Original Article

Association between Obesity and Chronic Kidney Disease in Japanese: Differences in Gender and Hypertensive Status?

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Obesity is a known risk factor for hypertension and diabetes, both of which ultimately promote renal dysfunction. In the current study, we investigated the association between body mass index (BMI) and chronic kidney disease (CKD) in 8,168 Japanese individuals (2,924 women, 5,244 men) who underwent general health screening. CKD was diagnosed if the estimated glomerular filtration rate (eGFR) was less than 60 mL/min/1.73 m² (designated as low eGFR) and/or if the urinary albumin/creatinine value was equal to or greater than 30 mg/g (designated as albuminuria). Logistic regression analysis adjusted for age, systolic blood pressure, fasting glucose, and smoking habits showed that, in men, both overweight (BMI 25–29 kg/m²) and obesity (BMI ≥ 30 kg/m²) were associated with increased prevalence of low eGFR and albuminuria, whereas, in women, obesity was associated with albuminuria, but neither overweight nor obesity was associated with low eGFR. After multivariate adjustment, logistic regression analysis showed that BMI had a graded association with both low eGFR and albuminuria in men. On the other hand, in women, the second and third BMI quartiles were associated with a lower prevalence of albuminuria in comparison with the first BMI quartile. Essentially the same results were obtained when the subjects were subdivided according to the presence and absence of hypertension. Our data showed that overweight and obesity were associated with increased risk for CKD in Japanese individuals undergoing a general health screening, irrespective of the presence or absence of hypertension, although there was a gender difference in these associations. (*Hypertens Res* 2007; 30: 1059–1064)

Key Words: obesity, chronic kidney disease, gender difference, hypertension

Introduction

As in Western countries (1, 2), the prevalence of obesity among Japanese is increasing, especially in men and women older than 40 years of age (3). Several cross-sectional and longitudinal epidemiological studies have shown that obesity may increase the prevalence and incidence of chronic kidney

disease (CKD) (4–8). Care must be taken in interpreting these data, since several of the studies have diagnosed CKD based on an estimated glomerular filtration rate (eGFR) lower than a certain cutoff value, while others have defined CKD based on either low eGFR or the presence of albuminuria/proteinuria. Nevertheless, it is of note that one study found a gender-related difference in the association between obesity and CKD (9), whereas other reports did not (4, 5). Obesity

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increases renal sodium reabsorption, which results in an elevation of blood pressure (6, 10, 11) and may explain the observed link between obesity and CKD, as hypertension is one of the most important factors associated with the progression of both diabetic and nondiabetic CKD (7). On the other hand, Kramer *et al.* noted a significant association between obesity and the risk for CKD, defined as ≥ 1 + proteinuria and/or eGFR < 60 mL/min/1.73 m², in a cohort of hypertensive adults, which was statistically significant after adjustment for blood pressure and diabetes (8). This finding suggested that obesity and overweight increase the incidence of CKD independent of the degree of hypertension.

In the current study, we sought to investigate whether body mass index (BMI) was associated with CKD and its components, which are low eGFR and albuminuria, in Japanese individuals who underwent general health screening, and whether the mode of this association, if present, differed according to gender and hypertensive status.

Methods

Study Population

The study was approved by the Ethical Committee of the Mitsui Memorial Hospital. Between April 2004 and August 2006, 12,535 individuals (4,481 women and 8,054 men) undergoing a general health screen at this institute, including an estimation of urinary excretion of albumin, and who completed a questionnaire concerning the amount and duration of their alcohol consumption, were enrolled in the present study. In Japan, regular health check-ups for employees are a legal requirement; all or most of the costs of the screening are paid for either by the place of employment or by the subjects themselves. Ideal BMI, overweight, and obesity were defined as BMI < 25 kg/m², BMI 25–29 kg/m², and BMI ≥ 30 kg/m², respectively.

