2.8	<0.001	22.4±2.8	24.7±3.1	<0.001
WC, cm	87.1±7.2	90.8±7.4	<0.001	77.8±7.7	84.4±7.2	<0.001
ASM, kg	23.9±2.8	24.5±3.1	<0.001	16.2±1.9	16.7±2.1	<0.001
Body fat mass, kg	15.7±4.9	17.9±5.3	<0.001	16.4±5.1	20.3±5.6	<0.001
Body fat, %	21.5±4.9	23.4±4.7	<0.001	28.6±6.0	32.4±5.8	<0.001
SBP, mm Hg	123.8±12.7	126.2±12.9	<0.001	115.6±13.5	123.3±14.6	<0.001
DBP, mm Hg	80.0±10.0	81.4±10.4	<0.001	72.3±10.2	76.2±10.1	<0.001
Glucose, mg/dL	96.4±9.1	108.0±10.3	<0.001	93.1±8.5	106.2±10.3	<0.001
Cholesterol, mg/dL	194.1±33.2	192.9±35.3	0.440	198.9±32.6	200.5±34.9	0.553
HDL-C, mg/dL	52.6±12.9	49.0±12.1	<0.001	63.1±14.9	55.6±12.6	<0.001
LDL-C, mg/dL	123.5±29.7	122.2±31.4	0.361	122.5±29.6	126.6±31.3	0.084
Triglyceride, mg/dL	111.0 (81.0–155.0)	137.0 (98.0–190.0)	<0.001	83.0 (62.0–113.0)	121.0 (90.3–157.8)	<0.001
HbA1c, %	5.45±0.31	5.90±0.33	<0.001	5.44±0.31	5.99±0.28	<0.001
Insulin, μIU/mL	4.8 (2.8–6.8)	6.4 (4.1–8.6)	<0.001	4.1 (2.5–6.2)	6.5 (4.6–9.8)	<0.001
HOMA-IR	1.13 (0.65–1.68)	1.72 (1.05–2.36)	<0.001	0.93 (0.56–1.47)	1.74 (1.11–2.47)	<0.001
hsCRP, mg/dL	0.05 (0.03–0.10)	0.06 (0.03–0.12)	<0.001	0.03 (0.02–0.07)	0.06 (0.04–0.12)	<0.001
Current smoker	1,895 (30.2)	189 (34.1)	0.046	95 (2.5)	3 (1.7)	0.441
Alcohol consumption, g/day	14.4 (4.3–43.5)	22.3 (5.3–52.7)	0.004	0.4 (0.0–2.3)	0.0 (0.0–1.4)	0.002
Regular aerobic exercise	592 (9.4)	62 (11.2)	0.181	329 (8.5)	20 (11.4)	0.213
Regular resistance exercise	1,109 (17.7)	98 (17.7)	1.00	410 (10.6)	18 (10.2)	1.000
Menopause						0.003
Natural menopause	-	-		1,854 (47.9)	97 (55.1)	
Surgical menopause	-	-		459 (11.9)	28 (15.9)	
Hypertension	2,332 (37.1)	292 (52.7)	<0.001	728 (18.8)	78 (44.3)	<0.001
Taking lipid-lowering drugs	789 (12.6)	111 (20.0)	<0.001	365 (9.4)	45 (25.6)	<0.001
Family history of T2DM	1,223 (19.5)	155 (28.0)	<0.001	892 (23.0)	50 (28.4)	0.100
VFA, cm^2	130.7 (93.1–171.5)	164.1 (130.7–204.8)	<0.001	62.0 (37.9–91.9)	112.7 (89.2–142.9)	<0.001
SFA, cm^2	118.7 (95.3–146.4)	130.0 (104.3–157.5)	<0.001	142.8 (115.2–175.4)	165.2 (134.1–201.7)	<0.001
VSR	1.05 (0.79–1.37)	1.24 (0.93–1.56)	<0.001	0.41 (0.29–0.58)	0.66 (0.51–0.85)	<0.001
VFA/height^2, cm^2/m^2	44.6 (31.9–58.6)	55.7 (44.1–70.4)	<0.001	24.5 (14.7–36.5)	45.1 (35.4–57.3)	<0.001
VFA/weight, cm^2/kg	1.8 (1.4–2.3)	2.2 (1.8–2.6)	<0.001	1.1 (0.7–1.6)	1.8 (1.5–2.2)	<0.001
VFA/BMI	5.3 (4.0–6.7)	6.4 (5.2–7.7)	<0.001	2.8 (1.8–3.9)	4.6 (3.8–5.5)	<0.001

