



Normal body mass index with central obesity has increased risk of coronary artery calcification in Korean patients with chronic kidney disease

Mi Jung Lee^{1,10}, Jung Tak Park^{2,10}, Kyoung Sook Park², Young Eun Kwon², Seung Hyeok Han², Shin-Wook Kang², Kyu Hun Choi², Kook-Hwan Oh³, Sue Kyung Park⁴, Dong Wan Chae³, Kyubeck Lee⁵, Young-Hwan Hwang⁶, Soo Wan Kim⁷, Yeong Hoon Kim⁸, Sun Woo Kang⁸, Joongyub Lee⁹, Curie Ahn³ and Tae-Hyun Yoo²

¹Department of Internal Medicine, CHA Bundang Medical Center, CHA University, Seongnam-si, Republic of Korea; ²Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea; ³Department of Internal Medicine, Seoul National University, Seoul, Republic of Korea; ⁴Department of Preventive Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea; ⁵Department of Internal Medicine, Kangbuk Samsung Medical Center, Sungkyunkwan University, Seoul, Republic of Korea; ⁶Department of Internal Medicine, Eulji University, Eulji General Hospital, Seoul, Republic of Korea; ⁷Department of Internal Medicine, Chonnam National University Medical School, Gwangju, Republic of Korea; ⁸Department of Internal Medicine, Inje University, Pusan Paik Hospital, Busan, Republic of Korea; and ⁹Medical Research Collaborating Center, Seoul National University Hospital and Seoul National University College of Medicine, Seoul, Republic of Korea

In chronic kidney disease (CKD), overweight and mild obesity have shown the lowest cardiovascular (CV) risk. However, central obesity has been directly associated with CV risk in these patients. This bidirectional relationship of body mass index (BMI) and central obesity prompted us to evaluate CV risk based on a combination of BMI and waist-to-hip ratio (WHR) in nondialysis CKD patients. We included 1078 patients with CKD stage 2 through 5 (nondialysis) enrolled in a nationwide prospective cohort of Korea. Patients were divided into 3 groups by BMI (normal BMI, 18.5–22.9; overweight, 23.0–27.4; and obese, 27.5 and over kg/m²) and were dichotomized by a sex-specific median WHR (0.92 in males and 0.88 in females). Coronary artery calcification (CAC) was determined by multislice computed tomography. CAC (score above 10 Agatston units) was found in 477 patients. Multivariate logistic regression analysis indicated that BMI was not independently associated with CAC. However, WHR showed an independent linear and significant association with CAC (odds ratio, 1.036; 95% confidence interval, 1.007–1.065 per 0.01 increase). Furthermore, when patients were categorized into 6 groups according to a combination of BMI and WHR, normal BMI but higher WHR had the highest risk of CAC compared with the normal BMI with lower WHR group (2.104; 1.074–4.121). Thus, a normal BMI with central obesity was associated with the highest risk of CAC, suggesting that considering BMI and WHR, 2 surrogates of

obesity, can help to discriminate CV risk in Korean nondialysis CKD patients.

Kidney International (2016) **90**, 1368–1376; <http://dx.doi.org/10.1016/j.kint.2016.09.011>

KEYWORDS: body mass index; cardiovascular disease; central obesity; chronic kidney disease; coronary artery calcification; waist-to-hip ratio

Copyright © 2016, International Society of Nephrology. Published by Elsevier Inc. All rights reserved.

In the general population, obesity, defined by an increased body mass index (BMI), is a well-established risk factor for cardiovascular (CV) disease and mortality.^{1,2} However, the paradoxical survival benefit of a high BMI, which is referred to as reverse epidemiology, has been shown in patients with chronic diseases including congestive heart failure,³ cancer,⁴ and end-stage renal disease^{5–8} as well as nondialysis-dependent chronic kidney disease (CKD).^{9,10} In contrast to the BMI, anthropometric indexes representing central obesity such as waist-to-hip ratio (WHR) or waist circumference (WC) were found to be directly associated with CV disease and mortality in these populations.^{11–17} As the BMI increases, CV risk or mortality is decreased, whereas the risk increases with higher WHR or WC. In this regard, the CREDIT study demonstrated that the incidence of all-cause and CV death in hemodialysis patients was highest in patients with a relatively lower BMI and higher WC but was minimal in patients with a higher BMI and smaller WC.¹⁴ This bidirectional association of BMI and WC with clinical outcomes led us to suggest that patients with a normal BMI but central obesity may have a higher CV risk than other subgroups with a different body composition, in subjects showing reverse epidemiology according to the BMI. Although opposing associations of BMI and WHR with CV disease were observed in nondialysis CKD patients,¹² so far, a comprehensive

Correspondence: Tae-Hyun Yoo, Department of Internal Medicine, College of Medicine, Yonsei University, 134 Shinchon-Dong, Seodaemun-Gu, Seoul 120-752, Republic of Korea. E-mail: yoo0316@yuhs.ac

¹⁰M.J.L. and J.T.P. contributed equally to this work.

Received 4 April 2016; revised 18 August 2016; accepted 8 September 2016

investigation of the combined effects of BMI and central obesity on CV risk has not been performed in these patients. Therefore, our hypothesis was that CV risk may be highest in nondialysis CKD patients who have a normal BMI with central obesity. To address this issue, we determined the amount of coronary artery calcification (CAC) as a surrogate for CV disease and evaluated the CV risk based on the combination of BMI and WHR in a nationwide prospective cohort of South Korean nondialysis CKD patients.

RESULTS

Baseline characteristics of the subjects

A total of 1078 subjects were included in this study (Figure 1). Baseline characteristics of the 1078 subjects are shown in Table 1. The mean age was 55.2 ± 11.6 years, and 679 patients (63.0%) were male. The mean estimated glomerular filtration rate (eGFR) was 41.8 ± 20.8 ml/min per 1.73 m^2 . The main CKD etiology was glomerulonephritis (316 patients, 29.3%), followed by diabetic nephropathy, hypertensive nephrosclerosis, and polycystic kidney disease. The mean BMI was $24.6 \pm 3.1 \text{ kg/m}^2$ ($24.8 \pm 3.0 \text{ kg/m}^2$ in male patients and $24.3 \pm 3.3 \text{ kg/m}^2$ in female patients). According to the World Health Organization (WHO) recommendations for Asian populations,¹⁸ subjects were categorized as normal BMI (BMI $18.5\text{--}22.9 \text{ kg/m}^2$), overweight (BMI $23.0\text{--}27.4 \text{ kg/m}^2$), or obese (BMI $\geq 27.5 \text{ kg/m}^2$) group. There were 332 patients (30.8%) in the normal BMI group, 563 (52.2%) in the overweight group, and 183 (17.0%) in the obese group. There were only 65 patients (6.0%) who were in the obese group (BMI $\geq 30.0 \text{ kg/m}^2$) by the WHO criteria for a Western population.¹⁹ The mean WHR was 0.90 ± 0.06 (0.92 ± 0.05 in male subjects and 0.88 ± 0.07 in female subjects). Subjects were divided based on the sex-specific median value for the WHR, and each sex-specific dichotomized group was

combined. Patients with a higher WHR (WHR \geq sex-specific median, 0.92 in male patients and 0.88 in female patients) were referred to as patients with central obesity and those with a lower WHR (WHR $<$ sex-specific median) were regarded as patients without central obesity. Of the 1078 patients, 477 patients (44.2%) had CAC (CAC score >10 Agatston units [AU]). In patients who had CAC, the median CAC score was 164.8 AU (interquartile range, 51.8–582.6 AU). The mean age, urinary protein-to-creatinine ratio, systolic blood pressure, triglyceride level, calcium \times phosphorus products, and C-reactive protein (CRP) levels were significantly higher in patients with CAC, whereas eGFR, hemoglobin, and serum albumin levels were significantly lower in patients with CAC. Patients with CAC were more likely to be male and smokers and to have a higher prevalence of diabetes, CV disease, and dyslipidemia requiring lipid-lowering agents. Among the anthropometric indexes, patients with CAC had a higher BMI, WC, hip circumference, and WHR values.