Laboratory Analysis

Blood samples were taken from the subjects after an overnight fast. Serum levels of total cholesterol (TC), high-density lipoprotein (HDL)-cholesterol (HDL-C), and triglycerides (TG) were determined enzymatically. Serum uric acid (UA) was measured by the uricase-peroxidase method, hemoglobin A1c was determined using the latex agglutination immunoassay, and creatinine was determined by the enzymatic method. Plasma glucose was measured by the hexokinase method and serum insulin was measured by enzyme immunoassay. Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated in these individuals according to the following formula: HOMA-IR = [fasting immunoreactive insulin (μ U/mL) $\times$ fasting plasma glucose (FPG; mg/dL)]/405. Metabolic syndrome was said to be present when three or more of the following conditions were met: TG levels ≥ 150 mg/dL; HDL-C levels < 40 mg/dL; FPG levels ≥ 110 mg/dL

Table 1. Baseline Characteristics

	Women (<i>n</i> =2,924)	Men (<i>n</i> =5,244)
Age (years)	52.0 $\pm$ 10.7	53.8 $\pm$ 10.5
Waist circumference (cm)	76.8 $\pm$ 9.0	85.8 $\pm$ 7.8
Body mass index (kg/m ²)	21.2 $\pm$ 3.0	23.7 $\pm$ 2.9
Systolic blood pressure (mmHg)	117 $\pm$ 19	125 $\pm$ 19
Diastolic blood pressure (mmHg)	73 $\pm$ 12	79 $\pm$ 11
Lipid data		
LDL-cholesterol (mg/dL)	127 $\pm$ 33	129 $\pm$ 31
HDL-cholesterol (mg/dL)	68 $\pm$ 15	55 $\pm$ 13
Triglycerides (mg/dL)	85 $\pm$ 47	133 $\pm$ 89
Glucose metabolism		
Fasting glucose (mg/dL)	90 $\pm$ 15	100 $\pm$ 21
Hemoglobin A1c (%)	5.2 $\pm$ 0.5	5.4 $\pm$ 0.8
HOMA-IR	1.2 $\pm$ 0.9	1.7 $\pm$ 1.3
Metabolic syndrome (<i>n</i> (%))	103 (3.5)	744 (14.2)
Renal data		
Serum urea nitrogen (mg/dL)	13.6 $\pm$ 3.5	14.6 $\pm$ 3.5
Serum creatine (mg/dL)	0.63 $\pm$ 0.24	0.86 $\pm$ 0.20
eGFR (mL/min/1.73 m ²)	69 $\pm$ 10	70 $\pm$ 10
Urinary albumin/creatinine ratio (mg/g)	18 $\pm$ 68	26 $\pm$ 182
Smoking status		
Non-smokers (<i>n</i> (%))	2,510 (86)	1,743 (33)
Former smokers (<i>n</i> (%))	177 (6)	1,893 (36)
Current smokers (<i>n</i> (%))	243 (8)	1,608 (31)

LDL, low-density lipoprotein; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; eGFR, estimated glomerular filtration rate.

or current use of antidiabetic medication; systolic blood pressure (SBP) ≥ 130 mmHg or diastolic blood pressure (DBP) ≥ 85 mmHg or current use of antihypertensive medication; BMI ≥ 25 kg/m².

Estimated Glomerular Filtration Rate, Albuminuria, and Definition of CKD

Serum creatinine was calibrated using the following formula: serum creatinine (Jaffe method) = 0.2 + serum creatinine (enzyme method). Serum creatinine was measured in mg/dL and age in years; GFR was estimated using the equation from a simplified version of the Modification of Diet in Renal Disease (MDRD) (12) as follows: eGFR (mL/min/1.73 m²) = $186.3 \times (\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203} \times 0.881$ ($\times 0.742$ if female). In this MDRD formula, 0.881 is a coefficient for eGFR specific to the Japanese population (13). An eGFR of < 60 mL/min/1.73 m² was designated as low eGFR. For the diagnosis of albuminuria, spot urine samples were collected and analyzed; albuminuria was considered to be present when the urinary albumin excretion ratio (UAER) was ≥ 30 mg/g-creatinine. Normoalbuminuria, microalbuminuria, and macroalbuminuria were defined as an UAER of < 30 mg/g, 30–

Fig. 1. Prevalence of low eGFR and albuminuria according to BMI quartiles.

299 mg/g, and 300 mg/g, respectively (14). Individuals were said to have CKD when they had either or both of low eGFR and albuminuria (15).

Statistical Analysis

The data in this study were analyzed by multivariate logistic regression analysis using computer software, StatView ver. 5.0 (SAS Institute, Cary, USA). A value of $p < 0.05$ was taken to be statistically significant. Results are expressed as the means $\pm$ SD unless stated otherwise.

Results

Baseline Characteristics

Characteristics of the enrolled subjects are shown in Table 1. The numbers of women with overweight and obesity were 254 (8.7%) and 32 (1.1%), respectively, and the numbers in men were 1,361 (26.0%) and 147 (2.8%), respectively.