Values are presented as mean±standard deviation, median (range), or number (%).
T2DM, type 2 diabetes mellitus; BMI, body mass index; WC, waist circumference; ASM, appendicular skeletal muscle mass; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HbA1c, glycosylated hemoglobin; HOMA-IR, homeostasis model assessment of insulin resistance; hsCRP, high-sensitivity C-reactive protein; CT, computed tomography; VFA, visceral fat area; SFA, subcutaneous fat area; VSR, visceral-to-subcutaneous fat ratio.

Table 3. Incident T2DM and baseline characteristics according to the quartiles of VFA in men and women

Variable	Men					Women				
	Quartile 1 (<95.6) (*n*=1,711)	Quartile 2 (95.6–133.9) (*n*=1,707)	Quartile 3 (133.9–174.8) (*n*=1,710)	Quartile 4 (>174.8) (*n*=1,707)	*P* value	Quartile 1 (<38.6) (*n*=1,009)	Quartile 2 (38.6–63.7) (*n*=1,016)	Quartile 3 (63.7–94.8) (*n*=1,011)	Quartile 4 (>94.8) (*n*=1,011)	*P* value
Incident T2DM	45 (2.6)	110 (6.4)	159 (9.3)	240 (14.1)	<0.001	2 (0.2)	14 (1.4)	40 (4.0)	120 (11.9)	<0.001
Age, yr	52.0±8.1	52.5±7.7	52.9±7.7	53.9±7.7	<0.001	48.7±6.9	51.1±6.8	53.4±7.0	56.0±7.8	<0.001
BMI, kg/m^2	22.2±1.9	24.0±1.7	25.2±1.9	26.8±2.4	<0.001	20.0±1.8	21.7±1.8	23.0±2.0	25.2±2.7	<0.001
WC, cm	80.1±5.1	85.7±4.4	89.3±4.7	94.4±5.9	<0.001	70.7±5.2	76.1±5.1	79.7±5.3	85.7±6.6	<0.001
ASM, kg	22.9±2.7	23.5±2.6	24.2±2.4	25.0±2.9	<0.001	15.8±1.8	16.0±1.8	16.2±1.9	16.8±2.1	<0.001
Body fat mass, kg	17.2±3.8	21.0±3.4	22.9±3.4	25.8±4.1	<0.001	11.9±3.1	15.2±3.1	17.6±3.5	21.7±4.9	<0.001
Body fat, %	11.2±3.0	14.7±3.0	16.9±3.5	20.5±4.8	<0.001	23.0±4.7	27.6±4.2	30.4±4.2	34.2±4.7	<0.001
SBP, mm Hg	120.2±13.0	122.7±13.0	125.3±12.4	127.9±12.2	<0.001	110.3±12.4	113.7±12.6	117.5±13.1	122.5±13.5	<0.001
DBP, mm Hg	77.0±10.0	79.3±9.6	81.1±9.7	83.0±10.0	<0.001	69.1±10.1	71.2±9.9	73.3±10.1	76.2±9.6	<0.001
Glucose, mg/dL	94.7±9.1	96.7±9.5	98.1±9.6	99.8±10.1	<0.001	90.5±8.1	92.4±8.4	94.0±8.7	97.8±9.1	<0.001