Association of clinical and biochemical variables with BMI and WHR

BMI and WHR were likely to be associated with known CV risk factors (Supplementary Tables S1 and S2). BMI and WHR were positively associated with systolic blood pressure, glucose level, triglyceride level, and CRP concentrations, but negatively associated with high-density lipoprotein cholesterol. The proportion of patients who were male, diabetic, and smokers and had dyslipidemia requiring lipid-lowering therapy was greater in patients with higher BMI and WHR values.

Independent association BMI and WHR with CAC

On univariate analysis, BMI and WHR were significantly associated with a higher risk of CAC (Table 2). Age, sex, diabetes mellitus, history of CV disease, smoking status, cause of CKD, systolic blood pressure, the use of lipid-lowering therapy, hemoglobin, serum albumin, calcium \times phosphorus products, eGFR, and urinary protein-to-creatinine ratio were also significantly associated with CAC on univariate analysis (Supplementary Table S3). After adjustment for demographic characteristics and laboratory variables, WHR had a direct association with CAC (model 2 in Table 2; per 0.01 increase, odds ratio [OR] = 1.036, 95% confidence interval [CI] 1.007–1.065, $P = 0.014$). However, BMI did not have a significant association on multivariate logistic analysis (OR = 1.026, 95% CI 0.973–1.082, $P = 0.345$). Restricted cubic splines showed that the risk of CAC increased steadily with higher WHR values, but BMI showed a trend toward reduced risk in the obese group (Figure 2). Moreover, the effect of CKD stages on the association of BMI and WHR with CAC was also analyzed. Patients were divided into CKD stage 2 (eGFR, 60–89 ml/min per 1.73 m^2 , $n = 226$), CKD stage 3 (eGFR, 30–59 ml/min per 1.73 m^2 , $n = 475$), CKD stages 4 to 5 (eGFR, <30 ml/min per 1.73 m^2 , $n = 377$) groups according to eGFR. In all 3 subgroups, restricted cubic splines demonstrated a similar trend in the results of 1078

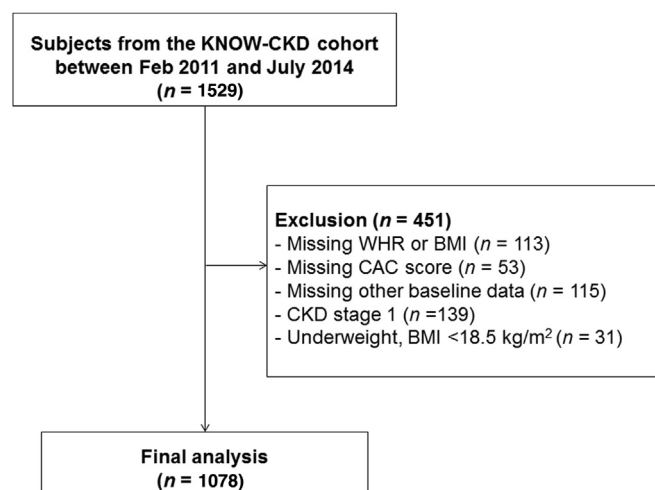


Figure 1 | Flow diagram of patients. Of 1529 CKD stages 1 to 5 nondialysis patients, 451 patients were excluded. A total of 1078 patients were analyzed. BMI, body mass index; CAC, coronary artery calcification; CKD, chronic kidney disease; KNOW-CKD, KoreaN Cohort Study for Outcome in Patients With Chronic Kidney Disease; WHR, waist-to-hip ratio.

Table 1 | Baseline characteristics of the subjects with and without CAC

	All (N = 1078)	With CAC (n = 477)	Without CAC (n = 601)	P Value
CAC score, AU	3.0 (0–130.14)	164.8 (51.8–582.6)	—	—
Age, yr	55.2 ± 11.6	60.6 ± 9.7	50.9 ± 11.1	<0.001
Male	679 (63.0)	352 (73.7)	327 (54.4)	<0.001
DM	378 (35.1)	276 (57.9)	102 (17.0)	<0.001
CVD ^a	218 (20.2)	144 (30.2)	74 (12.3)	<0.001
CAD	91 (8.4)	78 (16.4)	13 (2.2)	<0.001
PAD	22 (2.0)	17 (3.6)	5 (0.8)	<0.001
CHF	12 (1.1)	7 (1.5)	5 (0.8)	0.25
Arrhythmia	27 (2.5)	11 (2.3)	16 (2.7)	0.85
CVA	108 (10.0)	63 (13.2)	45 (7.5)	<0.001
Smoker	542 (50.3)	286 (60.0)	256 (42.6)	<0.001
Cause of CKD				<0.001
Diabetic nephropathy	268 (25.8)	210 (44.0)	58 (9.7)	
Hypertension	233 (21.6)	118 (24.7)	115 (19.1)	
GN	316 (29.3)	80 (16.8)	236 (39.3)	
PKD	174 (16.1)	28 (5.9)	146 (24.3)	
Interstitial/unspecified	9/78 (0.8/7.2)	7/34 (1.5/7.1)	2/44 (0.3/7.3)	
eGFR, ml/min per 1.73 m ²	41.8 ± 20.8	37.9 ± 18.7	44.9 ± 21.7	<0.001
eGFR categories				<0.001
G2 (60–89)	226 (21.0)	66 (13.8)	160 (26.6)	
G3 (30–59)	475 (44.1)	212 (44.4)	263 (43.8)	
G4 (15–29)	287 (26.6)	155 (32.5)	132 (22.0)	
G5 (<15)	90 (8.3)	44 (9.2)	46 (7.7)	
UPCR, g/g	0.49 (0.15–1.49)	0.65 (0.23–2.08)	0.41 (0.12–1.21)	<0.001
SBP, mm Hg	127.9 ± 16.4	130.9 ± 17.3	125.5 ± 15.2	<0.001
Hemoglobin, g/l	127 ± 20	125 ± 20	129 ± 20	0.001
Glucose, mmol/l	6.0 ± 2.1	6.4 ± 2.4	5.7 ± 1.8	<0.001
BUN, mmol/l	10.9 ± 5.7	12.0 ± 5.9	10.0 ± 5.3	<0.001
Creatinine, μmol/l	177 ± 106	194 ± 106	168 ± 97	<0.001
Albumin, g/l	42 ± 4	41 ± 4	42 ± 4	0.002
TG, mmol/l	1.8 ± 1.0	1.8 ± 1.0	1.7 ± 1.0	0.13
Total cholesterol, mmol/l	4.4 ± 0.9	4.3 ± 0.9	4.5 ± 0.9	<0.001
LDL-C, mmol/l	2.5 ± 0.8	2.4 ± 0.8	2.5 ± 0.8	0.002
HDL-C, mmol/l	1.3 ± 0.4	1.2 ± 0.4	1.3 ± 0.4	<0.001
Ca × P product, mmol ² /l ²	2.7 ± 0.5	2.8 ± 0.5	2.7 ± 0.5	0.02
Intact PTH, ng/l	53.6 (35.0–88.9)	55.5 (36.0–96.5)	51.5 (34.0–86.0)	0.07
CRP, mg/l	0.07 (0.03–0.19)	0.09 (0.04–0.19)	0.06 (0.03–0.19)	0.02
Lipid-lowering agents	581 (53.9)	300 (62.9)	281 (46.8)	<0.001
Ca-based P binders	102 (9.5)	35 (7.3)	67 (11.1)	0.08
BMI, kg/m ²	24.6 ± 3.1	25.0 ± 3.1	24.3 ± 3.1	<0.001
Normal (18.5–22.9)	332 (30.8)	119 (24.9)	213 (35.4)	
Overweight (23.0–27.4)	563 (52.2)	271 (56.8)	292 (48.6)	
Obese (≥27.5)	183 (17.0)	87 (18.2)	96 (16.0)	
Obese (≥30.0) ^b	65 (6.0)	39 (8.2)	26 (4.3)	
Waist circumference, cm	87.9 ± 9.3	90.4 ± 9.0	86.0 ± 9.0	<0.001
Hip circumference, cm	97.1 ± 6.6	97.7 ± 6.9	96.7 ± 6.3	0.013
WHR	0.90 ± 0.06	0.93 ± 0.06	0.89 ± 0.06	<0.001