Among women, 432 (14.8%) had low eGFR, 254 (8.7%) had albuminuria, and 55 (1.9%) had both low eGFR and albuminuria. Therefore, 631 (21.6%) women were considered to have CKD. In men, low eGFR was found in 739 (14.1%) and albuminuria in 535 (10.2%), and both low eGFR and albuminuria were present in 122 (2.3%). Therefore, 1,152 men (22.0%) were considered to have CKD. Micro- and macroalbuminuria were found in 236 (8.1%) and 18 (0.6%) women, respectively, and in 467 (8.9%) and 68 (1.3%) men, respectively. Pearson's correlation coefficients for the relationship between BMI and UA were 0.29 ($p < 0.0001$) in women and 0.23 ($p < 0.0001$) in men.

The interquartile cutoff values for BMI were 19.2, 20.7, and 22.8 kg/m² in women and 21.9, 22.5, and 25.3 kg/m² in men. The correlation coefficient between WC and BMI was 0.79 in women and 0.84 in men.

Association among BMI, Overweight, Obesity and CKD

In both genders, the prevalence of low eGFR and that of albuminuria was greatest in the highest BMI quartile (Fig. 1). Age-adjusted logistic regression analysis showed that women in the second and third BMI quartiles had a lower prevalence of CKD and albuminuria after adjustment for age, SBP, FPG, and smoking status. On the other hand, in men, the prevalence of CKD and albuminuria was increased according to BMI in the multivariate adjusted model. BMI showed a graded association with low eGFR in men (Table 2). When data on only male never smokers ($n = 1,743$) were analyzed, the first, second, third, and fourth BMI quartiles were associated with low eGFR with an odds ratio of 1 (referent), 1.21 (95% confidence interval [CI] 0.83–1.77, $p = 0.33$), 1.18 (95% CI 0.80–1.74, $p = 0.41$), and 1.76 (95% CI 1.16–2.67, $p = 0.0077$), respectively.

We then analyzed the association between overweight and obesity and CKD components in a logistic regression analysis after adjusting for age, SBP, FPG, and smoking status; the ideal BMI was used as the reference (Table 3). Both overweight and obesity were associated with low eGFR in men, but again not in women. Obesity in women and both overweight and obesity in men were associated with albuminuria.

Association between BMI and CKD Components in Hypertensive and Non-Hypertensive Subjects

We next evaluated whether hypertension modified the association between BMI and CKD. Hypertension was found in 502 (17.2%) of the women and 1,658 (31.6%) of the men. The mode of association between BMI and CKD (and its components) was similar between hypertensive and non-hypertensive individuals (Table 4). In women without hypertension, individuals in the second BMI quartile had significantly lower prevalence of low eGFR when compared with those in the

Table 2. Association between Body Mass Index and CKD and Its Components

	Odds ratio (95% CI)		Odds ratio (95% CI)		Odds ratio (95% CI)	
	For CKD	<i>p</i> value	For low eGFR	<i>p</i> value	For albuminuria	<i>p</i> value
Women						
Model 1						
BMI-Q1	1	—	1	—	1	—
BMI-Q2	0.63 (0.48–0.84)	0.0017	0.69 (0.50–0.97)	0.032	0.61 (0.40–0.92)	0.020
BMI-Q3	0.86 (0.66–1.13)	0.28	0.93 (0.68–1.27)	0.64	0.76 (0.51–1.11)	0.16
BMI-Q4	0.99 (0.76–1.29)	0.96	0.86 (0.63–1.18)	0.36	1.39 (0.98–1.96)	0.065
Model 2						
BMI-Q1	1	—	1	—	1	—
BMI-Q2	0.60 (0.45–0.80)	0.0004	0.72 (0.51–1.01)	0.055	0.48 (0.32–0.74)	0.0009
BMI-Q3	0.80 (0.61–1.05)	0.10	0.99 (0.72–1.36)	0.94	0.57 (0.38–0.85)	0.0062
BMI-Q4	0.82 (0.62–1.09)	0.17	1.01 (0.72–1.41)	0.97	0.73 (0.50–1.07)	0.11
Men						
Model 1						
BMI-Q1	1	—	1	—	1	—
BMI-Q2	1.50 (1.22–1.85)	0.0001	1.40 (1.11–1.78)	0.0055	1.45 (1.06–1.98)	0.019
BMI-Q3	1.56 (1.27–1.92)	<0.0001	1.44 (1.13–1.83)	0.0028	1.71 (1.27–2.32)	0.0005
BMI-Q4	2.66 (2.18–3.25)	<0.0001	1.71 (1.35–2.17)	<0.0001	3.81 (2.88–5.03)	<0.0001
Model 2						
BMI-Q1	1	—	1	—	1	—
BMI-Q2	1.41 (1.14–1.74)	0.0016	1.43 (1.12–1.82)	0.040	1.27 (0.92–1.75)	0.16
BMI-Q3	1.38 (1.11–1.70)	0.0032	1.47 (1.15–1.88)	0.0019	1.32 (0.96–1.82)	0.088
BMI-Q4	2.05 (1.66–2.54)	<0.0001	1.82 (1.42–2.34)	<0.0001	2.26 (1.68–3.06)	<0.0001