Cholesterol, mg/dL	190.7±31.4	194.2±33.2	195.2±33.5	196.0±35.2	<0.001	191.5±29.5	199.0±31.8	202.3±32.6	203.2±35.4	<0.001
HDL-C, mg/dL	58.6±14.0	52.3±12.3	49.5±11.6	48.5±11.3	<0.001	71.7±14.9	64.1±13.7	59.7±13.6	55.5±12.3	<0.001
LDL-C, mg/dL	118.7±27.7	124.3±30.1	125.3±29.7	125.1±31.2	<0.001	110.4±25.0	122.3±28.2	127.8±29.1	130.1±32.1	<0.001
Triglyceride, mg/dL	85.0 (65.0–113.0)	109.0 (81.0–151.0)	123.0 (92.0–170.0)	140.0 (105.0–189.0)	<0.001	65.0 (51.0–84.0)	77.0 (61.0–102.0)	91.0 (70.0–122.0)	109.0 (84.0–154.0)	<0.001
HbA1c, %	5.39±0.31	5.45±0.32	5.51±0.34	5.58±0.35	<0.001	5.33±0.30	5.40±0.31	5.49±0.32	5.63±0.33	<0.001
Insulin, μIU/mL	2.9 (1.9–4.8)	4.2 (2.8–6.3)	5.6 (3.8–7.4)	6.9 (5.0–9.2)	<0.001	2.8 (1.9–4.4)	3.6 (2.3–5.6)	4.7 (3.0–6.5)	6.4 (4.3–8.4)	<0.001
HOMA-IR	0.67 (0.43–1.13)	1.01 (0.64–1.52)	1.36 (0.89–1.82)	1.70 (1.19–2.32)	<0.001	0.64 (0.41–1.00)	0.81 (0.51–1.29)	1.07 (0.66–1.56)	1.55 (1.01–2.09)	<0.001
hsCRP, mg/dL	0.03 (0.02–0.07)	0.05 (0.03–0.09)	0.06 (0.03–0.11)	0.08 (0.04–0.14)	<0.001	0.02 (0.02–0.04)	0.03 (0.02–0.06)	0.04 (0.02–0.08)	0.06 (0.04–0.13)	<0.001
Current smoker	516 (30.2)	523 (30.6)	526 (30.8)	519 (30.4)	0.001	132 (3.2)	24 (2.4)	22 (2.2)	20 (2.0)	0.004
Alcohol consumption, g/day	10.5 (3.1–33.0)	14.1 (4.3–40.1)	17.2 (4.6–45.3)	24.0 (6.3–52.8)	<0.001	0.8 (0.0–2.7)	0.5 (0.0–2.3)	0.4 (0.0–2.1)	0.0 (0.0–1.5)	<0.001
Regular aerobic exercise	204 (11.9)	173 (10.1)	148 (8.7)	129 (7.6)	<0.001	100 (9.9)	73 (7.2)	89 (8.8)	87 (8.6)	0.191
Regular resistance exercise	368 (21.5)	347 (20.3)	274 (16.0)	218 (12.8)	<0.001	116 (11.5)	102 (10.0)	104 (10.3)	106 (10.5)	0.732
Menopause										<0.001
Natural menopause	-	-	-	-	-	346 (34.3)	478 (47.0)	517 (51.1)	610 (60.3)	
Surgical menopause	-	-	-	-	-	96 (9.5)	98 (9.6)	145 (14.3)	148 (14.6)	
Hypertension	378 (22.1)	578 (33.9)	718 (42.0)	757 (55.7)	<0.001	91 (9.0)	137 (13.5)	205 (20.3)	373 (36.9)	<0.001