AU, Agatston unit; BMI, body mass index; BUN, blood urea nitrogen; Ca, calcium; CAC, coronary artery calcification; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; CRP, C-reactive protein; CVA, cerebrovascular accident; CVD, cardiovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; GN, glomerulonephritis; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; P, phosphorus; PAD, peripheral artery disease; PKD, polycystic kidney disease; PTH, parathyroid hormone; SBP, systolic blood pressure; TG, triglyceride; UPCR, urine protein-to-creatinine ratio; WHR, waist-to-hip ratio.

Data are expressed as mean ± SD, median (interquartile range), or number of patients (percentage).

^aA composite of CAD, PAD, CHF, arrhythmia, and CVA.

^bObese group by the World Health Organization criteria for Western populations.

subjects such that the risk of CAC increased along with the WHR increase, but the risk decreased in the obese group (Supplementary Figure S1).

The highest risk of CAC in the normal BMI with central obesity group

To test our main hypothesis, cross-categorization was performed based on the combination of BMI and WHR. The crude prevalence rate of CAC in the 6 groups is depicted in

Figure 3 and Supplementary Table S4. The crude prevalence rate of CAC was minimal in normal BMI or obese patients without central obesity (WHR < sex-specific median; 29.5% in both), but maximal in patients with normal BMI with central obesity (WHR ≥ sex-specific median; 56.4%). Of note, the prevalence rate of CAC was greater in patients with higher WHR compared with those with lower WHR throughout all BMI categories. To determine the independent risk of CAC according to the 6 combined groups, logistic

Table 2 | Associations of BMI and WHR for the presence of coronary artery calcification

	Univariate		Model 1 ^a		Model 2 ^b	
	OR (95% CI)	P Value	OR (95% CI)	P Value	OR (95% CI)	P Value
BMI (per kg/m ² increase)	1.073 (1.032–1.116)	<0.001	1.019 (0.969–1.072)	0.455	1.026 (0.973–1.082)	0.345
WHR (per 0.01 increase)	1.112 (1.087–1.137)	<0.001	1.034 (1.006–1.063)	0.017	1.036 (1.007–1.065)	0.014

BMI, body mass index; CI, confidence interval; OR, odds ratio; WHR, waist-to-hip ratio.

^aAdjusted for age, sex, diabetes mellitus, cardiovascular disease, smoking status, primary kidney disease, systolic blood pressure, and the use of lipid-lowering agent.

^bAdjusted for model 1 + hemoglobin, albumin, calcium \times phosphorus, log C-reactive protein, estimated glomerular filtration rate, and urine protein-to-creatinine ratio.

regression analyses were used. On univariate analysis, compared with the normal BMI without central obesity group, normal BMI with central obesity (OR = 3.089, 95% CI 1.832–5.208, $P < 0.001$), overweight without central obesity (OR = 2.766, 95% CI 1.956–3.911, $P = 0.011$), overweight with central obesity (OR = 2.766, 95% CI 1.956–3.911, $P < 0.001$), and obese with central obesity (OR = 2.717, 95% CI 1.770–4.171, $P < 0.001$) group were significantly associated with a higher risk of CAC (Table 3). Furthermore,

adjusted ORs were determined by a multivariate logistic regression analysis. Patients with a normal BMI and central obesity had the highest risk of CAC compared with the normal BMI without central obesity group (OR = 2.104, 95% CI 1.074–4.121, $P = 0.030$) (Figure 4). A gradual decrease in the risk of CAC was observed in patients with central obesity, representing reverse epidemiology according to the BMI (Figure 4).

Sensitivity analysis

First, the impact of a normal BMI with central obesity on CAC was further evaluated in the subgroup that included CKD stages 3 to 5 patients ($n = 852$). The highest risk of the normal BMI with central obesity group was robust in CKD stage 3 to 5 patients (adjusted OR = 2.501, 95% CI 1.196–5.230, $P = 0.015$). Second, the highest risk of CAC in the normal BMI with central obesity group remained consistent using different cutoff values of CAC (normal BMI without central obesity as reference; CAC score >100 AU, adjusted OR = 1.990, 95% CI 1.007–3.931, $P = 0.048$; CAC score >400 AU, adjusted OR = 2.347, 95% CI 1.050–5.247, $P = 0.038$) (Supplementary Tables S5 and S6). Last, because 31 underweight (BMI <18.5 kg/m²) were excluded from the primary analysis, we performed a sensitivity analysis including these patients. Of 1109 subjects, CAC was present in 485 patients (43.7%). In accord with the primary results, WHR showed a direct association with CAC (per 0.01 increase, OR = 1.030, 95% CI 1.002–1.058, $P = 0.033$), but the BMI was not significantly associated with CAC (OR = 1.010, 95% CI 0.961–1.062, $P = 0.690$) (Table 4). Furthermore, after cross-categorization by BMI and WHR, multivariate logistic regression analysis demonstrated that the underweight to normal BMI (BMI <23.0 kg/m²) with central obesity group had the highest risk of CAC (underweight to normal BMI without central obesity as reference, OR = 2.040, 95% CI 1.062–3.919, $P = 0.032$) (Table 5).

