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Obesity is associated with incident chronic kidney disease in individuals with normal renal function

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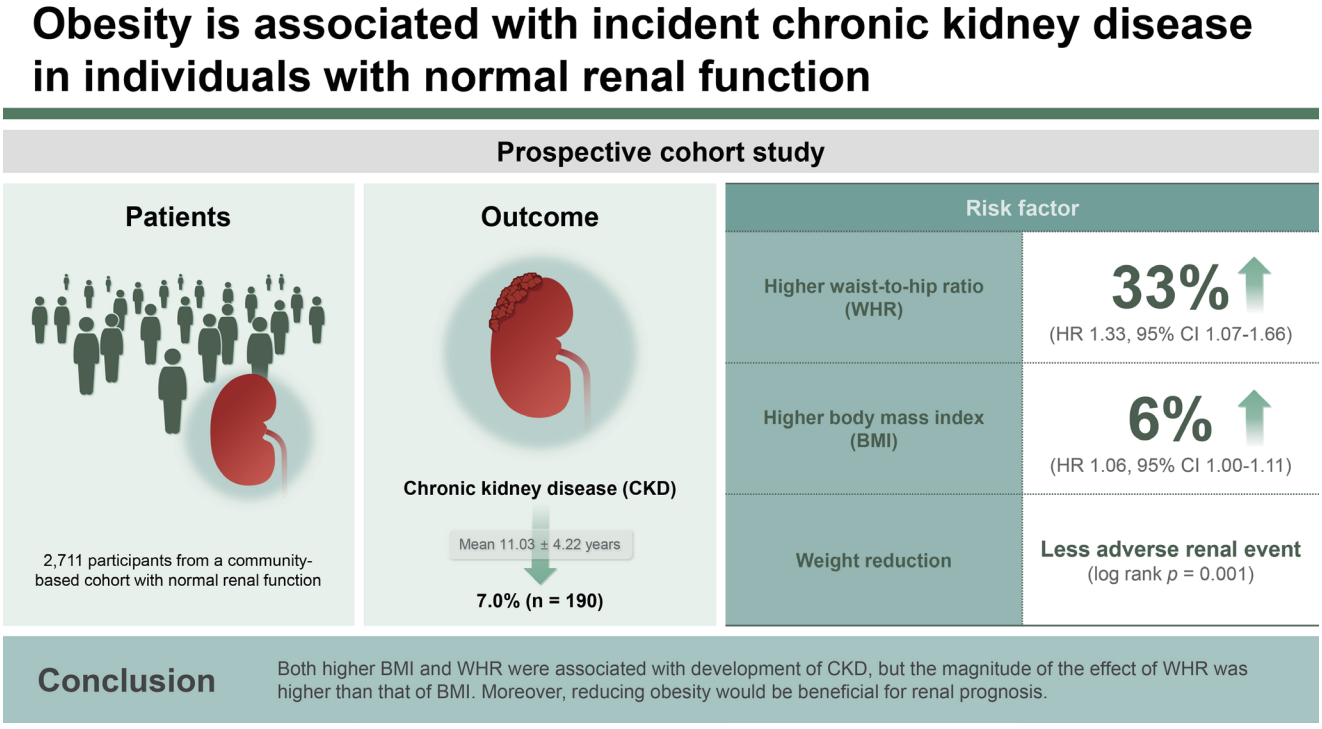

Background/Aims: Obesity has known to be a modifiable risk factor associated with worse outcomes in chronic kidney disease (CKD), but few studies have examined the impact of obesity on CKD incidence in the general population. The purpose of this study was to investigate the role of body mass index (BMI) and waist-to-hip ratio (WHR) as predictors of incident CKD and to evaluate the impact of weight reduction on CKD prevention.

Methods: A total of 2,711 participants from a community-based cohort with normal renal function were prospectively analyzed. Among participants with obesity, we analyzed the change in WHR to evaluate the association of obesity reduction with CKD development.

Results: During a mean follow-up of 11.03 ± 4.22 years, incident CKD occurred in 190 (7.0%) participants. In the fully adjusted multivariable Cox proportional hazard models, the risk of incident CKD increased with higher BMI (hazard ratio, 1.06; 95% confidence interval, 1.00–1.11; p = 0.033) and higher WHR (hazard ratio, 1.33; 95% confidence interval, 1.07–1.66; p = 0.009). In the Kaplan–Meier analysis, cumulative adverse renal events were significantly more common in the maintained

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obesity group than in the reduced obesity group (p = 0.001).
Conclusions: Both higher BMI and WHR were associated with development of CKD, but the magnitude of the effect of WHR was higher than that of BMI. Moreover, reducing obesity would be beneficial for renal prognosis.