(*Continued to the next page*)

Table 3. Continued

Variable	Men					Women				
	Quartile 1 (<95.6) (*n*=1,711)	Quartile 2 (95.6–133.9) (*n*=1,707)	Quartile 3 (133.9–174.8) (*n*=1,710)	Quartile 4 (>174.8) (*n*=1,707)	*P* value	Quartile 1 (<38.6) (*n*=1,009)	Quartile 2 (38.6–63.7) (*n*=1,016)	Quartile 3 (63.7–94.8) (*n*=1,011)	Quartile 4 (>94.8) (*n*=1,011)	*P* value
Taking lipid-lowering drugs	134 (7.8)	209 (12.2)	241 (14.1)	316 (18.5)	<0.001	30 (3.0)	73 (7.2)	114 (11.3)	193 (19.1)	<0.001
Family history of T2DM	325 (19.0)	356 (20.9)	357 (20.9)	340 (19.9)	0.460	246 (24.4)	254 (25.0)	224 (22.2)	218 (21.6)	0.191
VFA, cm^2	68.9 (48.2–84.7)	115.6 (105.6–124.4)	152.3 (142.9–163.0)	206.0 (187.7–233.4)	<0.001	26.8 (19.8–32.6)	50.6 (44.6–57.1)	77.0 (70.1–85.2)	121.4 (105.7–142.2)	<0.001
SFA, cm^2	90.2 (70.2–113.4)	116.0 (97.7–140.3)	129.9 (108.2–153.9)	141.4 (117.1–173.1)	<0.001	106.3 (83.5–130.7)	138.7 (119.3–163.4)	158.2 (133.7–187.3)	175.4 (144.8–206.9)	<0.001
VSR	0.70 (0.56–0.87)	0.98 (0.81–1.19)	1.18 (0.99–1.41)	1.49 (1.24–1.82)	<0.001	0.24 (0.19–0.30)	0.36 (0.30–0.42)	0.49 (0.42–0.59)	0.72 (0.59–0.88)	<0.001
VFA/height^2, cm^2/m^2	23.5 (16.5–28.6)	39.6 (36.2–42.8)	52.2 (48.3–55.9)	70.7 (64.1–79.9)	<0.001	10.5 (7.7–12.8)	20.2 (17.5–22.6)	30.7 (27.7–34.1)	48.6 (42.4–57.7)	<0.001
VFA/weight, cm^2/kg	1.0 (0.8–1.2)	1.6 (1.5–1.8)	2.1 (1.9–2.3)	2.7 (2.4–3.0)	<0.001	0.5 (0.4–0.6)	0.9 (0.8–1.0)	1.3 (1.2–1.5)	2.0 (1.8–2.2)	<0.001
VFA/BMI	3.1 (2.2–3.6)	4.8 (4.4–5.2)	6.1 (5.7–6.5)	7.8 (7.2–8.7)	<0.001	1.3 (1.0–1.6)	2.3 (2.1–2.6)	3.4 (3.1–3.7)	4.6 (4.4–5.6)	<0.001

Values are presented as number (%), mean±standard deviation, or median (range).
T2DM, type 2 diabetes mellitus; VFA, visceral fat area; BMI, body mass index; WC, waist circumference; ASM, appendicular skeletal muscle mass; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HbA1c, glycosylated hemoglobin; HOMA-IR, homeostasis model assessment of insulin resistance; hsCRP, high-sensitivity C-reactive protein; CT, computed tomography; SFA, subcutaneous fat area; VSR, visceral-to-subcutaneous fat ratio.

Table 4. ORs and 95% CIs of visceral fat area for incident T2DM in men and women in unadjusted and adjusted models

Variable	Men					Women				
	Quartile 1 (<95.6)	Quartile 2 (95.6–133.9)	Quartile 3 (133.9–174.8)	Quartile 4 (>174.8)	*P* for trend	Quartile 1 (<38.6)	Quartile 2 (38.6–63.7)	Quartile 3 (63.7–94.8)	Quartile 4 (>94.8)	*P* for trend
Incident T2DM	45 (2.6)	110 (6.4)	159 (9.3)	240 (14.1)	<0.001	2 (0.2)	14 (1.4)	40 (4.0)	120 (11.9)	<0.001
Unadjusted	1	2.55 (1.79–3.63)	3.80 (2.71–5.32)	6.06 (4.37–8.39)	<0.001	1	7.04 (1.60–31.03)	20.74 (5.00–86.06)	67.81 (16.72–275.07)	<0.001
Model 1	1	2.38 (1.67–3.40)	3.44 (2.44–4.85)	5.17 (3.70–7.24)	<0.001	1	6.68 (1.51–29.54)	18.23 (4.37–75.99)	51.40 (12.52–210.96)	<0.001
Model 2	1	2.21 (1.54–3.18)	3.05 (2.12–4.39)	4.24 (2.86–6.29)	<0.001	1	6.65 (1.50–29.54)	18.07 (4.27–76.48)	50.65 (11.82–217.06)	<0.001
Model 3	1	2.12 (1.47–3.05)	2.78 (1.93–4.02)	3.54 (2.37–5.28)	<0.001	1	6.60 (1.48–29.33)	16.32 (3.85–69.23)	39.35 (9.13–169.61)	<0.001
Model 4	1	1.84 (1.25–2.69)	2.25 (1.54–3.30)	2.62 (1.73–3.97)	<0.001	1	5.74 (1.26–26.14)	14.02 (3.25–60.49)	32.49 (7.43–142.02)	<0.001