DISCUSSION

This study investigated the comprehensive effect of 2 independent anthropometric indexes on CV disease in nondialysis CKD patients. We demonstrated for the first time that the coincidence of a normal BMI and higher WHR was independently associated with the highest risk of CAC compared with a normal BMI and lower WHR in these patients. Furthermore, the highest risk of patients with a normal BMI and central obesity was robust in patients with CKD stages 3 to 5. These findings suggest that determining both BMI and

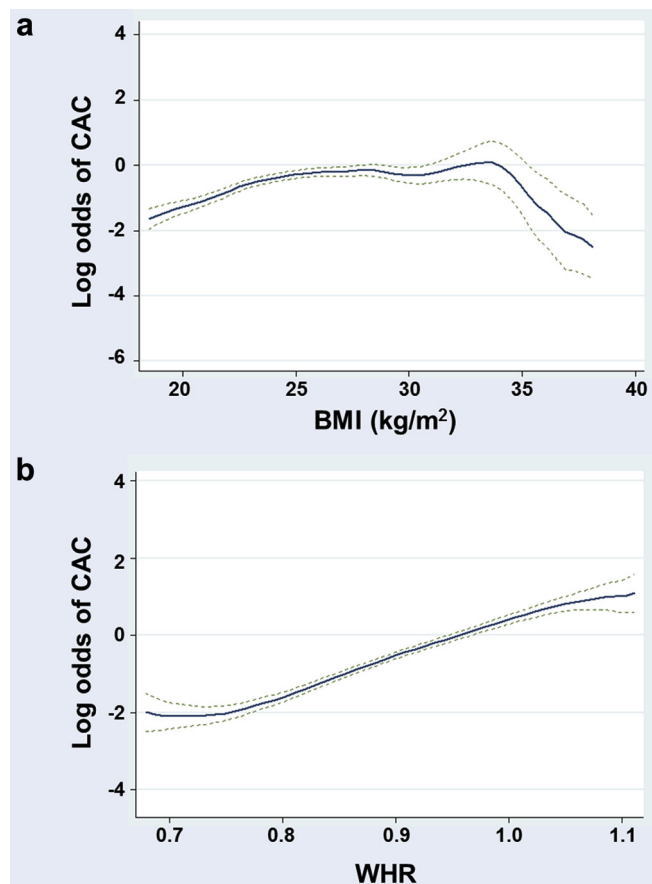


Figure 2 | Restricted cubic splines of BMI and WHR on the risk of CAC. Log odds of CAC with BMI (a) and WHR (b) was depicted in the fully adjusted models. The odds ratio was derived after adjustment for age, sex, diabetes mellitus, cardiovascular disease, smoking status, cause of chronic kidney disease, systolic blood pressure, lipid-lowering therapy, hemoglobin, albumin, calcium \times phosphorus, log C-reactive protein, estimated glomerular filtration rate, and urinary protein-to-creatinine ratio. The dotted line represents the 95% confidence interval. BMI, body mass index; CAC, coronary artery calcification; WHR, waist-to-hip ratio.

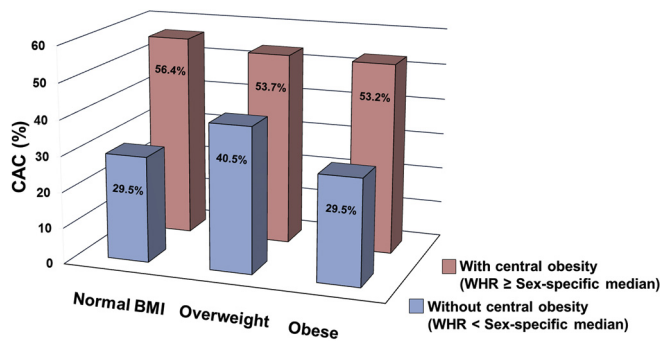


Figure 3 | Crude prevalence rate of CAC in the 6 groups based on the combination of BMI and WHR. Cross-categorization was performed based on the combined BMI and WHR category. Subjects were divided into normal BMI (18.5–22.9 kg/m²), overweight (23.0–27.4 kg/m²), or obese (≥27.5 kg/m²) groups. Patients with a higher WHR (WHR ≥ sex-specific median, 0.92 in male and 0.88 in female patients) were referred to as patients with central obesity. The crude prevalence rate of CAC was minimal in normal BMI without central obesity patients (*n* = 75, 29.5%) and obese without central obesity patients (*n* = 13, 29.5%), but maximal in patients with a normal BMI with central obesity (*n* = 44, 56.4%). BMI, body mass index; CAC, coronary artery calcification; WHR, waist-to-hip ratio.

metrics representing central obesity could be helpful for stratifying CV risk than BMI or WHR alone in nondialysis CKD patients.

Because CV disease is the leading cause of death in CKD patients,²⁰ investigating modifiable risk factors for CV disease has been regarded as a critical issue in clinical practice. In the general population, obesity is a well-known risk factor for mortality and CV disease.^{1,2} However, in patients with CKD, there are conflicting results regarding the association of obesity with mortality or CV risk.^{5–10,12,14,15,17,21–24} Several large-scale studies have shown that a high BMI is associated with low mortality in dialysis patients, which has been referred to as reverse epidemiology.^{5,7,8} In contrast, a high BMI was a significant risk factor for death and technique failure in another study of peritoneal dialysis patients.²¹ In a recent study of nondialysis CKD patients, BMI showed a relative U-shaped association with mortality, independent of CKD stages.¹⁰ The normal BMI and underweight groups (BMI <25 kg/m²) had a higher mortality, but the best outcomes were observed in overweight (25–29.9 kg/m²) and mildly obese (30–34.9 kg/m²) patients.¹⁰ Notably, most previous epidemiologic studies defined obesity using only the BMI.^{2–5,7–10,22,23} However, emerging evidence has indicated that the BMI is not an ideal surrogate marker for obesity, especially for stratifying CV risk.^{11–17,24–26} The BMI presents a

body size, reflecting muscle, bone, and fluid status, as well as fat mass.^{24,26} Moreover, the BMI cannot provide details on the composition of excess fat. Therefore, the predictive role of other anthropometric indexes representing central obesity have been investigated as well as the BMI.^{7,11–17,24,25} The INTERHEART study demonstrated that the BMI in the general population was not an independent predictor of myocardial infarction, whereas the WHR had the strongest predictive power.²⁵ The crucial contribution of central obesity to CV disease was consistent in CKD populations.^{12,14,15,17,24}

Elsayed *et al.*¹² showed that the highest WHR group had a higher risk of myocardial infarction/fatal coronary heart disease compared with the lowest WHR group, whereas a high BMI (>30 kg/m²) was not associated with cardiac events in CKD stages 3 to 4 patients. In another study of 471 CKD patients, the baseline CAC score was not significantly different between the high BMI (≥25 kg/m²) and normal BMI groups, and progression of CAC was not associated with BMI levels.¹⁷ In the current study, the WHR had a direct association with the presence of CAC, whereas the BMI had an inverse relationship with CAC in the univariate analysis. After adjustment for known confounding factors, the WHR, but not the BMI, was an independent risk factor for CAC, in accordance with previous studies.^{12,17} Although this study has not fully determined all possible mechanisms associated with CAC, we surmise that WHR might be implicated in CAC through another mechanism, independent of traditional CV risk factors, suggesting the distinct role of central fat distribution in promoting CAC.

