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ScienceDirect
Metabolism Clinical and Experimental 58 (2009) 1737–1742
Metabolism
Clinical and Experimental
www.metabolismjournal.com

Obesity and metabolic syndrome–related chronic kidney disease in nondiabetic, nonhypertensive adults

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Received 6 October 2008; accepted 29 May 2009

Abstract

Metabolic syndrome (MS) is associated with chronic kidney disease (CKD). The objective of this study is to examine the association between obesity and MS-related CKD in nondiabetic, nonhypertensive Korean adults. Korea National Health and Nutrition Examination Survey III data from 3771 nondiabetic, nonhypertensive Koreans were analyzed. *Metabolic syndrome* was defined according to the National Cholesterol Education Program–Adult Treatment Panel III, and CKD was diagnosed at an estimated glomerular filtration rate less than 60 mL/(min 1.73m^2). The crude and multivariate-adjusted odds ratios (ORs) of CKD associated with MS and its individual components were calculated using logistic regression models in a study population stratified by obesity. The prevalence of MS and CKD was 13.4% and 3.2%, respectively. The association between MS and CKD was significant in obese (OR, 2.91; 95% confidence interval [CI] = 1.34-6.34), but not nonobese (OR, 1.38; 95% CI = 0.60-3.17), subjects. In obese subjects, impaired fasting glucose (OR, 2.47; 95% CI = 1.10-5.57) and high triglyceride levels (OR, 2.42; 95% CI = 1.01-5.83) were risk factors for CKD, whereas no components were significantly associated with CKD in nonobese subjects. Our findings suggest that even in nondiabetic, nonhypertensive Korean adults, early detection and prevention of CKD in obese subjects with MS are critical.

1. Introduction

Chronic kidney disease (CKD) is associated with end-stage renal disease, as well as cardiovascular morbidity and mortality [1-3]. Chronic kidney disease is currently a worldwide public health problem; and thus, identification and management of the modifiable risk factors for this disease are important for preventing adverse effects.

The most important established risk factors for CKD are diabetes and hypertension [4]. In addition, obesity and metabolic syndrome (MS) are independent predictors of CKD [5-7]. Population-based cross-sectional studies [8-11] and prospective cohort studies [12-14] disclose that MS is associated with CKD. Metabolic syndrome is a suggested independent risk factor for CKD, even in nondiabetic, nonhypertensive subjects [15-18].

As the clinical features of obesity overlap considerably with those of the components of MS, the specific impact of obesity on MS-related CKD is currently unclear. A recent study reported that nondiabetic obese individuals (body mass index [BMI] ≥30 kg/m^2) are not susceptible to further metabolic deleterious effects on kidney function on top of that played by obesity itself [19].

There is an epidemic of obesity and MS across the world, accompanied by an increase in the incidence of CKD. However, the association between obesity and MS-related CKD in the Asian population (with a generally lower mean BMI than in the West) remains to be established. This study was performed to determine the association between obesity with MS-related CKD in nondiabetic, nonhypertensive Korean adults.

2. Subjects and methods

2.1. Study population

The Korean Ministry of Health and Welfare conducts a Korean National Health and Nutrition Examination Survey

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0026-0495/$ – see front matter © 2009 Published by Elsevier Inc.
doi:10.1016/j.metabol.2009.05.029

(KNHANES) periodically in noninstitutionalized Korean civilians. Our study was based on the 2005 KNHANES III using a multistage stratified clustered probability sampling design. The completion rate of the health examination study was 70.2% (7597 of 10 816 individuals). Among the 5440 KNHANES III participants who were 20 years or older, we excluded subjects with diabetes (n = 422, 7.8%), hypertension (n = 1366, 25.1%), history of stroke (n = 122, 2.3%), history of ischemic heart disease (n = 122, 2.3%), and missing BMI or MS (n = 15), leaving 3771 individuals (1496 men and 2275 women) for study.

2.2. Basic questionnaire and health examination

Socioeconomic and demographic data were obtained through direct interviews using standardized questionnaires. The survey questionnaire included questions on previous and current diseases, dietary intake, alcohol consumption, smoking habits, and physical exercise. Dietary intake was assessed with a single 24-hour dietary recall method. Alcohol intake was categorized into current drinkers or nondrinkers. In terms of smoking, individuals were grouped based on whether the respondent was a nonsmoker, an ex-smoker, or a current smoker. Physical exercise was divided into 3 groups, specifically, none, 1 to 2 times a week, and at least 3 times a week.