Values are presented as number (%) or odds ratio (95% confidence interval). Model 1: Adjusted for age, smoking, alcohol consumption, regular aerobic exercise, regular resistance exercise, hypertension, use of lipid-lowering medication, family history of T2DM and menopausal status (only adjusted in women); Model 2: Model 1+body fat mass; Model 3: Model 2+homeostasis model assessment of insulin resistance; Model 4: Model 2+fasting glucose.
OR, odds ratio; CI, confidence interval; T2DM, type 2 diabetes mellitus.

ments, biochemical data, lifestyle, and the prevalence of hypertension, taking lipid-lowering drugs, and family history of T2DM; LDL-C levels and the percentage of individuals with regular aerobic exercise were not significantly different according to sex. VFA was approximately two times larger in men (133.9 cm^2 vs. 63.7 cm^2, $P<0.001$), whereas SFA was significantly larger in women (119.7 cm^2 vs. 144.0 cm^2, $P<0.001$). Consequently, VSR and VFIs were significantly higher in men (all $P<0.001$).

Baseline characteristics of the study population according to the presence of incident T2DM

Compared with non-diabetic controls, individuals with incident T2DM were older, more obese, and more likely to have received lipid-lowering medications; those with incident T2DM also had metabolically less favorable laboratory findings except cholesterol level, and had a higher prevalence of hypertension regardless of sex (Table 2). Individuals who developed incident T2DM had a significantly larger VFA compared with non-diabetic controls (164.1 cm^2 vs. 130.7 cm^2 in men; 112.7 cm^2 vs. 62.0 cm^2 in women). SFA, VSR, and the VFIs were significantly higher in those with incident T2DM regardless of sex.

Incident T2DM and baseline characteristics according to the quartiles of VFA and VSR

As shown in Table 3, higher baseline VFA quartiles were significantly associated with a higher incidence of T2DM in both men and women. As shown in Supplementary Table 1, higher baseline VSR quartiles were significantly associated with a higher incidence of T2DM in both men and women. The patterns