Keywords: Body mass index; Chronic kidney disease; Obesity; Waist-to-hip ratio

INTRODUCTION

Obesity is a serious health problem worldwide with increasing prevalence, which has reached 40% in the United States and has been consistently rising in Asia [1]. Obesity is strongly associated with metabolic abnormalities, such as high blood pressure, dyslipidemia, high blood sugar levels, insulin resistance, and increased inflammation [2-4], as well as with increased risk for cardiovascular and all-cause mortality [5,6]. In addition, obesity is associated with development of chronic kidney disease (CKD). A high body mass index (BMI) is strongly related to decrease in estimated glomerular filtration rate (eGFR) and progression to end-stage CKD [7,8]. Several mechanisms have been proposed to promote renal dysfunction in people with obesity, such as glomerular hyperfiltration, inflammation, and endothelial dysfunction [9,10]. CKD is a major public burden with rising global prevalence, imposing the need to identify and mitigate its associated risk factors.

The World Health Organization defines obesity as "an excessive fat accumulation [11]." Although BMI is a simple and useful tool, it tends to be affected by muscle mass. In addition, the BMI does not address regional adiposity. Thus, the waist-to-hip ratio (WHR), a measure of central obesity, may be a better tool for assessing obesity.

Obesity might be a representative modifiable risk factor for incident CKD. However, many studies have looked at obesity's impact on outcomes in CKD patients, there's little research on how obesity in the general population can lead to CKD. In this study, we evaluated both BMI and WHR as risk factors for the development of incident CKD in the general population from the Korean Genome and Epidemiology Study (KoGES), which is a community-based prospective cohort study [12]. Moreover, to determine whether reducing obesity is beneficial for preventing renal dysfunction, we also compared renal function between individuals with maintained obesity and those with reduced obesity.

METHODS

Study population

The KoGES is a large, prospective, community-based cohort study funded by the government. The detailed profile and methods concerning the development of KoGES have been previously described [12]. The present study included KoGES participants who were residents of Ansan, Korea. We excluded participants with an eGFR < 60 mL/min/1.73 m^2 and those with missing follow-up data on serum creatinine levels and body weight.

All study participants voluntarily enrolled the KoGES after providing informed consent. This study was performed in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of Chonnam National University Hospital (CNUH-EXP-2022-094).

Anthropometric and laboratory data

All participants underwent comprehensive health examinations and filled out questionnaires on health and lifestyle at the time of enrollment. Serial health examinations and surveys were performed biennially from 2001 to 2018.

The following demographic and socioeconomic data were collected from the KoGES database: age, sex, alcohol intake, smoking status, and medical history. Diabetes mellitus (DM) and hypertension (HTN) were diagnosed based on the responses to the past medical history in the administered questionnaire. Information on alcohol intake and smoking status were obtained through questionnaires. Anthropometric parameters, including height, weight, waist circumference, and hip circumference, were measured by skilled study workers following standard methods. Blood pressure was measured after resting for more than 5 minutes in a sitting position.

Blood and urine samples were obtained after an 8-hour fasting and transported to a central laboratory (Seoul Clinical Laboratories, Seoul, Korea). The following biochemical data were determined: concentrations of blood urea nitrogen, creatinine, albumin, glucose, total cholesterol, triglyceride,

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low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, glycated hemoglobin (HbA1c), hemoglobin, and C-reactive protein (CRP). Serum creatinine levels were measured using an isotope dilution mass spectrometry-traceable method. The eGFR was calculated using the CKD-EPI equation [13]. Proteinuria was measured categorically, and we defined proteinuria by classifying the 'negative' and 'trace' group as group without proteinuria, and '1 positive' to '4 positive' as group with proteinuria. Insulin resistance was determined by the homeostasis model assessment of insulin resistance (HOMA-IR): Fasting glucose (mg/dL) × fasting insulin (μIU/mL) / 405.

Definitions of obesity, obesity reduction, and study outcomes

Obesity was defined both by the BMI and WHR. BMI was calculated by dividing the weight (kg) by the squared height (m^2) and categorized as normal weight (BMI 18.5–22.9 kg/m^2), overweight (BMI 23–24.9 kg/m^2), or obesity (BMI ≥ 25 kg/m^2) according to the International Association for the Study of Obesity, International Obesity Task Force (2000), and Committee of Clinical Practice Guidelines and Korean Society for the Study of Obesity Guidelines [14]. WHR was calculated by dividing waist circumference by hip circumference. Obesity was defined as an WHR ≥ 0.9 for men and ≥ 0.85 for women [15].