Notably, BMI showed an inverse relationship with CAC on a restricted cubic spline, especially in the obese group. Because our main hypothesis was based on the opposing relationships of the BMI and WHR with CV disease, we speculated that combining the BMI and WHR might modify the CV risk in our subjects. To date, there have been few studies that have investigated the combination of BMI and anthropometric indexes representing central obesity.^{14,16} In the CREDIT study, 537 end-stage renal disease patients were divided into four groups according to the median value of the BMI and WC. The crude CV death rates were the highest in patients with a lower BMI (below the median) and a higher WC (above the median) and were lowest in patients with a higher BMI and a lower WC.¹⁴ Another *post hoc* analysis of coronary artery disease patients showed that the group with a normal BMI and a higher WHR (≥0.98) had the worst survival rate.¹⁶ In the current study, the highest risk of CAC was observed in patients with a normal BMI and a higher WHR

Table 3 | Unadjusted ORs for the presence of CAC based on the cross-categorization of BMI and WHR

	Normal BMI (BMI, 18.5–22.9 kg/m ²)		Overweight (BMI, 23.0–27.4 kg/m ²)		Obese (BMI, ≥27.5 kg/m ²)	
	OR (95% CI)	P Value	OR (95% CI)	P Value	OR (95% CI)	P Value
Without central obesity (WHR < sex-specific median)	1 (reference)		1.625 (1.118–2.362)	0.011	1.001 (0.496–2.018)	0.9
With central obesity (WHR ≥ sex-specific median)	3.089 (1.832–5.208)	<0.001	2.766 (1.956–3.911)	<0.001	2.717 (1.770–4.171)	<0.001

BMI, body mass index; CAC, coronary artery calcification; CI, confidence interval; OR, odds ratio; WHR, waist-to-hip ratio.

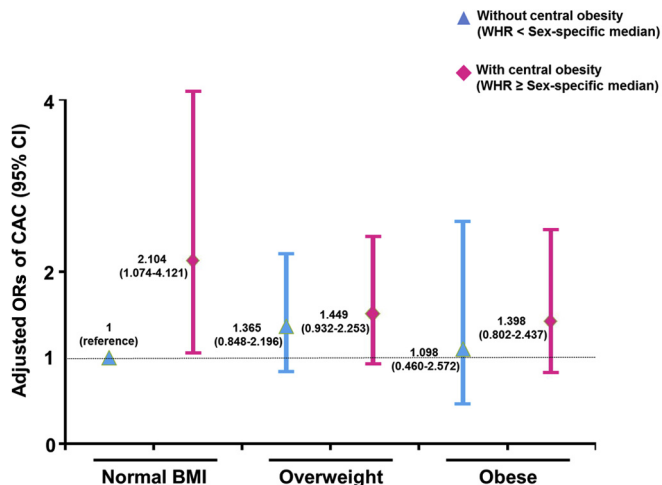


Figure 4 | Graphic presentation of adjusted ORs for the presence of CAC based on the cross-categorization of BMI and WHR. Cross-categorization was performed based on the combination of BMI and WHR category. Subjects were divided into normal BMI (18.5–22.9 kg/m²), overweight (23.0–27.4 kg/m²), or obese (≥27.5 kg/m²) groups. Patients with a higher WHR (WHR ≥ sex-specific median, 0.92 in male and 0.88 in female patients) were referred to as patients with central obesity. Adjusted OR was determined by a multivariate logistic regression analysis after adjustment for age, sex, diabetes mellitus, cardiovascular disease, smoking status, cause of chronic kidney disease, systolic blood pressure, lipid-lowering therapy, hemoglobin, albumin, calcium × phosphorus, log C-reactive protein, estimated glomerular filtration rate, and urinary protein-to-creatinine ratio. Patients with normal BMI and central obesity (OR = 2.104, 95% CI 1.074–4.121, *P* = 0.030) had the highest risk of CAC (normal BMI without central obesity, as reference; overweight without central obesity, OR = 1.365, 95% CI 0.848–2.196, *P* = 0.20; overweight with central obesity, OR = 1.449, 95% CI 0.932–2.253, *P* = 0.10; obese without central obesity, OR = 1.098, 95% CI 0.460–2.572, *P* = 0.83; and obese with central obesity, OR = 1.398, 95% CI 0.802–2.437, *P* = 0.24). BMI, body mass index; CAC, coronary artery calcification; CI, confidence interval; OR, odds ratio; WHR, waist-to-hip ratio.

compared with a normal BMI and a lower WHR, consistent with our hypothesis. In addition, the prevalence rate of CAC was greater throughout all BMI categories in patients with a higher WHR compared with those with a lower WHR. From this result, we infer that the relative contribution of central obesity to CV disease may be greater than that of the BMI. Another interesting finding was that a gradual decrease in CAC risk according to BMI categories was found only in patients with central obesity. Although the underlying cause is unknown, we speculate that this association exists because being noncentrally obese is associated with a constitutionally low CV risk. By contrast, patients with central obesity had much higher CV risk, which can lead to vulnerability to the

hazardous effects of a low BMI, such as decreased muscle mass. Furthermore, the prominence of reverse epidemiology according to the BMI in advanced CKD or end-stage renal disease populations could be another possible explanation. In this study, the lower WHR group had fewer comorbid diseases, such as diabetes and underlying CV disease and the eGFR was significantly higher in the lower WHR group.

There are several possible mechanisms by which a normal BMI with central obesity may cause the highest CV risk in CKD patients. Based on our hypothesis proposed in this study, our observation might be explained by the net additive effect between the adverse effect of central obesity and the lack of a protective effect of a high BMI. Central obesity is associated with a proinflammatory and prothrombotic status resulting from the accumulation of visceral fat.^{24,26} Visceral fat has been regarded as a metabolically active source that secretes various adipokines, inflammatory signals, and immune modulatory factors, which lead, in turn, to insulin resistance, inflammation, oxidative stress, and atherosclerosis.^{24,26–28} Visceral fat increases leptin, which contributes to atherosclerosis by endothelial cell activation, smooth muscle cell proliferation, and vascular calcification.¹⁵ Chronic inflammation is also a well-known risk factor for the development and progression of atherosclerosis.²⁷ In contrast to visceral fat, peripheral fat may confer a protective effect on CV disease that may explain the protective effect of having a high BMI.²⁴ Other factors causing the protective effect of a high BMI include better nutritional status, high muscle mass, and low metabolic rates in these patients.¹⁰ Based on these findings, we surmise that the group with a normal BMI with central obesity might have little muscle mass or subcutaneous fat and relatively greater visceral fat, leading to the highest CV risk. However, anthropometric indexes representing central obesity are used less frequently than the BMI and determining both metrics is rare in clinical practice. Therefore, although a normal BMI but centrally obese patients have a higher CV risk than their overweight or obese counterparts, they tend to receive little information regarding risk reduction, such as life-style modification, resulting in a vicious cycle.¹⁶

Our study has several limitations. First, we excluded 31 underweight patients in the primary analysis, and there were very few morbidly obese patients (*n* = 5, BMI ≥35.0 kg/m²) which was associated with a worse outcome in previous study.¹⁰ We performed sensitivity analyses including underweight patients, and the results were consistent even after inclusion of underweight patients. However, because only a small number of patients at both extremes of a BMI were

Table 4 | Associations of BMI and WHR for the presence of CAC in 1109 patients including 31 underweight subjects

	Univariate		Model 1 ^a		Model 2 ^b	
	OR (95% CI)	<i>P</i> value	OR (95% CI)	<i>P</i> value	OR (95% CI)	<i>P</i> value
BMI (per kg/m ² increase)	1.077 (1.038–1.117)	<0.001	1.007 (0.960–1.055)	0.787	1.010 (0.961–1.062)	0.690
WHR (per 0.01 increase)	1.107 (1.083–1.131)	<0.001	1.029 (1.002–1.056)	0.036	1.030 (1.002–1.058)	0.033

BMI, body mass index; CAC, coronary artery calcification; CI, confidence interval; OR, odds ratio; WHR, waist-to-hip ratio.