Height, body weight, and waist circumference were measured in households by trained interviewers. Height was measured to the nearest 0.1 cm with the subject standing barefoot. Body weight was measured to the nearest 0.1 kg on a balanced scale with the subject wearing a lightweight gown or underwear. Body mass index was calculated as (weight in kilograms)/(height in meters)^2. Waist circumference was used to assess abdominal obesity and was measured to the nearest 0.1 cm at the narrowest point between the lowest rib and the uppermost lateral border of the right iliac crest.

Blood pressure was measured with a mercury sphygmomanometer after a 5-minute rest in the sitting position. Study subjects refrained from smoking or ingesting caffeine for 30 minutes before the measurement. Blood samples were collected from the antecubital vein to determine serum concentrations of creatinine, triglycerides, high-density lipoprotein cholesterol (HDL-C), and glucose after 10 to 12 hours of starvation. All biochemical analyses were performed within 2 hours of blood sampling. Total cholesterol, triglycerides, HDL-C, and glucose were estimated with enzymatic methods using a Hitachi 747 autoanalyzer and commercially available kits.

2.3. Criteria for MS, obesity, and CKD

Metabolic syndrome was diagnosed in patients who met 3 of the 5 revised National Cholesterol Education Program–Adult Treatment Panel III criteria of the American Heart Association/National Heart, Lung, and Blood Institute [20], specifically, elevated blood pressure (130-139/85-89 mm Hg), impaired fasting glucose (100-125 mg/dL), high triglycerides (≥150 mg/dL), low HDL-C (<40 mg/dL in men and <50 mg/dL in women), and abdominal obesity (cutoff of 90 cm in men and 80 cm in women for Asian population). *Obesity* was defined as BMI of at least 25 kg/m^2 using the World Health Organization Asia-Pacific guidelines [21]. The estimated glomerular filtration rates (eGFRs; in milliliters per minute per 1.73 square meters) were calculated using the abbreviated equation developed from the Modification of Diet in Renal Disease study [22], as follows: $186.3 \times (\text{serum creatinine})^{-1.154} \times \text{age}^{-0.203}$ (× 0.742 for women). *Chronic kidney disease* was defined as eGFR less than 60 mL/(min 1.73 m^2).

2.4. Statistical analysis

All statistical analyses were performed using the Stata survey suite of commands in Stata SE 10.0 (Stata, College Station, TX). We followed the analytical guidelines for KNHANES data proposed by the Korea Centers for Disease Control and considered survey weights to allow the extrapolation of findings for the entire Korean population. To compare the parameters between subjects with CKD and those without, we selected age-matched control subjects (1:2 matched) within the CKD-negative group to serve as a control for age-related abnormalities. We used Student t test for metric variables and χ^2 test for categorical variables. We analyzed the prevalence of CKD according to the MS or its individual components stratified by obesity status as BMI less than 25 kg/m^2 or at least 25 kg/m^2. Logistic regression analyses were conducted to assess the association of MS and its individual components with CKD. After testing several models using a hierarchical approach, we constructed a final multiple logistic regression model. Age (years), sex, household income (continuous), total energy intake (kilocalories per day), alcohol intake (current drinkers or nondrinkers), smoking status (nonsmoker, ex-smoker, or current smoker), and exercise (none, irregular, or regular) were included in multiple logistic regression model. The odds ratios (ORs) are presented together with their 95% confidence intervals (CIs) for CKD as a dependent variable and MS or its individual components as independent variables stratified by obesity status among our study subjects. All analyses were 2-tailed, and a P value < .05 was considered statistically significant.

3. Results

The mean age of participants was 40.0 ± 0.5 years, and 47.8% were men. Mean BMI was 23.5 kg/m^2, and mean eGFR was 83.0 mL/(min 1.73 m^2). The overall prevalence of MS was 13.4%, and 3.2% of the participants were diagnosed with CKD (Table 1).