The study outcome was incident CKD rate during the follow-up period, which was defined as a composite eGFR of < 60 mL/min/1.73 m^2 for at least two consecutive measurements.

To evaluate the effect of obesity reduction on CKD development, we analyzed the changes in WHR from baseline to year 4. For this purpose, participants with an WHR ≥ 0.9 for men and ≥ 0.85 for women at both baseline and year 4 were defined as the maintained obesity group, while those with an WHR ≥ 0.9 for men and ≥ 0.85 for women at baseline and WHR < 0.9 for men and < 0.85 for women at year 4 were defined as the reduced obesity group. To determine the relationship between early WHR changes and subsequent CKD development, we only analyzed adverse renal events that occurred 4 years after the WHR assessment period.

Statistical analysis

Statistical analyses were performed using R version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were summarized as mean ± standard deviation, and categorical variables as number (percentage). All data were tested for normality before analysis. A t-test or Mann–Whitney's U test was conducted to compare continuous variables, and the chi-square test was used to compare categorical variables. To analyze the changes in participants' metabolic profile parameters during the follow-up period, we compared time-averaged values of fasting glucose, HbA1c, the HOMA-IR, CRP, and lipid profiles, which were analyzed as an average of the parameters examined at every follow-up visit.

Multivariable Cox regression models using cubic spline curves were used to determine the nonlinear association between the BMI or WHR and the risk of incident CKD. Kaplan–Meier survival curves with log-rank tests and univariable Cox proportional hazards models were used to examine the effect of BMI or WHR on incident CKD. Multivariable Cox proportional hazards regression analysis was employed to identify independent risk factors for incident CKD. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated to estimate the risk of incident CKD. We examined the assumption of the proportional hazard in the Cox model using cox.zph() in R. Age- and sex-adjusted HRs were first calculated (model 1), and the results were further adjusted for HTN, DM, alcohol consumption, and smoking (model 2), and further for LDL cholesterol, hemoglobin, CRP, and baseline eGFR (model 3). For all analyses, a p value < 0.05 was considered to indicate statistical significance.

RESULTS

Baseline characteristics of the study population

Of the 5,012 participants screened, 2,711 (age range: 40–

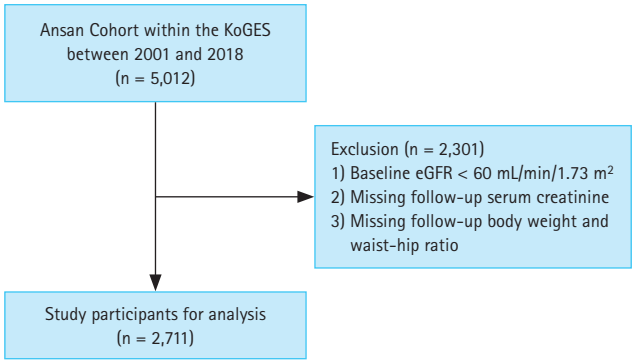

Figure 1. Study flow diagram. KoGES, Korean Genome and Epidemiology Study; eGFR, estimated glomerular filtration rate.

69 yr) were included in the final analysis (Fig. 1). The baseline characteristics of the total study population according to their BMI are presented in Table 1. Participants in the obesity group were predominantly older, had lower income, higher incidence of DM and HTN, higher HbA1c and triglyceride levels, and lower HDL cholesterol levels than those in the normal weight group.