^aAdjusted for age, sex, diabetes mellitus, cardiovascular disease, smoking status, cause of chronic kidney disease, systolic blood pressure, and the use of lipid-lowering agent.

^bAdjusted for model 1 + hemoglobin, albumin, calcium × phosphorus, log C-reactive protein, estimated glomerular filtration rate, and urine protein-to-creatinine ratio.

Table 5 | Adjusted ORs for the presence of CAC based on the cross-categorization of BMI and WHR in 1109 patients including 31 underweight subjects

	Underweight to normal BMI (BMI <23.0 kg/m ²)		Overweight (BMI 23.0–27.4 kg/m ²)		Obese (BMI ≥27.5 kg/m ²)	
	OR (95% CI) ^a	P value	OR (95% CI) ^a	P value	OR (95% CI) ^a	P value
Without central obesity (WHR < sex-specific median)	1 (reference)		1.282 (0.806–2.039)	0.293	1.006 (0.433–2.338)	0.9
With central obesity (WHR ≥ sex-specific median)	2.040 (1.062–3.919)	0.032	1.353 (0.881–2.078)	0.167	1.290 (0.748–2.225)	0.359

^aAdjusted for age, sex, diabetes mellitus, cardiovascular disease, smoking status, cause of chronic kidney disease, systolic blood pressure, lipid-lowering agent, hemoglobin, albumin, calcium × phosphorus, log C-reactive protein, estimated glomerular filtration rate, urine protein-to-creatinine ratio.

available for study, we cannot fully clarify the adverse effect of underweight and morbidly obese CKD patients in this study. Furthermore, we also found that the availability of patients having a normal BMI with central obesity or a high BMI without central obesity was not high. When we explored the statistical power for the comparisons with the control group exposure (the group with a normal BMI and no central obesity) being 35%, which was revealed by a descriptive analysis, group sample sizes of 150 in each group achieved 84% power to detect an OR of 2.00, with an α of 0.05 in the 2-sided statistical test. Therefore, negative results of the statistical tests for these groups may be due to the lack of statistical power. Second, there is a lack of a definite cutoff value for CAC in nondialysis CKD patients. In the current study, CAC was defined as a CAC score >10 AU in accordance with other studies that included the general population,^{11,13} dialysis patients,^{29,30} and nondialysis CKD patients.^{15,31} Moreover, the highest risk of CAC in the normal BMI with central obesity group remained significant, even when different cutoff values of CAC (CAC score >100 AU or >400 AU)^{17,32} were used. Third, we included only stage 2 to 5 nondialysis CKD patients in Korea, so our observations might not generalize to other populations. In particular, the mean BMI and WHR were lower in this study compared with other studies in Western countries.^{10,12,14,15,17} The mean BMI of our subjects was 24.6 kg/m², which is regarded as a normal BMI for Western individuals but as overweight among Asians. The difference in the BMI value between Western and Korean cohorts could account for the lack of an independent association of BMI with CAC. In addition, in our study, the most common cause of CKD was glomerulonephritis, in contrast to diabetic nephropathy in Western cohort. Considering the significant association of diabetes with obesity and cardiovascular disease, a lower proportion of diabetic nephropathy could contribute to the nonsignificant association of BMI with CAC. In 860 subjects who had no CV disease history in this study, patients with a normal BMI and central obesity had the highest risk of CAC (a normal BMI without central obesity as reference; adjusted OR = 2.053, 95% CI 1.006–4.191, $P = 0.048$), suggesting that prevalent CV disease did not alter the impact of a normal BMI with central obesity on the CAC risk. Nevertheless, we did not confirm a preceding relationship between a normal BMI with central obesity and CV disease in this study. Furthermore, we cannot clarify whether this combination of effects predicts future CV events or mortality. Because this study is ongoing and a follow-up of

10 years is planned, we will continue to investigate this issue. Last, by virtue of its cross-sectional study design, this study does not include any information regarding interventions. Thus, our data cannot support a benefit of therapeutic weight gain in normal BMI patients with central obesity. The effect of an intervention on weight or central obesity might be also worth investigating. Notwithstanding these limitations, this study is the first investigation to clarify the comprehensive effect of body weight and central obesity on CV disease in nondialysis CKD patients. Patients with a normal BMI but with central obesity, in particular, are likely to be overlooked in clinical practice because of their normal BMI. We believe that our study provides useful information to determine and manage obesity in this population.

In conclusion, nondialysis CKD patients with a normal BMI but central obesity had the highest risk of CAC compared with the normal BMI without central obesity group. This result suggests that considering the BMI and WHR, 2 independent surrogates of obesity, in aggregate can help to determine CV risk in Korean nondialysis CKD patients.

METHODS

Ethics statement

This study was carried out in accordance with the Declaration of Helsinki, and the study protocol was approved by the Institutional Review Board at each participating hospital's Clinical Trial Center, including at Seoul National University Hospital, Yonsei University Severance Hospital, Kangbuk Samsung Medical Center, Seoul St. Mary's Hospital, Gil Hospital, Eulji General Hospital, Chonnam National University Hospital, and Pusan Paik Hospital. All patients provided written informed consent before entering the study.

Study design and subjects

Subjects from the KoreaN Cohort Study for Outcome in Patients With Chronic Kidney Disease (KNOW-CKD) (NCT01630486 at <http://www.clinicaltrials.gov>) between February 2011 and July 2014 were initially screened for this study. The KNOW-CKD study is an ongoing, nationwide, prospective cohort study that included CKD stages 1 to 5 nondialysis patients and designed to clarify the natural course, complication profiles, and risk factors of Asian populations with CKD. The detailed design and methods of the KNOW-CKD were previously published.³³ Among the 1529 patients initially recruited, 281 patients were excluded due to following reasons: missing WHR, BMI, CAC score, or other baseline characteristics. We also excluded 139 CKD stage 1 patients because their clinical characteristics were closer to the general population rather than to CKD patients. Moreover, because being underweight is an established risk

factor for CV disease in CKD, 31 underweight patients (BMI <18.5 kg/m²) were also excluded. Finally, a total of 1078 patients were analyzed in the primary analysis (Figure 1).