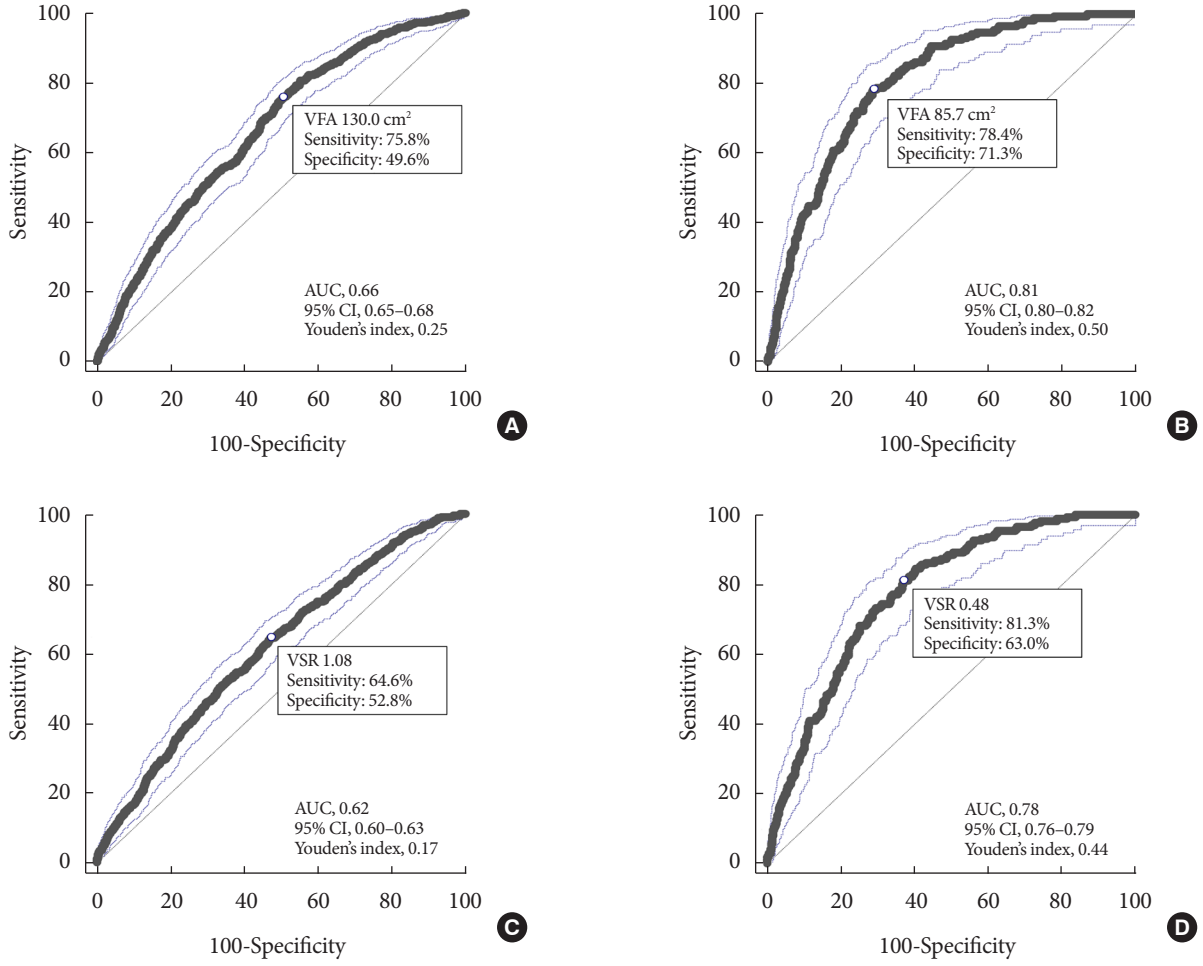

Fig. 1. Receiver operating characteristic curve of visceral fat area (VFA) and visceral-to-subcutaneous fat ratio (VSR) for predicting incident type 2 diabetes mellitus in men (A, C) and women (B, D). AUC, area under the curve; CI, confidence interval.

of most metabolic variables were similar to those of VFA quartiles regardless of sex. In contrast to VFA and the VFIs, SFA tended to decrease according to increasing VSR quartiles in men; in women, SFA increased from Q1 to Q3, then decreased at Q4.

Cut-off values of VFA and VSR for the prediction of incident T2DM

ROC analysis showed that the optimal VFA cut-off values for the prediction of incident T2DM in men and women were 130.0 cm^2 (sensitivity, 75.8%; specificity, 49.6%; area under the curve [AUC], 0.66; 95% CI, 0.65 to 0.68; $P<0.001$) and 85.7 cm^2 (sensitivity, 78.4%; specificity, 71.3%; AUC, 0.81; 95% CI, 0.80 to 0.82; $P<0.001$), respectively (Fig. 1). The optimal cut-off values of VSR in men and women were 1.08 (sensitivity, 64.6%; specificity, 52.8%; AUC, 0.62; 95% CI, 0.60 to 0.63; $P<0.001$) and 0.48 (sensitivity, 81.3%; specificity, 63.0%; AUC=0.78; 95% CI, 0.76 to 0.79; $P<0.001$), respectively.

Risk of incident T2DM according to VFA and VSR

As shown in Table 4, higher quartiles of VFA at baseline was significantly associated with higher risks of incident T2DM in both unadjusted and adjusted models regardless of sex. Compared with the lowest quartile (Q1) of VFA, the ORs of the highest quartiles (Q4) were 5.17 (95% CI, 3.70 to 7.24) in men and 51.40 (95% CI, 12.52 to 210.96) in women after multivariable adjustment; after additional adjustment for obesity with body fat mass, the ORs of Q4 were 4.24 in men and 50.65 in women; after further adjustment for HOMA-IR and fasting glucose, the ORs of Q4 were 3.54 and 2.62 in men, respectively, and 39.35 and 32.49 in women, respectively (all $P<0.001$).