Table 1. Baseline characteristics of the total study population according to BMI

Variable	Total population (n = 2,712)			*p* value
	Normal (n = 1,542)	Overweight (n = 1,045)	Obesity (n = 125)	
Age (yr)	48.2 ± 7.4	49.3 ± 7.5	50.2 ± 8.2	< 0.001
Male, sex	778 (50.5)	573 (54.8)	42 (33.6)	< 0.001
Education				< 0.001
No education or elementary school graduate	180 (11.7)	166 (15.9)	33 (26.4)	
Middle school graduate	339 (22.0)	224 (21.4)	27 (21.6)	
High school graduate	715 (46.4)	428 (41.0)	45 (36.0)	
More than college graduate	308 (19.9)	227 (21.7)	20 (16.0)	
Alcohol drinking status				0.022
Never	687 (44.6)	414 (39.6)	64 (51.2)	
Former drinker	85 (5.5)	54 (5.2)	8 (6.4)	
Drinker	770 (49.9)	577 (55.2)	53 (42.4)	
Smoking status				< 0.001
Never	910 (59.0)	575 (55.0)	92 (73.6)	
Former smoker	276 (17.9)	225 (21.5)	14 (11.2)	
Current smoker	356 (23.1)	245 (23.5)	19 (15.2)	
Household income/mo, in won (more than 2,000 USD)[a]	867 (56.2)	597 (57.1)	61 (48.8)	0.028
Diabetes mellitus	78 (5.1)	62 (5.9)	17 (13.6)	< 0.001
Hypertension	108 (7.0)	177 (16.9)	33 (26.4)	< 0.001
Systolic BP (mmHg)	114.3 ± 16.8	120.7 ± 16.1	125.0 ± 16.8	< 0.001
Diastolic BP (mmHg)	76.4 ± 11.3	80.8 ± 11.3	84.5 ± 11.6	< 0.001
BUN (mg/dL)	14.0 ± 3.3	14.6 ± 3.6	14.7 ± 3.2	< 0.001
Creatinine (mg/dL)	0.856 ± 0.2	0.893 ± 0.2	0.851 ± 0.2	< 0.001
eGFR (mL/min/1.73 m^2)	94.7 ± 15.3	91.5 ± 16.1	90.9 ± 15.7	< 0.001
Hemoglobin (g/dL)	13.5 ± 1.6	14.0 ± 1.6	13.6 ± 1.4	< 0.001
HbA1c (%)	5.7 ± 0.9	5.8 ± 0.9	6.2 ± 1.2	< 0.001
Na (mmol/L)	142.7 ± 2.2	142.9 ± 2.2	142.4 ± 2.2	0.007
K (mmol/L)	4.5 ± 0.4	4.4 ± 0.5	4.4 ± 0.5	0.584
CRP (mg/dL)	0.2 ± 0.4	0.2 ± 0.4	0.3 ± 0.3	< 0.001
HDL cholesterol (mg/dL)	51.1 ± 12.0	46.5 ± 10.3	46.4 ± 10.5	< 0.001
Triglyceride (mg/dL)	144.3 ± 98.3	177.0 ± 101.2	210.8 ± 160.5	< 0.001
LDL cholesterol (mg/dL)	117.2 ± 32.1	122.3 ± 33.1	118.8 ± 39.3	0.001

Values are presented as mean ± standard deviation or number (%).
BMI, body mass index; BP, blood pressure; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; Na, sodium; K, potassium; CRP, C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
[a]$1 USD ≒ 1,000 won.

