Original Article

An Association between Body Mass Index and Estimated Glomerular Filtration Rate

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Chronic kidney disease (CKD) is a major public health problem. However, few studies have examined the significance of body mass index (BMI) as a risk factor for the development of CKD in the general Japanese population. Study participants without a clinical history of stroke, transient ischemic attack, myocardial infarction, angina or renal failure (754 men aged 56±15 [mean±SD] years and 962 women aged 59±13 years) were randomly recruited from a single community at the time of their annual health examination. We examined the relationship between increased weight (*i.e.*, BMI) and renal function evaluated by the estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease Study Group equation. Increased BMI was consistently associated with reduced eGFR. Estimated GFR was lower in participants with upper normal body weight (BMI, 22.0 to 24.9 kg/m^2) or who were overweight or obese (BMI≥25 kg/m^2), compared with participants with lower normal body weight (BMI, 18.5 to 21.9 kg/m^2). Stepwise multiple regression analysis using eGFR as an objective variable, adjusted for various risk factors as explanatory variables, showed that BMI (β=−0.075) was significantly and independently associated with eGFR, in addition to age, log triglycerides, low-density lipoprotein cholesterol and log fasting blood glucose. Compared with those with lower normal body weight, multivariate-adjusted odds ratios for moderately reduced renal function, defined as an eGFR <60 mL/min/1.73 m^2, were 1.86 (1.01–3.42) for upper normal weight and 2.02 (1.01–4.03) for overweight or obese individuals. In conclusion, increased BMI is strongly associated with decreased eGFR in community-dwelling healthy persons. (*Hypertens Res* 2008; 31: 1559–1564)

Key Words: **overweight, risk factor, renal function, estimated glomerular filtration rate, chronic kidney disease**

Introduction

The increasing prevalence of chronic kidney disease (CKD), with its associated high annual rates of mortality and cardiovascular complications (*1*–*3*), is a major public health problem. In Japan, clinical practice guidelines established by the Japanese Society of Nephrology estimate that 18.7% of adults have CKD, which is defined as kidney damage or glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 for 3 months or more regardless of cause (*4*), and 4.1% have moderate or severe CKD (*5*). Identifying risk factors for CKD is critical in order to devise effective, population-based preventive strategies.

Obesity is also a major worldwide public health problem. Obesity increases the risk of cardiovascular disease, diabetes, hypertension, and dyslipidemia (*6*, *7*). However, few studies have examined the relationship between excess weight and CKD risk. Obese patients are at a higher risk for focal segmental glomerulosclerosis and glomerulomegaly (*8*), and almost half of patients rapidly develop advanced renal failure

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This work was supported in part by a grant-in-aid for Scientific Research from the Foundation for Development of Community (2008).
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Received January 9, 2008; Accepted in revised form May 1, 2008.

Table 1. Characteristics of Various Risk Factors of Subjects Categorized by Body Mass Index

Characteristics	Body mass index† (kg/m^2)				p for trend*
	BMI-1 <18.5 (n=100)	BMI-2 18.5–21.9 (n=579)	BMI-3 22.0–24.9 (n=620)	BMI-4 ≥25.0 (n=417)	
Sex (male/female)	34/66	242/337	280/340	198/219	0.055
Age (years)	59±15	57±15	59±13	56±13	0.006
Body mass index† (kg/m^2)	17.4±1.0	20.5±0.9	23.4±0.8	27.2±2.3	<0.001
Smoking status‡ (pack year)	9±18	8±15	8±17	10±18	—
Log smoking status‡ (pack year)	0.41±0.67	0.39±0.63	0.38±0.65	0.47±0.68	0.210
Systolic blood pressure (mmHg)	125±21	128±22	134±19	138±19	<0.001
Diastolic blood pressure (mmHg)	74±11	76±12	80±11	83±11	<0.001
Total cholesterol (mg/dL)	190±37	193±34	200±33	201±36	<0.001
Triglycerides (mg/dL)	79±32	90±43	106±52	128±68	—
Log triglycerides (mg/dL)	1.86±0.17	1.91±0.19	1.98±0.19	2.05±0.22	<0.001
HDL cholesterol (mg/dL)	70±15	67±16	60±14	56±13	<0.001
LDL cholesterol (mg/dL)	105±29	109±30	118±31	120±32	<0.001
Fasting blood glucose (mg/dL)	91±13	94±17	97±24	100±20	—
Log fasting blood glucose (mg/dL)	1.96±0.06	1.97±0.06	1.98±0.07	1.99±0.07	<0.001
Serum creatinine (mg/dL)	0.64±0.14	0.65±0.14	0.67±0.15	0.69±0.16	<0.001
Serum uric acid (mg/dL)	4.4±1.2	4.7±1.4	5.0±1.4	5.5±1.5	<0.001

†Body mass index (BMI) was calculated using weight in kg divided by the square of the height in m. ‡Smoking status: daily consumption (pack)×duration of smoking (year). HDL, high-density lipoprotein; LDL, low-density lipoprotein. *One-way ANOVA test or χ^2 test.