Model 1: adjusted for age. Model 2: adjusted for age, systolic blood pressure, fasting glucose and smoking habits. BMI, body mass index; CKD, chronic kidney disease; CI, confidence interval; eGFR, estimated glomerular filtration rate.

first BMI quartile, and individuals in the second or third BMI quartiles had significantly lower prevalence of albuminuria when compared with those in the first BMI quartile.

Discussion

In this cross-sectional study, we investigated the association between BMI and CKD components in individuals who underwent general health screening. BMI had a graded association with CKD, low eGFR, and albuminuria in men, whereas women in the second and the third BMI quartiles had a significantly lower prevalence of CKD and albuminuria. Modes of association between BMI and CKD (and its components) were similar between hypertensive and non-hypertensive individuals, especially in men.

Several previous studies have examined the association between BMI and CKD. In a community-based longitudinal cohort study in the U.S., BMI was found to be related to the development of kidney disease (16). Kramer *et al.* reported that overweight (BMI 25–29.9 kg/m²) and obesity (BMI ≥30 kg/m²) were associated with CKD, defined as the presence of 1+ or greater proteinuria and/or eGFR <60 mL/min/1.73 m², in hypertensive subjects, and that this association remained statistically significant even after adjustment for blood pressure and diabetes (8). Gelber *et al.* reported that BMI was

associated with low eGFR in a 14-year follow-up of apparently healthy men (17).

In the current study, we found a gender difference in the association between BMI and low eGFR: an increased BMI was a risk factor for low eGFR only in men, but not in women. Iseki *et al.* reported in their 17-year cohort study that elevations in BMI had a graded association with the cumulative incidence of end-stage renal disease (ESRD) compared with individuals with a baseline BMI of <21 kg/m² (9); however, this association was only found in men. In the same study, Iseki *et al.* suggested that this gender difference might be partly attributable to a difference in the prevalence of cigarette smoking (9). This was because cigarette smoking, prevalence of which is higher in men, is a risk factor for the ESRD and proteinuria (18, 19).

It is possible that the difference in the mode of association between BMI and low eGFR (or albuminuria) between genders was attributable to the usage of sex-specific quartiles, which resulted in different cutoff values between genders. And in fact, when we used the same cutoff values, the association between obesity and albuminuria was observed in both genders with similar odds ratios (Table 4). It should be noted, however, that overweight and obesity were associated with low eGFR in men, but again, not in women (Table 4). Thus, this concept could not explain the gender difference in the

Table 3. Association between Overweight, Obesity, and CKD and Its Components

	Odds ratio (95% CI)		Odds ratio (95% CI)		Odds ratio (95% CI)	
	For CKD	<i>p</i> value	For low eGFR	<i>p</i> value	For albuminuria	<i>p</i> value
Women						
Ideal BMI	1	—	1	—	1	—
Overweight	1.00 (0.72–1.39)	>0.99	1.06 (0.72–1.55)	0.78	1.07 (0.71–1.61)	0.74
Obesity	2.20 (0.98–4.96)	0.056	0.27 (0.03–2.09)	0.21	2.74 (1.20–6.27)	0.017
Men						
Ideal BMI	1	—	1	—	1	—
Overweight	1.56 (1.33–1.82)	<0.0001	1.44 (1.20–1.73)	0.0001	1.70 (1.38–2.08)	<0.0001
Obesity	2.77 (1.91–4.02)	<0.0001	2.14 (1.32–3.47)	0.0021	2.72 (1.77–4.17)	<0.0001

Odds ratios were obtained after adjusting for age, systolic blood pressure, fasting glucose and smoking habits. CKD, chronic kidney disease; BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate.