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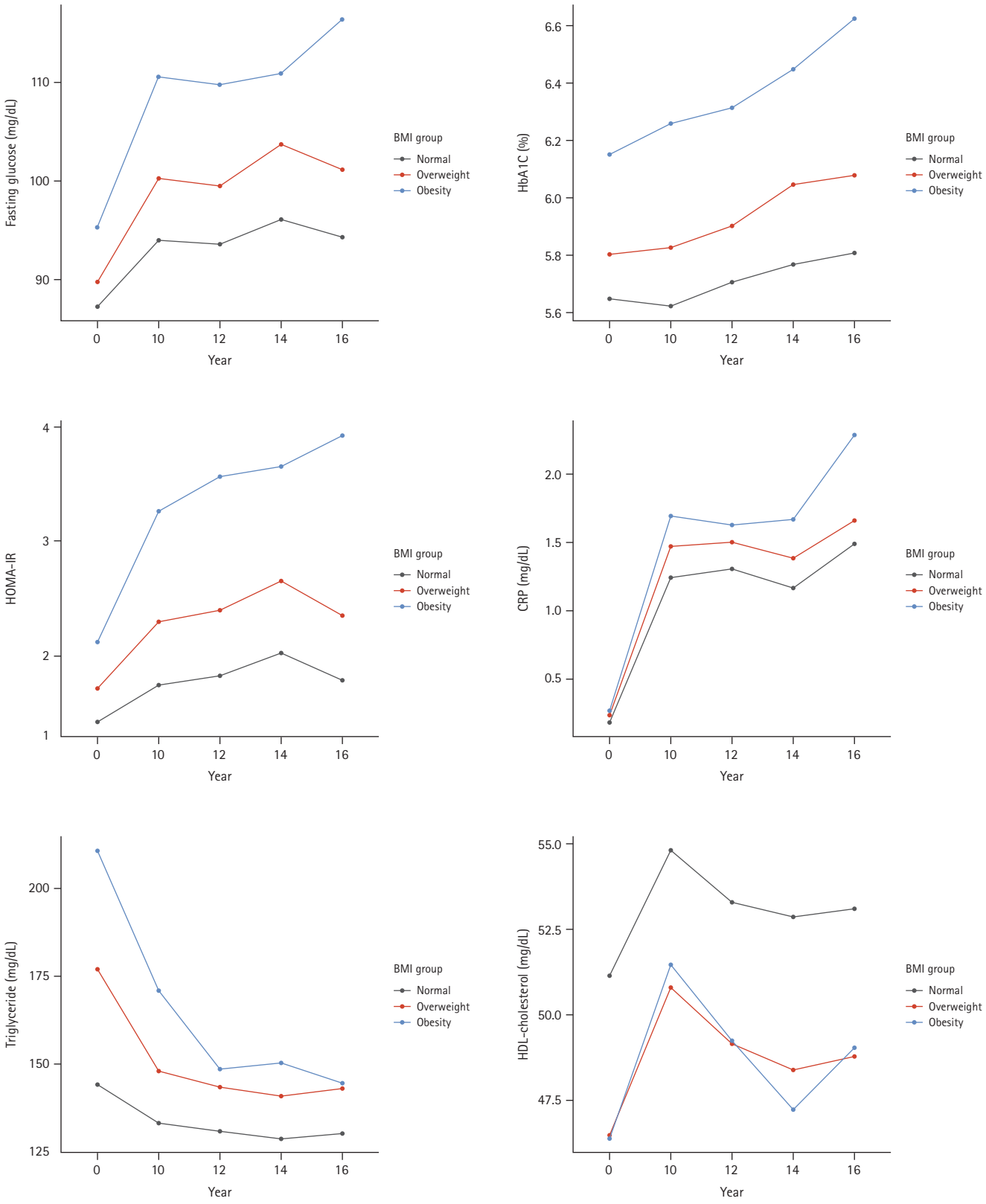

Figure 2. Longitudinal changes in metabolic profile parameters during the follow-up period. The X-axis denotes follow-up duration in years. BMI, body mass index; HbA1c, hemoglobin A1c; HOMA-IR, homeostasis model assessment-insulin resistance; CRP, C-reactive protein; HDL, high-density lipoprotein.

Table 2. HR for incident chronic kidney disease by BMI and WHR with Cox proportion hazard models

Variable	Unadjusted		Adjusted					
			Model 1		Model 2		Model 3	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
BMI	1.12 (1.07–1.17)	< 0.001	1.11 (1.06–1.17)	< 0.001	1.09 (1.04–1.15)	< 0.001	1.06 (1.00–1.11)	0.033
WHR	2.05 (1.72–2.45)	< 0.001	1.59 (1.29–1.96)	< 0.001	1.49 (1.19–1.85)	< 0.001	1.33 (1.07–1.66)	0.009

BMI, body mass index; WHR, waist-to-hip ratio; HR, hazard ratio; CI, confidence interval; DM, diabetes mellitus; LDL, low-density lipoprotein; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate.
Model 1: adjusted for age and sex; Model 2: Model 1 + hypertension, DM, alcohol consumption, and smoking; Model 3: Model 2 + LDL cholesterol, hemoglobin, CRP, and eGFR.