Data collection

Baseline demographics and laboratory data were retrieved from the electronic data management system (PhactaX, Seoul, Republic of Korea) with assistance from the Division of Data Management at Seoul National University Medical Research Collaborating Center. Demographic data, including the cause of CKD, smoking history, medications, and comorbidities were collected at the time of screening. CV disease was defined as a composite of coronary artery disease, peripheral artery disease, congestive heart failure, arrhythmia, and cerebrovascular accident history. Anthropometric indexes (height, weight, WC, and hip circumference) were measured as recommended by the WHO.³⁴ BMI was calculated as weight/height² (kg/m²), and WHR was calculated as WC/hip circumference. Whole blood (10 ml) was obtained using a serum separation tube and centrifuged within 1 hour for serum separation and sent to the central laboratory (Lab Genomics, Seoul, Republic of Korea) to measure creatinine, intact parathyroid hormone, and CRP. Serum creatinine was measured by an isotope dilution mass spectrometry-traceable method and eGFR was calculated by the 4-variable Modification of Diet in Renal Disease equation.³⁵ CKD stage from 1 to 5 (nondialysis) was classified by the Kidney Disease Improving Global Outcomes guidelines.³⁶ The following laboratory data were analyzed at the hospital laboratory of each participating center: hemoglobin, albumin, glucose, blood urea nitrogen, triglyceride, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, calcium, and phosphorus. Urine albumin, protein, and creatinine concentrations were measured using the first-voided urine at the central laboratory (Lab Genomics).

Measurement of CAC

CAC was determined by electrocardiography-gated multislice computed tomography scanning of the thorax. The CAC score was determined using AU on a digital radiologic workstation.³⁷ All data were carefully reviewed by the committee of investigators. In accordance with previous studies, clinically evident CAC was defined as a CAC score >10 AU.^{11,13,15,29–31}

Statistical analysis

Statistical analysis was performed using SPSS for Windows version 20.0 (IBM Corp., Armonk, NY) and Stata version 11.0 (StataCorp LP, College Station, TX). Continuous variables were expressed as the mean ± SD or median (interquartile range), and categorical variables were expressed as number (percentage). Normality of distribution was ascertained by the Kolmogorov-Smirnov test. To compare the baseline characteristics according to CAC (CAC score >10 AU), a Student *t* test or Mann-Whitney *U* test was used for continuous variables, and a χ^2 test was used for categorical variables. A linear regression analysis was performed to determine significant factors associated with the BMI and WHR, respectively. To evaluate the independent association of the BMI and WHR with CAC, a logistic regression analysis was used. First, univariate analysis of baseline characteristics for the presence of CAC was performed (Supplementary Table S3). Significant variables in the univariate analysis (*P* < 0.05) were included in the multivariate analysis, and an incremental adjustment was performed: (i) demographic characteristics including age, sex, diabetes mellitus, history of CV disease, smoking status, cause of CKD, systolic blood pressure, and the use of

lipid-lowering therapy and (ii) biochemical variables including hemoglobin, albumin, calcium × phosphorus products, log CRP, eGFR, and urinary protein-to-creatinine ratio. CRP was also included in the multivariate model because of its established significance with CAC despite the lack of statistical significance (Supplementary Table S3, *P* = 0.051). Moreover, because previous studies have shown a nonlinear relationship between BMI and CV risk,¹² the independent association of BMI and WHR with CAC was also evaluated by restricted cubic splines, and graphic illustrations were depicted. The number of knots was 5 and the corresponding values of each knot were as follows: BMI, knot 1 = 20.0, knot 2 = 22.7, knot 3 = 24.4, knot 4 = 26.1; and knot 5 = 30.305 kg/m²; WHR, knot 1 = 0.797, knot 2 = 0.872, knot 3 = 0.907, knot 4 = 0.941, and knot 5 = 1.000. The adjusted OR was calculated after adjusting the same variables of model 2 in Table 3. To test our main hypothesis, subjects were divided by the combination of BMI and WHR categories. Patients were categorized to underweight (BMI <18.5 kg/m²), normal BMI (BMI 18.5–22.9 kg/m²), overweight (BMI 23.0–27.4 kg/m²), or obese (BMI ≥27.5 kg/m²) groups by the WHO recommendations for Asian populations.¹⁸ Because there is a lack of a definite cutoff value for the WHR, subjects were dichotomized by a sex-specific median value for the WHR (0.92 in male and 0.88 in female subjects). Female and male subjects within each sex-specific dichotomized group were combined. Patients with higher WHR (WHR ≥ sex-specific median: 0.92 in male and 0.88 in female patients) were regarded as patients who had central obesity. Then the risk of CAC was determined using univariate and multivariate logistic regression analyses in 6 groups classified by the combination of BMI and WHR categories. For sensitivity analysis, 1109 patients were further analyzed including 31 underweight patients who were excluded in the primary analysis. However, 31 underweight patients were insufficient to configure a cross-categorization that there were only 3 patients who were underweight with central obesity. Therefore, the underweight to normal BMI (BMI <23.0 kg/m²), overweight (BMI 23.0–27.4 kg/m²), and obese (BMI ≥27.5 kg/m²) groups were used in the sensitivity analysis of 1109 patients. Two-sided *P* values <0.05 were considered statistically significant.

DISCLOSURE

All the authors declared no competing interests.

ACKNOWLEDGMENTS

This study was supported by grants 2011E3300300, 2012E3301100, and 2013E3301600 from the Research of Korea Centers for Disease Control and Prevention. This work was presented as an oral abstract at the Annual Meeting of the American Society of Nephrology (November 5–8, 2015), in San Diego, CA. The study was supervised by the CKD Advisory Committee composed of the members from the Korea Centers for Disease Control and Prevention and the Korean Society of Nephrology (NCT01630486 at <http://www.clinicaltrials.gov>).

SUPPLEMENTARY MATERIAL

Table S1. Associations of clinical and biochemical variables with BMI.

Table S2. Associations of clinical and biochemical variables with WHR.

Table S3. Univariate logistic regression analysis of clinical and biochemical variables for the presence of CAC.

Table S4. The crude prevalence of CAC based on the cross-categorization of BMI and WHR.

Table S5. Adjusted ORs for the presence of CAC based on the cross-categorization of BMI and WHR using cutoff of CAC score >100 Agatston unit.

Table S6. Adjusted ORs for the presence of CAC based on the cross-categorization of BMI and WHR using cutoff of CAC score >400 Agatston unit.

Figure S1. Restricted cubic splines of BMI and WHR on the risk of CAC according to CKD stages. In CKD stage 2 (A,B), in CKD stage 3(C,D), and in CKD stages 4 to 5 (E,F). A total of 1078 subjects were categorized to CKD stage 2 (eGFR, 60–89 ml/min per 1.73 m², $n = 226$), stage 3 (eGFR, 30–59 ml/min per 1.73 m², $n = 475$), and stages 4 to 5 (<30 ml/min per 1.73 m², $n = 377$) groups according to eGFR-based CKD stages. In each CKD stage group, log odds of CAC with BMI and WHR were depicted from the fully adjusted models. The odds ratio was derived after adjustment for age, sex, diabetes mellitus, cardiovascular disease, smoking status, cause of chronic kidney disease, systolic blood pressure, lipid-lowering therapy, hemoglobin, albumin, calcium \times phosphorus, log C-reactive protein, and urinary protein-to-creatinine ratio. Dotted line represents 95% confidence interval. BMI, body mass index; CAC, coronary artery calcification; WHR, waist-to-hip ratio.