High VSR at baseline was also significantly associated with higher risks of incident T2DM in both unadjusted and adjusted models regardless of sex (Supplementary Table 2). After adjustment for insulin resistance and glycemic status, the ORs of Q4 were 2.01 and 1.55 in men, respectively, and 13.06 and 11.07 in women, respectively, compared with the Q1 in each sex.

DISCUSSION

In this large-scale longitudinal study, we calculated the optimal cut-off values of VFA and VSR for predicting incident T2DM, which were markedly different between men and women (130.0 cm^2 vs. 85.7 cm^2; 1.08 vs. 0.48). To the best of our knowledge, this is the first longitudinal study to investigate the optimal cut-off values of CT-derived VFA for predicting incident T2DM. We also found that higher baseline values of VFA and VSR were significantly associated with higher risks of incident T2DM, which persisted even after adjustment for obesity, insulin resistance, and glycemic status. The ORs of higher quartiles of VFA and VSR for incident T2DM were much higher in women than in men, and higher VFA was more strongly associated with increased risks of incident T2DM compared with higher VSR. Sex differences of visceral adiposity for the risk of T2DM have been reported in previous studies [30-32]; consistent with these studies, the association between visceral adiposity and T2DM was stronger in women than in men in our study. These results collectively suggest that despite having less visceral fat compared with men in general, women are highly susceptible to the development of T2DM according to increases in visceral fat. The cause of this sex difference is unclear, but sex hormones are considered to play an important role in the distribution, function, and storage of adipose tissues [30-32]. Because women with higher quartiles of VFA and VSR were more likely to be postmenopausal in our study, the withdrawal of the protective effect of estrogen against T2DM may augment the largest difference in the ORs between the sexes.

To date, various cut-off values of VFA for predicting metabolic syndrome or obesity-related disorders have been proposed based on cross-sectional studies [12-22,24]. In 2002, the Japan Society for the Study of Obesity proposed a cut-off value of VFA at 100 cm^2 for assessing the risk of obesity-related disorders based on cross-sectional study [19]. In 2012, a cross-sectional study of Japanese general population also suggested an absolute VFA cut-off value of about 100 cm^2 in association with the accumulation of obesity-related cardiovascular risk factors irrespective of sex, age, and BMI [20]. These studies suggested absolute cut-off values for VFA at 100 cm^2 because of its usefulness, but the cut-off values accounting for sex differences would be more suitable for assessing obesity-related metabolic risk factors. Because of different patterns of body composition between men and women [23], an absolute VFA value of 100 cm^2 may be too high for women as shown in our data. Several Korean cross-sectional studies have suggested sex-specific cut-off values for VFA, which ranged from 100 to 136.5 cm^2 in men and from 70 to 134.5 cm^2 in women [12-18]. There have been only a few studies on this issue in ethnicities other than Asians. In a cross-sectional study on Caucasian and African American women, a VFA of 106 cm^2 or higher was associated with increases in metabolic risk factors for cardiovascular disease [21]. A

cross-sectional study on Japanese Americans study suggested age- and sex-specific cut-off values of VFA for predicting the development of metabolic syndrome (88.6 cm^2 in age ≤57 years and 96.1 cm^2 in age >57 years for men; 51.5 cm^2 in age ≤56 years and 86.3 cm^2 in age >56 years for women) [22]. The wide ranges of cut-off values for VFA in previous studies were influenced by different ethnicities, number of study participants, age distribution, inclusion and exclusion criteria, study design, and outcomes.

However, a VFA of 100 cm^2 is still widely used in clinical practice of managing patients with obesity or in health check-ups as the reference value for visceral fat obesity. It is probably due to the fact that there have been no well recognized studies about the reference value of VFA because previous studies were mostly cross-sectional studies and their main outcome measures varied.