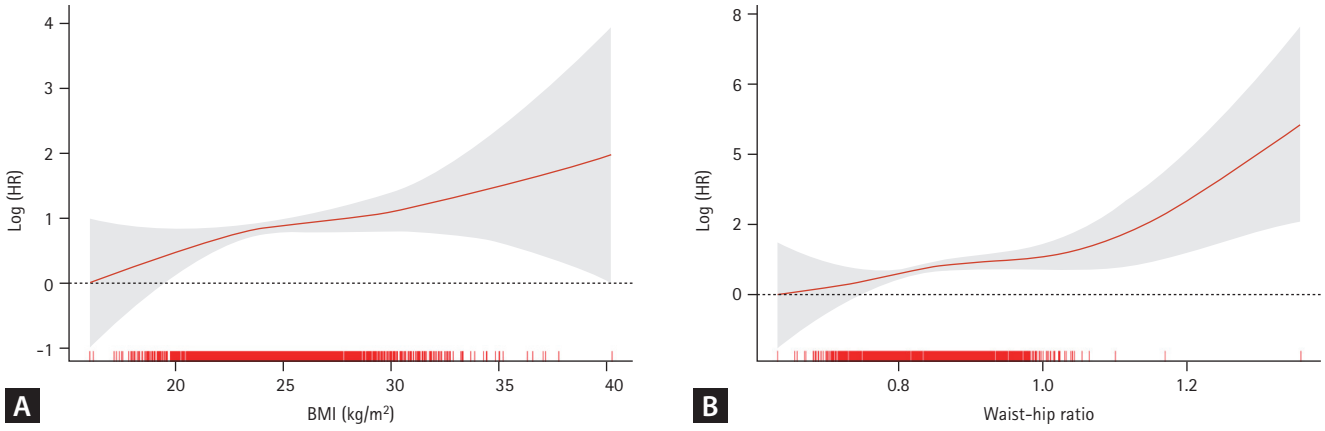

Figure 3. Log-transformed adjusted hazard ratio and 95% confidence interval for incident CKD probability associated with (A) BMI and (B) WHR. The BMI and WHR exhibited a positive correlation with the risk for incident CKD. CKD, chronic kidney disease; BMI, body mass index; WHR, waist-to-hip ratio.

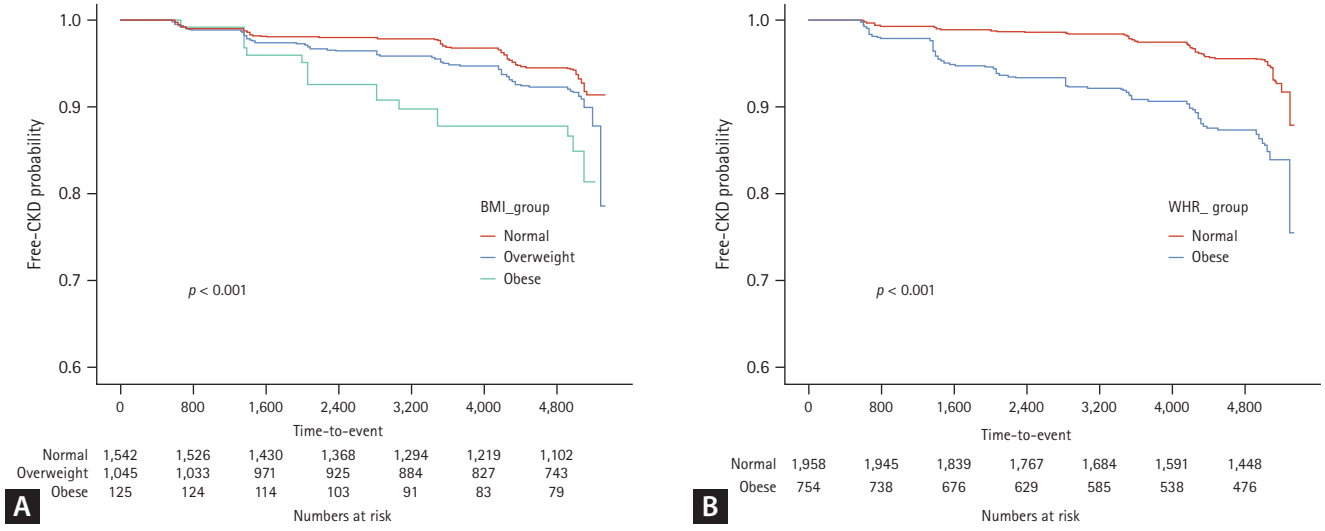

Figure 4. Kaplan–Meier free-of-CKD probability curve with log-rank test between the obesity group and incident CKD. Obesity according to the (A) BMI and (B) WHR was associated with poor free-of-CKD probability. The X-axis denotes time-to events duration in days. CKD, chronic kidney disease; BMI, body mass index; WHR, waist-to-hip ratio.

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Changes in metabolic profile parameters during follow-up

During the follow-up period, the obesity group had persistently lower levels of HDL-cholesterol, and higher levels of fasting glucose, HbA1c, HOMA-IR, CRP, and triglycerides (Fig. 2).

Risk of incident CKD

During a mean follow-up of 11.03 ± 4.22 years, incident CKD occurred in 190 (7.0%) participants. In the fully adjusted Cox proportional hazards model (Table 2), BMI and WHR exhibited a positive correlation with the risk for incident CKD (Fig. 3). The risk for incident CKD increased with higher BMI (HR, 1.06; 95% CI, 1.00–1.11; $p = 0.033$) and higher WHR (HR, 1.33; 95% CI, 1.07–1.66; $p = 0.009$).