Supplementary material is linked to the online version of the paper at www.kidney-international.org.

REFERENCES

- Kannel WB, Feinleib M, McNamara PM, et al. An investigation of coronary heart disease in families. The Framingham offspring study. *Am J Epidemiol.* 1979;110:281–290.
- Calle EE, Thun MJ, Petrelli JM, et al. Body-mass index and mortality in a prospective cohort of U.S. adults. *N Engl J Med.* 1999;341:1097–1105.
- Curtis JP, Selter JG, Wang Y, et al. The obesity paradox: body mass index and outcomes in patients with heart failure. *Arch Intern Med.* 2005;165:55–61.
- Mondello P, Mian M, Aloisi C, et al. Cancer cachexia syndrome: pathogenesis, diagnosis, and new therapeutic options. *Nutr Cancer.* 2015;67:12–26.
- Kopple JD, Zhu X, Lew NL, et al. Body weight-for-height relationships predict mortality in maintenance hemodialysis patients. *Kidney Int.* 1999;56:1136–1148.
- Glanton CW, Hypolite IO, Hsieh PB, et al. Factors associated with improved short term survival in obese end stage renal disease patients. *Ann Epidemiol.* 2003;13:136–143.
- Johansen KL, Young B, Kaysen GA, et al. Association of body size with outcomes among patients beginning dialysis. *Am J Clin Nutr.* 2004;80:324–332.
- Kalantar-Zadeh K, Kopple JD, Kilpatrick RD, et al. Association of morbid obesity and weight change over time with cardiovascular survival in hemodialysis population. *Am J Kidney Dis.* 2005;46:489–500.
- Kwan BC, Murtaugh MA, Beddhu S. Associations of body size with metabolic syndrome and mortality in moderate chronic kidney disease. *Clin J Am Soc Nephrol.* 2007;2:992–998.
- Lu JL, Kalantar-Zadeh K, Ma JZ, et al. Association of body mass index with outcomes in patients with CKD. *J Am Soc Nephrol.* 2014;25:2088–2096.
- See R, Abdullah SM, McGuire DK, et al. The association of differing measures of overweight and obesity with prevalent atherosclerosis: the Dallas Heart Study. *J Am Coll Cardiol.* 2007;50:752–759.
- Elsayed EF, Tighiouart H, Weiner DE, et al. Waist-to-hip ratio and body mass index as risk factors for cardiovascular events in CKD. *Am J Kidney Dis.* 2008;52:49–57.
- Ho JS, Cannaday JJ, Barlow CE, et al. Comparative relation of general, central, and visceral adiposity measures for coronary artery calcium in subjects without previous coronary events. *Am J Cardiol.* 2009;104:943–946.
- Postorino M, Marino C, Tripepi G, et al. Abdominal obesity and all-cause and cardiovascular mortality in end-stage renal disease. *J Am Coll Cardiol.* 2009;53:1265–1272.
- Cordeiro AC, Qureshi AR, Lindholm B, et al. Visceral fat and coronary artery calcification in patients with chronic kidney disease. *Nephrol Dial Transplant.* 2013;28(Suppl 4):iv152–iv159.
- Coutinho T, Goel K, Correa de Sa D, et al. Combining body mass index with measures of central obesity in the assessment of mortality in subjects with coronary disease: role of “normal weight central obesity”. *J Am Coll Cardiol.* 2013;61:553–560.
- Russo D, Morrone LF, Errichiello C, et al. Impact of BMI on cardiovascular events, renal function, and coronary artery calcification. *Blood Purif.* 2014;38:1–6.
- WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet.* 2004;363:157–163.
- Obesity: preventing and managing the global epidemic. Report of a WHO consultation. *World Health Organ Tech Rep Ser.* 2000;894:i–xii, 1–253.
- Stevens PE, O'Donoghue DJ, de Lusignan S, et al. Chronic kidney disease management in the United Kingdom: NEOERICA project results. *Kidney Int.* 2007;72:92–99.
- McDonald SP, Collins JF, Johnson DW. Obesity is associated with worse peritoneal dialysis outcomes in the Australia and New Zealand patient populations. *J Am Soc Nephrol.* 2003;14:2894–2901.
- Kovesdy CP, Anderson JE, Kalantar-Zadeh K. Paradoxical association between body mass index and mortality in men with CKD not yet on dialysis. *Am J Kidney Dis.* 2007;49:581–591.
- Madero M, Sarnak MJ, Wang X, et al. Body mass index and mortality in CKD. *Am J Kidney Dis.* 2007;50:404–411.
- Lee MJ, Shin DH, Kim SJ, et al. Visceral fat thickness is associated with carotid atherosclerosis in peritoneal dialysis patients. *Obesity (Silver Spring).* 2012;20:1301–1307.
- Yusuf S, Hawken S, Ounpuu S, et al. Obesity and the risk of myocardial infarction in 27,000 participants from 52 countries: a case-control study. *Lancet.* 2005;366:1640–1649.
- Zoccali C. The obesity epidemics in ESRD: from wasting to waist? *Nephrol Dial Transplant.* 2009;24:376–380.
- Stenvinkel P, Chung SH, Heimbürger O, et al. Malnutrition, inflammation, and atherosclerosis in peritoneal dialysis patients. *Perit Dial Int.* 2001;21(Suppl 3):S157–S162.
- Wisse BE. The inflammatory syndrome: the role of adipose tissue cytokines in metabolic disorders linked to obesity. *J Am Soc Nephrol.* 2004;15:2792–2800.
- Caliskan Y, Demirturk M, Ozkok A, et al. Coronary artery calcification and coronary flow velocity in haemodialysis patients. *Nephrol Dial Transplant.* 2010;25:2685–2690.
- Turkmen K, Kayikcioglu H, Ozbek O, et al. The relationship between epicardial adipose tissue and malnutrition, inflammation, atherosclerosis/calcification syndrome in ESRD patients. *Clin J Am Soc Nephrol.* 2011;6:1920–1925.
- Aoqui C, Cuppari L, Kamimura MA, et al. Increased visceral adiposity is associated with coronary artery calcification in male patients with chronic kidney disease. *Eur J Clin Nutr.* 2013;67:610–614.
- Russo D, Corrao S, Battaglia Y, et al. Progression of coronary artery calcification and cardiac events in patients with chronic renal disease not receiving dialysis. *Kidney Int.* 2011;80:112–118.
- Oh KH, Park SK, Park HC, et al. KNOW-CKD (KoreaN cohort study for Outcome in patients With Chronic Kidney Disease): design and methods. *BMC Nephrol.* 2014;15:80.
- Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee. *World Health Organ Tech Rep Ser.* 1995;854:1–452.
- Levey AS, Coresh J, Greene T, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med.* 2006;145:247–254.
- Chapter 1: Definition and classification of CKD (2011). *Kidney Int Suppl.* 2013;3:19–62.
- Agatston AS, Janowitz WR, Hildner FJ, et al. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol.* 1990;15:827–832.