The clinical characteristics of age-matched subjects with and without CKD are presented in Table 2. Subjects with CKD displayed higher triglycerides, total cholesterol, and

Table 1
Basic characteristics of the study subjects (N = 3771)

	Mean	SEM
Age (y)	40.0	0.5
BMI (kg/m^2)	23.5	0.1
Systolic blood pressure (mm Hg)	114.2	0.5
Diastolic blood pressure (mm Hg)	75.9	0.4
Fasting blood glucose (mg/dL)	90.1	0.3
Triglycerides (mg/dL)	129.9	2.9
HDL-C (mg/dL)	43.6	0.3
Creatinine (mg/dL)	1.05	0.00
eGFR (mL/[min 1.73 m^2])	83.0	0.4
Total energy intake (kcal/d)	2401.4	41.0
	%	SE
Men	47.8	1.1
Alcohol		
Nondrinker	45.2	1.3
Current drinker	54.8	1.3
Smoking		
Nonsmoker	57.8	1.1
Ex-smoker	16.6	0.9
Current smoker	25.6	0.9
Regular exercise		
None	51.5	1.4
1-2 times/wk	15.7	1.0
≥3 times/wk	32.8	1.1
MS	13.4	0.7
CKD	3.2	0.3

low-density lipoprotein cholesterol levels than those without CKD. Subjects with CKD had a higher percentage of MS as well as abdominal obesity, impaired fasting glucose, high triglycerides, and low HDL-C.

Tables 3 and 4 present the prevalence and ORs of CKD with respect to MS in nonobese and obese subjects, respectively. In nonobese subjects, ORs for CKD with MS or individual components of MS were no longer statistically significant after adjusting for confounding factors. However, multivariate-adjusted OR of CKD in obese subjects with MS, compared with subjects without MS, was 2.91 (95% CI = 1.34-6.34). Among the individual components of MS, OR values for CKD with impaired fasting glucose and high triglyceride levels were 2.47 (95% CI = 1.10-5.57) and 2.42 (95% CI = 1.01-5.83), respectively.

4. Discussion

Previous studies disclosed a significant association between MS and CKD. Epidemiologic studies in US adults [9], Japanese adults [10], and Chinese adults [8] have indicated that MS could be an independent factor in the cause of CKD. Even for individuals with no diabetes or hypertension, MS can be a significant risk factor for the development of CKD [13,15-18]. In addition, obesity is also considered to be a major determinant of CKD [5-7,19]. Obesity is associated with an excess excretory load on the basis of increased body mass and induces hyperperfusion and hyperfiltration, followed by glomerular capillary hypertension and glomerulosclerotic damage [23]. A recent study reported that MS exerted no added deleterious effects on kidney dysfunction in obese (BMI ≥30 kg/m^2) nondiabetic subjects, suggesting that obesity per se plays a key role in kidney function and, therefore, obese nondiabetic subjects are not susceptible to further metabolic derangement of renal function [19]. In our study, *obesity* was defined as BMI of at least 25 kg/m^2, which is considerably lower than the figure chosen to represent obesity in the Western population [19]. We used these criteria on the basis of a report cosponsored by the World Health Organization Western Pacific Region [21] demonstrating that Asians have a lower average BMI value and higher percentage of body fat at a given BMI than white people [24-26]. As Koreans displaying BMI of at least 30 kg/m^2 constitute less than 5% of the population [27], we could not analyze data from this subgroup.

This is a large population-based study in Korea and showed that there is an association between MS and CKD only in obese, but not in nonobese, subjects. Although the mechanisms underlying this phenomenon are yet to be established, inflammation and lipotoxicity induced by

Table 2
Age-matched comparisons of subjects with and without CKD

	CKD (−) (n = 320)		CKD (+) (n = 160)		*P* value[a]
	Mean	SE	Mean	SE	
Age (y)	63.9	0.7	64.4	0.9	.6852
BMI (kg/m^2)	23.1	0.2	23.4	0.3	.3833
Waist circumference (cm)	81	0.5	80.1	0.8	.3233
Systolic blood pressure (mm Hg)	119.5	0.6	118.5	0.9	.3857
Diastolic blood pressure (mm Hg)	74.8	0.4	74.5	0.6	.602
Fasting blood glucose (mg/dL)	92.2	0.5	93.9	0.9	.0741
Triglycerides (mg/dL)	118.3	4.2	149.2	11.2	.0019
HDL-C (mg/dL)	45.4	0.6	44.7	0.9	.085
Total cholesterol (mg/dL)	185.7	1.8	198.1	3	.0003
LDL cholesterol (mg/dL)	117	1.7	126.1	2.8	.004
Creatinine(mg/dL)	0.95	0.007	1.11	0.015	.0000
eGFR (mL/[min 1.73 m^2])	74.7	0.5	56.7	0.4	.0000
	%		%		
Obesity	27.5		28.8		.774
Abdominal obesity	32.8		45.6		.006
Elevated blood pressure	31.3		23.8		.087
Impaired fasting glucose	19.1		28.1		.024
High triglycerides	21.3		31.3		.016
Low HDL-C	52.8		66.3		.005
MS	20.9		33.8		.002