In the Kaplan–Meier analysis for free-of-CKD probability (Fig. 4), the cumulative incidence of CKD development was significantly high ($p < 0.001$) in both obesity groups classified by BMI and WHR.

In the analysis of the effects of obesity reduction on incident CKD (Fig. 5), the Kaplan–Meier curves showed that the rate of cumulative adverse renal events was significantly in the maintained obesity group than in the reduced obesity group ($p = 0.001$).

Subgroup analyses

Finally, we conducted subgroup analyses to evaluate whether the association between obesity and the risk for incident CKD is modified by some factors (Fig. 6). We classified the degree of obesity according to the individual's WHR. The subgroups were stratified by age (< 60 or ≥ 60 yr), sex, HTN, DM, and proteinuria. Multivariable Cox regression analysis revealed that p for interaction was > 0.05 for all subgroups, suggesting that the association of obesity with increased risk for incident CKD is not modified by these factors.

An additional subgroup analysis was performed to examine whether the effect of obesity reduction on the risk for incident CKD is modified by some factors (Supplementary Fig. 1). In the multivariable Cox regression analysis, p for interaction was > 0.05 for all subgroups, suggesting that the association of obesity reduction with decreased risk for incident CKD is not modified by these factors.

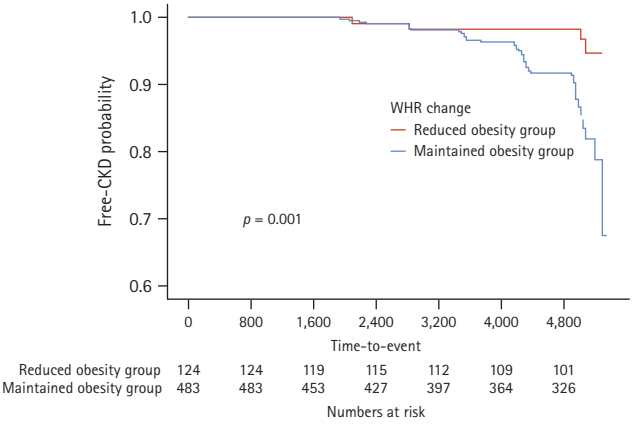

Figure 5. Kaplan–Meier free-of-CKD probability curve with log-rank test according to obesity reduction. The X-axis denotes time-to events duration in days. CKD, chronic kidney disease; WHR, waist-to-hip ratio.

DISCUSSION

In this study, we found that obesity has an effect on CKD development in a population with normal renal function. Higher BMI and WHR significantly increased the risk for incident CKD in the multivariable analyses. Moreover, reducing obesity was beneficial for renal prognosis. These findings suggest that maintaining an appropriate weight is important for preserving renal function in a population with normal renal function. In addition, longitudinal changes in the

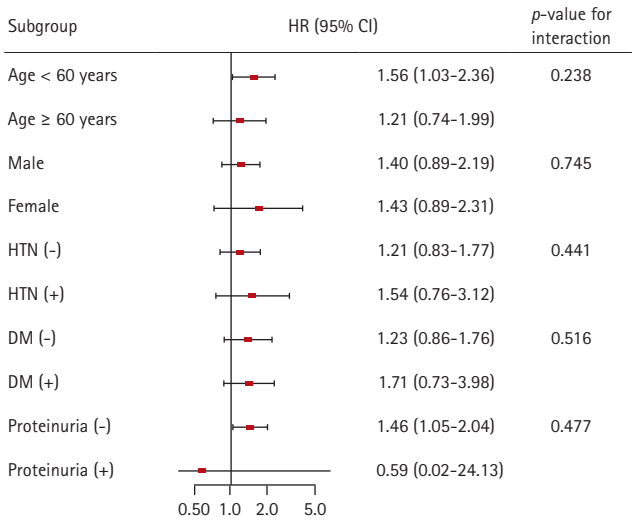

Figure 6. Multivariable Cox regression analysis for incident CKD according to WHR, stratified by subgroups. Models were adjusted for age, sex, HTN, DM, alcohol consumption, smoking, LDL cholesterol, hemoglobin, CRP, and baseline eGFR. HR, hazard ratio; CI, confidence interval; HTN, hypertension; DM, diabetes mellitus; CKD, chronic kidney disease; WHR, waist-to-hip ratio; LDL, low-density lipoprotein; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate.

metabolic profile showed that the obesity group had consistently poor metabolic profile. Moreover, our subgroup analyses suggest that obesity had an effect on development of CKD regardless of age, sex, HTN, and DM. This result reinforces the importance of obesity management in the general population.