(*9*). In Western countries, many patients have an estimated GFR (eGFR) of less than 60 mL/min/1.73 m^2 or a body mass index (BMI) of 30 kg/m^2 or more. However, the risk of slightly elevated weight (BMI, 22.0 to 24.9 kg/m^2) in a Japanese population for mildly reduced renal function (eGFR, 60 to 90 mL/min/1.73 m^2) is not clear.

We evaluated the relationship of BMI to potential risk factors such as hypertension, hyperglycemia, and lipids, as well as to renal function, using cross-sectional data from community-dwelling participants.

Methods

Subjects

Participants were recruited at the time of their annual health examination in a rural town that has a total population of 11,136 (as of April 2002) and located in Ehime Prefecture, Japan, in 2002. Among the 9,133 adults aged 19 to 90 years in this population, 3,164 (34.6%) subjects met the eligibility requirements to participate in the study. Information on medical history, present conditions, and drugs was obtained by interview. Subjects with a clinical history of stroke, transient ischemic attack, myocardial infarction, or angina were excluded. Subjects taking medications for hypertension, diabetes, or dyslipidemia were also excluded from the study. However, participants that met the eligibility requirements with BMI>30 kg/m^2 were included (37 subjects). The final study sample included 1,716 eligible persons. All procedures were approved by the Ethics Committee of Ehime University School of Medicine.

Evaluation of Risk Factors

We measured blood pressure in the right upper arm of participants in a seated position using an automatic oscillometric blood pressure recorder. Cigarette smoking was quantified based on daily consumption and on duration of smoking. Fasting total cholesterol (T-C), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), fasting blood glucose (FBG), creatinine (enzymatic method), and uric acid were measured during fasting. Low-density lipoprotein cholesterol (LDL-C) levels were calculated using the Friedewald formula (*10*). Participants with TG levels ≥400 mg/dL were excluded (24 cases). The presence of diabetes was defined as a history of treatment for diabetes. Estimated GFR was calculated using the following equation (*11*, *12*):

$$\mathrm{eGFR} = 194 \times \mathrm{Cr}^{-1.094} \times \mathrm{Age}^{-0.287} \times 0.739 \text{ (if female)}$$

where Cr is creatinine. Participants with an eGFR less than 30 mL/min/1.73 m^2 were excluded (4 cases). Regardless of the presence or absence of proteinuria, mildly reduced renal function was defined as an eGFR of 60 to 89.9 mL/min/1.73 m^2, and moderately reduced renal function as <60 mL/min/1.73 m^2.

Statistical Analysis

Statistical analysis was performed using SPSS 10.0J (Statistical Package for Social Science, Inc., Chicago, USA). All values are expressed as mean±SD, unless otherwise specified.

Table 2. Characteristics of Estimated Glomerular Filtration Ratio by Body Mass Index

Characteristics	Body mass index† (kg/m²)				p for trend*
	BMI-1 < 18.5 (n = 100)	BMI-2 18.5–21.9 (n = 579)	BMI-3 22.0–24.9 (n = 620)	BMI-4 ≥ 25.0 (n = 417)	
eGFR (mL/min/1.73 m²)	85.6 ± 17.8	85.9 ± 17.2	82.6 ± 16.2	82.6 ± 16.7	0.001
		p = 0.001**			
			p = 0.002**		
eGFR (n (%))					
≥ 90	37 (37.0)	230 (39.7)	193 (31.1)	137 (32.9)	0.015
60–89.9	57 (57.0)	331 (57.2)	389 (62.7)	254 (60.9)	
< 60	6 (6.0)	18 (3.1)	38 (6.1)	26 (6.2)	

†Body mass index (BMI) was calculated using weight in kg divided by the square of the height in m. eGFR (estimated glomerular filtration rate) was estimated using the following equation: $eGFR = 194 \times Cr^{-1.094} \times Age^{-0.287} \times 0.739$ (if female). Cr, creatinine. *One-way ANOVA test or χ^2 test. ** Student's t-test.