Metabolic syndrome was diagnosed when 3 of the following 5 criteria were met: elevated blood pressure (130-139/85-89 mm Hg), impaired fasting glucose (100-125 mg/dL), high triglycerides (≥150 mg/dL), low HDL-C (<40 mg/dL in men and <50 mg/dL in women), and abdominal obesity (cutoff of 90 cm in men and 80 cm in women). LDL indicates low-density lipoprotein.

[a] *P* value with Student *t* test for metric variables and χ^2 test for categorical variables.

Table 3
Prevalence of CKD with respect to MS in nondiabetic, nonhypertensive subjects according to obesity

Variables		Nonobese (n = 2796)[a]			Obese (n = 975)[a]		
		Sample size (n)[a]	% (95% CI)	*P* value[b]	Sample size (n)[a]	% (95% CI)	*P* value[b]
Abdominal obesity	Yes	293	9.1 (6.2-13.0)	<.0001	271	5.0 (3.5-7.1)	.0052
	No	2503	2.3 (1.8-3.1)		704	1.5 (0.6-3.6)	
Elevated blood pressure	Yes	326	5.9 (3.7-9.3)	.0016	216	3.7 (1.9-7.2)	.8779
	No	2470	2.6 (2.0-3.3)		759	3.9 (2.6-5.8)	
Impaired fasting glucose	Yes	268	6.4 (4.0-10.0)	.001	192	11.2 (6.6-18.3)	<.0001
	No	2528	2.6 (2.0-3.3)		783	2.5 (1.6-3.8)	
High triglycerides	Yes	476	3.8 (2.3-6.2)	.2822	344	6.2 (3.8-10.2)	.0155
	No	2320	2.7 (2.1-3.6)		631	2.6 (1.6-4.2)	
Low HDL-C	Yes	1365	3.7 (2.9-4.9)	.0208	332	5.0 (3.4-7.4)	.0259
	No	1431	2.2 (1.6-3.1)		643	1.9 (0.9-4.0)	
MS	Yes	196	9.8 (6.1-15.3)	<.0001	365	7.4 (4.9-11.0)	<.0001
	No	2600	2.5 (1.9-3.2)		610	2.0 (1.1-3.3)	

[a] The unweighted number of participants is noted.
[b] *P* value with χ^2 test between groups with and without individual components of MS.

obesity are possibly related [28,29]. Several studies concerning mechanisms of CKD among MS suggested that inflammatory cytokines (leptin, interleukin-6, tumor necrosis factor–α, adiponectin), adipocyte angiotensinogen production increase, and renal oppression by fat tissue have a role in renal damage in patients with MS [30,31]. Recent study showed that inflammation, which is a specific trait of obesity, was accountable for the increased risk for CKD in healthy obese individuals [30]. However, levels of inflammatory marker or cytokines possibly linking obesity and MS-related CKD could not be measured. The difference in risk for MS-related CKD between nonobese and obese individuals suggests that obesity might modulate the association between MS and CKD. We could assume that the current scope of defining MS might be weak for identifying nonobese individuals with a risk of contracting CKD, considering the fact that obesity-related inflammation, which may be the key factor, is not currently included in the definition.

Our study revealed no differences in obesity prevalence or BMI levels between subjects with and without CKD (Table 2). It is possible that subjects with diabetes or hypertension were excluded initially among those with higher prevalence of obesity. Regarding abdominal obesity, it seemed to be associated with CKD in the univariate analysis; however, the significance disappeared after adjustment for confounding variables in both nonobese and obese groups. We applied the cutoffs of waist circumference for Asian population to determine the definition of abdominal obesity [20]. The results might be different according to the criteria of abdominal obesity.

