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

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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/m^2) 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.

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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

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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 ± 3.1 kg/m^2 (24.8 ± 3.0 kg/m^2 in male patients and 24.3 ± 3.3 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 18.5–22.9 kg/m^2), overweight (BMI 23.0–27.4 kg/m^2), or obese (BMI ≥27.5 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 ≥30.0 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 ≥ 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 × 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.

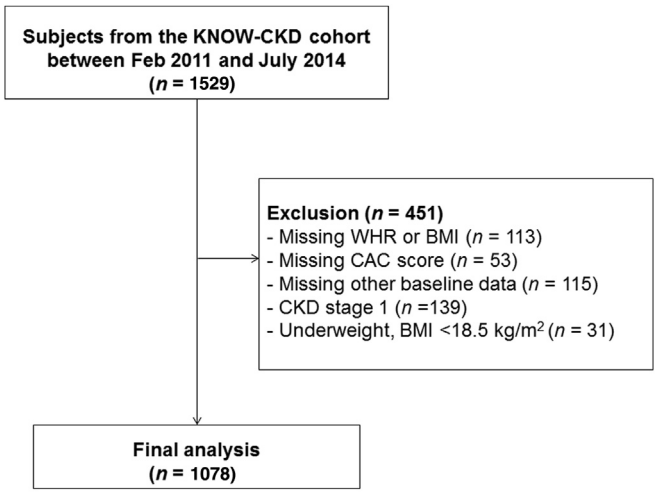

Figure 1 | Flow diagram of patients. Of 1529 CKD stages 1 to 5 nondialysis patients, 451 patients were excluded. A total of 1078 patients were analyzed. BMI, body mass index; CAC, coronary artery calcification; CKD, chronic kidney disease; KNOW-CKD, KoreaN Cohort Study for Outcome in Patients With Chronic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

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 × 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