Data for smoking status, TG, and FBG were skewed, and were log-transformed for analysis. Differences based on BMI groups (BMI-1, < 18.5 kg/m²; BMI-2, 18.5–21.9 kg/m²; BMI-3, 22.0–24.9 kg/m², BMI-4, ≥ 25.0 kg/m²) were analyzed by one-way ANOVA or the χ^2 test. Correlations between various characteristics and BMI were determined using Pearson's correlation test. Stepwise multiple regression analysis was used to evaluate the contribution of risk factors for eGFR. A value of $p < 0.05$ was considered significant.

Results

Background Factors in Subjects Categorized According to BMI

Table 1 shows the values of each subject's background factors categorized according to BMI. The subjects comprised 754 men aged 56 ± 15 (range, 20–87) years and 962 women aged 59 ± 13 (19–88) years. The mean BMI in the study sample was 23.0 kg/m² (SD, 3.2), with 5.8% underweight (BMI < 18.5 kg/m²), 33.7% lower normal weight (BMI, 18.5 to 21.9 kg/m²), 36.1% upper normal weight (BMI, 22.0 to 24.9 kg/m²), and 24.3% overweight or obese (BMI ≥ 25 kg/m²) subjects. Systolic blood pressure (SBP), diastolic blood pressure (DBP), T-C, log TG, LDL-C, log FBG, serum creatinine and uric acid were significantly higher in the higher BMI group, but age and HDL-C were significantly lower in that group. There were no inter-group differences in sex or smoking status.

Estimated GFR of Subjects Categorized by BMI

Estimated GFR values decreased progressively with increasing BMI (Table 2), especially in those with lower normal weight compared with the higher BMI groups. Moreover, the higher weight groups had a higher prevalence of participants with an eGFR of < 90 mL/min/1.73 m².

Relationship of Risk Factors, Including BMI, and eGFR

Table 3 shows the relationship between participant characteristics and eGFR. The BMI ($r = -0.054$), along with age, SBP, DBP, log TG, HDL-C and LDL-C, was significantly correlated with eGFR (Fig. 1). Stepwise multiple regression analysis using eGFR as an objective variable, adjusted for risk factors as explanatory variables, showed that BMI ($\beta = -0.075$) was significantly and independently associated with eGFR as well as log TG, LDL-C and log FBS.

Association between BMI Categories and Risk for Mildly or Moderately Reduced eGFR

Compared with participants with lower normal weight (BMI, 18.5 to 21.9 kg/m²), the non-adjusted odds ratio [OR] for mildly and moderately reduced renal function, defined as an eGFR of < 90 mL/min/1.73 m², was 1.46 (95% confidence interval [CI], 1.15–1.85) for upper normal weight (BMI, 22.0 to 24.9 kg/m²) and 1.35 (95% CI, 1.04–1.75) for overweight or obese individuals (BMI ≥ 25 kg/m²) (Table 4). The age-adjusted OR for mildly and moderately reduced renal function was 1.36 (95% CI, 1.06–1.75) for upper normal weight and 1.43 (95% CI, 1.08–1.88) for overweight or obese individuals, and the multivariate-adjusted OR was 1.36 (95% CI, 1.00–1.85) for overweight or obese. Moreover, for moderately reduced renal function, defined as an eGFR of < 60 mL/min/1.73 m², the multivariate-adjusted ORs were 1.86 (1.01–3.42) for upper normal weight and 2.02 (1.01–4.03) for those who were overweight or obese, compared with participants with lower normal weight.

Discussion

To examine the possible contribution of increased BMI to renal function in the general population, we studied the relationship between risk factors and eGFR. This study showed a

Table 3. Relationship between Various Risk Factors Including Body Mass Index and Estimated Glomerular Filtration Rate

Characteristics	Pearson's correlation coefficient		Stepwise multiple regression	
	r	*p*-value	*β*	*p*-value
Sex (male=0, female=1)	−0.021	0.377	—	—
Age (years)	−0.406	<0.001	−0.418	<0.001
Body mass index† (kg/m^2)	−0.054	0.026	−0.075	0.001
Log smoking status‡ (pack year)	0.029	0.231	—	—
Systolic blood pressure (mmHg)	−0.132	<0.001	—	—
Diastolic blood pressure (mmHg)	−0.130	<0.001	—	—
Log triglycerides (mg/dL)	−0.076	0.002	−0.055	0.017
HDL cholesterol (mg/dL)	0.081	<0.001	—	—
LDL cholesterol (mg/dL)	−0.152	<0.001	−0.046	0.044
Log fasting blood glucose (mg/dL)	−0.004	0.857	0.096	<0.001
r^2	—	—	0.185	<0.001

β, standardized coefficient. †Body mass index was calculated using weight in kg divided by the square of the height in m. Estimated glomerular filtration rate $=194\times Cr^{-1.094}\times Age^{-0.287}\times 0.739$ (if female). ‡Smoking status: daily consumption (pack)×duration of smoking (year). HDL, high-density lipoprotein; LDL, low-density lipoprotein; Cr, creatinine.