Visceral fat accumulation has a strong association with insulin resistance [3] and is a crucial risk factor for the development of T2DM and other obesity-related disorders [4,5]. A previous cross-sectional Korean study demonstrated that visceral adiposity is more strongly associated with T2DM than other indices of obesity such as BMI or WC [6]. Prospective studies of Japanese Americans have reported independent associations between baseline visceral fat and the development of T2DM after adjusting for general obesity indices such as BMI and body fat area [4,8]. The Dallas Heart Study (DHS), multiethnic population cohort study has reported higher baseline visceral fat were independently associated with incident T2DM through a median 7 years of follow-up [5]. Asians have relatively larger amounts of visceral fat than Caucasians with similar obesity or BMI values [33], and considering that the prevalence of T2DM in Asian populations is increasing, the measurement of visceral fat is crucial for distinguishing individuals at high risk of T2DM or other obesity-related disorders. The results of our study demonstrated that VFA is an important risk factor for the development of T2DM independent of total body fat and glycemic status, which is in line with the findings of previous studies [4,5,8]. However, there has not been a longitudinal study that suggested the optimal cut-off values of CT-derived VFA for predicting incident T2DM.

Previously, we found that the VFA cut-off values for predicting incident T2DM were markedly different between men and women in a 4-year follow-up longitudinal study [24]; however, the study had a methodologic limitation as it used BIA instead of CT scan for the measurement of VFA. In the current study, we used CT scan as the gold standard method for the measurement of VFA and showed that optimal cut-off values of VFA for men and women were markedly different (130 cm^2 for men vs. 85 cm^2 for women).

A Japanese study defined visceral obesity was defined as a VSR of 0.4 or higher, which showed a significant correlation with glucose intolerance and hyperlipidemia [25]. While there is no consensus on the useful cut-off values of VSR for predicting T2DM, the result of our study showed that the cut-off values of VSR for predicting T2DM were different between men and women (approximately 1.0 in men and 0.5 in women). VSR, which reflects the relative distribution of body fat, might be considered more important than the amount of visceral fat *per se*. Indeed, several previous studies proposed that VSR is a better predictor of cardiometabolic risk than visceral fat [26,27]. Our study also showed that VSR was an independent risk factor, but the predictive ability of VSR for the development of T2DM was smaller than that of VFA in multivariable-adjusted analyses. The predictive power of VSR on the risk of incident T2DM may be attenuated, considering that SFA accumulation in abdominal area could also contribute to insulin resistance [34,35]. Therefore, we suggest that VFA, rather than VSR, can be used as a primary indicator for assessing visceral obesity in people with a high risk of T2DM.

Our study has several limitations and strengths. This study is prone to selection bias and may have limited generalizability because the study population was composed of individuals who visited a single health screening center for routine health check-ups. However, this study population has strengths such as the large sample size, thorough measurements, high reproducibility (use of automated software in measuring the body composition), and rigorously controlled data after thorough exclusion of health conditions that may affect the body composition. Moreover, unlike previous cross-sectional studies, this longitudinal study followed the individuals who were free of T2DM at baseline for approximately 4.8 years and analyzed the incident cases of T2DM. Although we performed logistic regression analysis in this study, it would have been better to conduct survival analysis to estimate the hazard ratios of T2DM. Nevertheless, considering that the frequency of follow-up health examinations was not predetermined and irregular, the timing of the detection of incident T2DM could have been inaccurate and led to errors in survival analysis. The sex-specific cut-off values of VFA and VSR in our study were limited to Korean adults, but the assessment for visceral fat obesity should be distinguished

between men and women in every ethnic or racial group.

In conclusion, our study suggests sex-specific reference values for visceral fat obesity (VFA ≥130 cm^2 or VSR ≥1.0 for men; VFA ≥85 cm^2 or VSR ≥0.5 for women) for predicting the risk of incident T2DM in Asian populations. The prognostic powers of VFA and VSR for incident T2DM were stronger in women than in men, and baseline VFA was more strongly associated with the risk of incident T2DM compared with VSR. Further interventional studies with proper lifestyle modification should be followed.

SUPPLEMENTARY MATERIALS

Supplementary materials related to this article can be found online at https://doi.org/10.4093/dmj.2021.0095.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

Conception or design: H.K.K., W.J.L.
Acquisition, analysis, or interpretation of data: E.H.K., H.K.K., M.J.L., S.J.B., J.C., C.H.J., C.H.K., J.Y.P.
Drafting the work or revising: E.H.K., H.K.K., M.J.L., S.J.B., J.C., C.H.J., C.H.K., J.Y.P., W.J.L.
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