Previous large surveys in a multiracial population documented that high BMI is strongly associated with the risk for CKD [8]. Another study showed that high BMI was a risk factor for CKD in Japanese men, but not in Japanese women [16]. Although BMI is the most useful index for obesity, it cannot distinguish between weight from muscle and fat, and between central and peripheral obesity. A previous study showed that WHR was more independently predictive of coronary heart disease than waist circumference or BMI in a general population cohort [17]. Elsayed et al. demonstrated that WHR but not BMI was a risk factor for incident CKD [18]. In the current study, both BMI and WHR were independent risk factors for incident CKD, but the magnitude of the effect of WHR was higher than that of BMI. BMI only provides body mass volume based on height, whereas WHR provides information about body shape and fat distribution, such as central obesity, which is the true meaning of obesity.

This study also showed that renal prognosis was better in individuals with reduced than in those with maintained obesity. Obesity is a well-known risk factor for cardiovascular disease, DM, stroke, and all-cause mortality [5,6,19,20]. HTN and DM are established risk factors for CKD, and a recent study showed that dyslipidemia is independently associated with incident CKD in the general population [21,22]. Obesity would affect renal function by causing these diseases. However, as mentioned in the studies above, obesity itself is a risk factor for CKD. The current study also revealed that obesity was independently associated with incident CKD after adjustment for HTN, DM, and LDL cholesterol. The mechanisms by which obesity directly affects renal function are unclear. One possible explanation is glomerular hyperfiltration/HTN. Bosma et al. [23] revealed that as BMI increases, effective renal plasma flow decreases and filtration fraction (the ratio of GFR and effective renal plasma flow) increases. The only way to explain GFR maintenance despite decreased renal plasma flow is glomerular hyperfiltration. Animal data also showed that obesity was associated with increased arterial pressure, glomerular hyperfiltration, and structural kidney damage, such as increased mesangial matrix and thickening of the glomerular and tubular basement membranes [24,25]. In fact, adipocytes produce a variety of factors that may affect renal microcirculation, such as angiotensinogen, leptin, and asymmetric dimethyl arginine, which is the most important endogenous inhibitor of nitric oxide synthase [9]. Adipocyte secretory products also directly stimulate aldosterone secretion that may be responsible for obesity-related HTN [26,27]. A previous study showed that weight reduction decreases plasma renin activity and aldosterone levels, and improves high blood pressure [28]. Although it has not yet been investigated whether these mechanisms observed in experiments also apply to healthy human, efforts to improve obesity, a modifiable factor, would be valuable for protecting renal function.

This study has several limitations. First, a causal relationship between obesity and CKD development could not fully be established due to the observational study design. Second, in the evaluation of the effect of obesity reduction, the sample size was small because only the obesity group at baseline was included. Further studies with larger sample sizes are needed.

However, our study also has certain strengths. Namely, both BMI and WHR were used to measure obesity and their influence on CKD development was compared. In addition, to assess the significance of obesity reduction, we categorized obesity reduction using the baseline and 4-year WHR. With these strengths, this study demonstrated that obesity, particularly the group with high WHR, was an independent risk factor for CKD development, suggesting that reducing obesity is beneficial for renal prognosis.

In conclusion, High BMI and high WHR were associated with incident CKD. Efforts to reduce fat tissue and obesity, such as weight loss, exercise, and diet control, can protect renal function in the healthy population.

KEY MESSAGE

1. Higher BMI and WHR significantly increased the risk for incident CKD, and the magnitude of the effect of WHR was higher than that of BMI.
2. Renal prognosis was better in individuals with reduced obesity than in those with maintained obesity.
3. Obesity has an effect on CKD development in a population with normal renal function, and this finding suggest that maintaining an appropriate weight is important for preserving renal function.

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Su Hyun Song: conceptualization, methodology, formal analysis, writing - original draft; Tae Ryom Oh: methodology, investigation, data curation, validation, software; Sang Heon Suh: formal analysis, validation, software, visualization; Hong Sang Choi: methodology, investigation, data curation, validation, software, writing - original draft; Chang Seong Kim: validation, software, visualization; Seong Kwon Ma: writing - review & editing, visualization, supervision; Soo Wan Kim: resources, supervision, funding acquisition; Eun Hui Bae: conceptualization, writing - review & editing, supervision, project administration, funding acquisition

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