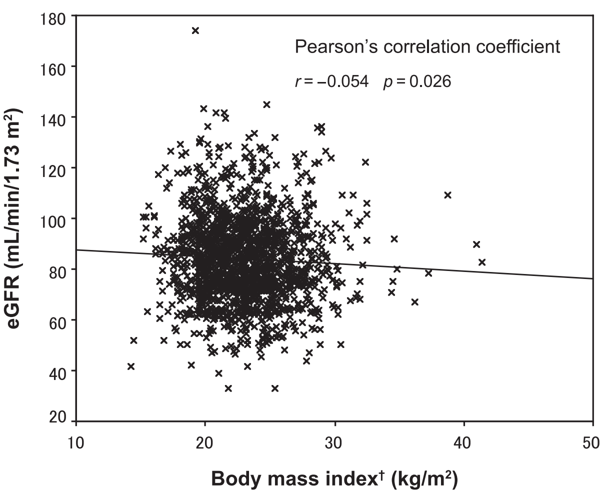

Fig. 1. *Relationship between body mass index and estimated glomerular filtration rate (eGFR). †Body mass index was calculated using weight in kg divided by the square of the height in m. eGFR (estimated glomerular filtration rate)* $=194\times Cr^{-1.094}\times Age^{-0.287}\times 0.739$ *(if female). Cr, creatinine.*

graded decrease in eGFR with increasing BMI, starting at a BMI of 22.0 kg/m^2. Upper normal weight and overweight or obese individuals showed a mildly reduced eGFR. Few epidemiologic studies have quantified the link between increased weight and renal function in population-based settings in Japan.

Several previous studies have shown that increased BMI is a risk factor for development of CKD. In a community-based cross-sectional study in Japan, Ishizaka *et al*. found that increased BMI was associated with low eGFR only in men (*13*). The OR for developing new-onset kidney disease, defined as a GFR of less than 59.3 mL/min/1.73 m^2 in women and less than 64.3 mL/min/1.73 m^2 in men, was 23% (OR, 1.23; 95% CI, 1.08–1.41) for one SD increase in BMI (*14*). Gelber *et al*. (*15*) reported that baseline BMI was consistently associated with increased CKD risk in a study of 11,104 initially healthy men who participated in the Physicians' Health Study. After a follow-up that occurred an average of 14 years later, 1,377 participants (12.4%) had a GFR of <60 mL/min/1.73 m^2. Baseline BMI can also predict future risk for end-stage renal disease (ESRD) (*16*). Baseline BMI predicted future risk for ESRD in Japanese men (OR, 1.27; 95% CI, 1.12–1.45), but not women (OR, 0.95; 95% CI, 0.83–1.09) (*17*), as well as in a Chinese cohort, for which there was a J-shaped association between BMI and all-cause ESRD (*18*). Most studies found CKD risks only among persons with a baseline BMI greater than or equal to 25 kg/m^2, whereas we found that upper normal weight (BMI, 22.0 to 24.9 kg/m^2), as well as overweight or obesity (≥25 kg/m^2), was significantly associated with a risk for mildly and moderately decreased eGFR (<90 and <60 mL/min/1.73 m^2, respectively).

The mechanisms that lead to renal dysfunction in overweight and obese individuals are not completely understood. Being overweight markedly increases risk for hypertension and diabetes (*19*), which can contribute to CKD (*20*–*22*). In the current study, BMI remained a risk factor even after adjustment for smoking status, blood pressure, lipids and FBG. However, some participants may have had undiagnosed hypertension and diabetes, and participants with increased BMI are more likely to develop diabetes and hypertension. Moreover, in men, the prevalence of microalbuminuria increased from 9.5% for normal weight individuals (BMI<25.0 kg/m^2) to 18.3% in overweight individuals (BMI, 25.0 to 29.9 kg/m^2) and to 29.3% in those with obesity (BMI≥30.0 kg/m^2). In women, these percentages were 6.6%, 9.2% and 16.0%, respectively. Renal blood flow and glomerular filtration rate increases in obesity, which may be fol-