Our results clearly show that impaired fasting glucose is a risk factor for CKD in obese, nondiabetic, nonhypertensive subjects. Based on these findings, we propose that renal dysfunction occurs long before the appearance of diabetes in obese subjects. Insulin resistance or hyperinsulinemia could induce glomerular hypertrophy either directly or by stimulating the insulin-like growth factor–1 receptor [32]. In addition, glomerular hypertrophy appears in the prediabetic hyperinsulinemic phase, despite lack of hyperglycemia, hypertension, renal dysfunction, or increase in mesangial matrix deposition [33]. Previous studies reported that insulin

Table 4
Odds ratios for CKD with respect to MS in nondiabetic, nonhypertensive subjects according to obesity

Variables	Nonobese (n = 2796)				Obese (n = 975)			
	Crude		Adjusted		Crude		Adjusted	
	OR (95% CI)	*P* value[a]	OR (95% CI)	*P* value[b]	OR (95% CI)	*P* value[a]	OR (95% CI)	*P* value[b]
Abdominal obesity	4.15 (2.54-6.78)	<.0001	1.16 (0.64-2.09)	.620	3.53 (1.39-9.01)	.009	1.70 (0.53-5.43)	.371
Elevated blood pressure	2.39 (1.38-4.14)	.002	0.69 (0.35-1.34)	.268	0.94 (0.42-2.11)	.878	0.56 (0.23-1.38)	.206
Impaired fasting glucose	2.57 (1.45-4.58)	.001	1.19 (0.52-2.70)	.675	5.00 (2.42-10.31)	<.0001	2.47 (1.10-5.57)	.029
High triglycerides	1.39 (0.76-2.54)	.284	1.41 (0.66-2.98)	.372	2.52(1.17-5.46)	.019	2.42 (1.01-5.83)	.048
Low HDL-C	1.71 (1.08-2.71)	.022	0.83 (0.47-1.45)	.509	2.71 (1.09-6.72)	.032	2.23 (0.84-5.93)	.106
MS	4.25 (2.31-7.82)	<.0001	1.38 (0.60-3.17)	.451	4.00 (2.02-7.93)	<.0001	2.91 (1.34-6.34)	.007

[a] *P* value with logistic analysis.
[b] *P* value with multiple logistic analysis adjusted for age (years), sex, household income (continuous), total energy intake (kilocalories per day), alcohol intake (current drinkers or nondrinkers), smoking status (nonsmoker, ex-smoker, or current smoker), and exercise (none, irregular, or regular).

resistance estimated from homeostasis model assessment was associated with increased risk for CKD in nondiabetic subjects [13,34]. However, we did not observe insulin resistance in the study population, as fasting insulin was not measured in the Korean national survey.

High triglycerides additionally constitute a risk factor for CKD in obese, nondiabetic, nonhypertensive subjects. Much epidemiologic data confirm that hypertriglyceridemia and low HDL-C are associated risk factors for the development of CKD [8,9,11,13]. Results from a recent meta-analysis suggest that lipid lowering preserves the GFR and decreased proteinuria levels in patients with renal disease [35]. Animal and experimental studies show that dyslipidemia can initiate glomerular injury and enhance the progression of CKD [36]. Lipotoxicity involves the cellular accumulation of nonesterified free fatty acids and triglycerides.

This study has several potential limitations, despite being conducted on a large representative sample of the general population. First, the cross-sectional design makes it difficult to infer a causal relationship between obesity and MS-related CKD. Therefore, we could not exclude the possibility that the presence of CKD may confound the diagnosis of MS. Certainly, kidney disease predisposes to high blood pressure. Insulin resistance and glucose intolerance have been well recognized in patients with advanced CKD. Finally, glucose and insulin abnormalities in nondiabetic CKD patients are implicated in the pathogenesis of hyperlipidemia and may contribute to accelerated atherosclerosis. Second, we could not measure levels of insulin or cytokines possibly linking obesity and MS-related CKD. A prospective study is required to investigate the relationship between obesity and MS-related CKD. Third, we used eGFR rather than direct measurements of GFR to define CKD, as data on our study population were obtained from the Korean National database that contained only the information requested by the Korean government.

In summary, MS is associated with significantly higher risk for CKD in obese, but not nonobese, individuals. This finding suggests that obesity might modulate MS-related CKD. Early detection and appropriate management of CKD would be helpful in obese individuals with MS. Further studies are required to establish the benefits of weight reduction for ameliorating the risk of MS-related CKD.

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