Table 4. Association between Body Mass Index and CKD and Its Components According to Hypertensive Status

	Odds ratio (95% CI)		Odds ratio (95% CI)		Odds ratio (95% CI)	
	For CKD	<i>p</i> value	For low eGFR	<i>p</i> value	For albuminuria	<i>p</i> value
Women						
HT (+)						
BMI-Q1	1	—	1	—	1	—
BMI-Q2	0.73 (0.32–1.63)	0.44	1.17 (0.43–3.18)	0.75	0.75 (0.30–1.87)	0.53
BMI-Q3	0.82 (0.38–1.78)	0.61	1.13 (0.43–2.94)	0.81	0.79 (0.33–1.92)	0.61
BMI-Q4	1.08 (0.53–2.22)	0.83	1.34 (0.55–3.26)	0.52	1.16 (0.53–2.57)	0.71
HT (–)						
BMI-Q1	1	—	1	—	1	—
BMI-Q2	0.60 (0.44–0.81)	0.0011	0.67 (0.47–0.97)	0.033	0.45 (0.27–0.74)	0.0017
BMI-Q3	0.85 (0.63–1.14)	0.28	1.01 (0.72–1.41)	0.97	0.57 (0.36–0.91)	0.018
BMI-Q4	0.80 (0.57–1.10)	0.17	1.00 (0.69–1.46)	1.00	0.61 (0.38–1.00)	0.052
Men						
HT (+)						
BMI-Q1	1	—	1	—	1	—
BMI-Q2	1.36 (0.91–2.01)	0.13	1.45 (0.90–2.35)	0.13	1.19 (0.72–1.96)	0.49
BMI-Q3	1.56 (1.06–2.28)	0.023	1.78 (1.13–2.82)	0.014	1.28 (0.79–2.07)	0.32
BMI-Q4	1.90 (1.32–2.74)	0.0006	1.81 (1.15–2.83)	0.0097	1.86 (1.18–2.91)	0.0071
HT (–)						
BMI-Q1	1	—	1	—	1	—
BMI-Q2	1.43 (0.11–1.85)	0.0053	1.45 (0.19–1.93)	0.010	1.19 (0.77–1.83)	0.44
BMI-Q3	1.25 (0.96–1.64)	0.099	1.32 (0.98–1.79)	0.070	1.14 (0.74–1.78)	0.55
BMI-Q4	2.13 (1.61–2.81)	<0.0001	1.87 (1.35–2.61)	0.0002	2.20 (1.44–3.34)	0.0002

Odds ratios were obtained after adjusting for age, systolic blood pressure, fasting glucose and smoking habits. BMI, body mass index; CKD, chronic kidney disease; CI, confidence interval; eGFR, estimated glomerular filtration rate; HT (+), hypertensive; HT (–), non-hypertensive.

association between obesity and low eGFR in both genders. A study in the U.S. showed a relationship between obesity and nephrosclerosis in women only (20), and a study in Norway showed an association between obesity (BMI ≥ 30 kg/m²) and decreased eGFR (eGFR < 45 mL/min/1.73 m²) in both genders. Together with these previous findings, our data suggested that the gender difference in the mode of association between BMI and CKD might differ according to racial

groups and ethnicities. On the other hand, recent studies analyzing the data of Japanese hypertensive patients showed that the mode of association between UA and left ventricular hypertrophy (LVH) (21), and that between insulin resistance and LVH (22) differed according to gender. Considering the possible association between CKD and LVH (23), it is possible that the gender difference in the association between BMI and CKD components that was observed in the current study

might be attributed to certain variables that may also underlie the gender difference in the association between insulin resistance, UA, and LVH. This possibility should be investigated in future studies.

We also showed that the pattern of association between BMI and low eGFR was not significantly affected by the hypertension status. Together with the finding that the association between BMI and CKD was only slightly altered when SBP was used as a covariate (Model 2 in Tables 2 and 3), this result indicates that the effect of blood pressure on the association between obesity and CKD may not be as pronounced as previously thought.

In conclusion, we analyzed cross-sectional data on 8,168 individuals (2,924 women, 5,244 men) who underwent general health screening and found that BMI showed a graded association with both low eGFR and albuminuria in men. In women, on the other hand, the second and third quartiles of WC and BMI were associated with lower prevalence of albuminuria when compared with the first BMI quartile. Obesity (BMI ≥ 30 kg/m²) was associated with albuminuria in both genders, whereas the association between obesity and low eGFR was observed only in men. Modes of association between BMI and CKD (or its components) were similar in hypertensive and non-hypertensive individuals, especially in men. Our data showed that overweight and obesity have already become associated with an increased risk of CKD in low risk Japanese individuals, such as general health screening participants, although there is a slight gender difference.

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