Table 4. Multivariate Associations between Body Mass Index and Risk for Mildly and Moderately Reduced Estimated Glomerular Filtration Rate

Characteristics	Odds ratio (95% confidence interval)			
	BMI-1† <18.5 (*n*=100)	BMI-2† 18.5–21.9 (*n*=579)	BMI-3† 22.0–24.9 (*n*=620)	BMI-4† ≥25.0 (*n*=417)
eGFR <90 mL/min/1.73 m^2				
Non-adjusted	1.12 (0.72–1.74)	1.00 (referent)	1.46 (1.15–1.85)	1.35 (1.04–1.75)
Age-adjusted	1.05 (0.66–1.67)	1.00 (referent)	1.36 (1.06–1.75)	1.43 (1.08–1.88)
Multivariate-adjusted*	1.15 (0.72–1.84)	1.00 (referent)	1.29 (1.00–1.68)	1.36 (1.00–1.85)
eGFR <60 mL/min/1.73 m^2				
Non-adjusted	1.99 (0.77–5.14)	1.00 (referent)	2.04 (1.15–3.61)	2.07 (1.12–3.83)
Age-adjusted	1.75 (0.66–4.64)	1.00 (referent)	2.07 (1.15–3.73)	2.68 (1.42–5.07)
Multivariate-adjusted*	1.59 (0.55–4.55)	1.00 (referent)	1.86 (1.01–3.42)	2.02 (1.01–4.03)

†Body mass index (BMI) was calculated using weight in kg divided by the square of the height in m. eGFR (estimated glomerular filtration rate) $= 194 \times Cr^{-1.094} \times Age^{-0.287} \times 0.739$ (if female). *Models adjusted for sex, age, log smoking status, systolic blood pressure, diastolic blood pressure, log triglycerides, high density lipoprotein cholesterol, low density lipoprotein cholesterol and log fasting blood glucose. Cr, creatinine.

lowed by microalbuminuria, leading to the development of overt proteinuria and, eventually, progressive CKD (*23*). This microalbuminuria phase is followed by a progressive fall in GFR (*24*).

Increased BMI and decreased renal function may be associated with other non-traditional risk factors not examined in this study, including low-grade inflammation (*i.e.*, C-reactive protein) (*25*), homocysteinemia (*26*), oxidative stress (*27*), hyperlipidemia (*6*, *7*), hyperleptinemia (*28*), increased sympathetic activity (*29*), hyperfiltration caused by insulin resistance (*30*), renin-angiotensin system (*31*), and elevated cytokines (*32*). All these risk factors result in atherosclerosis. CKD may be complicated by both the severity and duration of atherosclerosis, and *vice versa*.

In our study, 26.3% of men and 22.8% of women were overweight or obese (with a BMI of ≥25 kg/m^2); in another study of Japanese workers, 31.2% of men and 19.5% of women were reported to be overweight or obese (*33*). Moreover, these tendencies are expected to increase in Japan in the future. Excess body weight could therefore contribute to the substantially large burden of CKD in such populations. We have modeled a 5.0 kg/m^2 increase in BMI, which corresponds to weight gains of about 13 kg in men and 11 kg in women who have an average BMI of 23.0 kg/m^2 as in this population. Therefore, excess body weight could become the important life style factor that contributes to CKD occurrence in Japan.

Some limitations of this study must be considered. First, the cross-sectional study design is limited in its ability to eliminate causal relationships between BMI and eGFR. The cumulative effects of excess body weight over several decades, the effect of weight-change periods or past maximum weight in the life-course of individuals, and interactions with other risk factors remain to be explored (*34*). Second, estimation of GFR tends to be less accurate in subjects with normal renal function and CKD than estimation of GFR when inulin clearance is used, but is more accurate than serum creatinine or the Cockcroft-Gault equation (*35*). Third, our definition of eGFR is based on a single assessment of serum creatinine, which may introduce a misclassification bias. Finally, in this study, we might misclassify CKD with eGFR>60 mL/min/1.73 m^2 and proteinuria as mildly reduced renal function because we defined reduced renal function as reduced eGFR irrespective of the presence or absence of proteinuria. Therefore the demographics and referral source may limit the generalization of the results.

In conclusion, the present study showed that BMI is strongly associated with decreased eGFR in the general population. The underlying mechanism behind this relationship is unclear, but it seems to be independent from traditional cardiovascular risk factors such as age, hypertension, dyslipidemia, and diabetes. For community-dwelling healthy persons, prospective population-based studies are needed to investigate the mechanisms underlying this association and to determine whether effective interventions that reduce BMI in adult populations will reduce CKD risks.

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