Original Article

Metabolic Syndrome and Risk of Developing Chronic Kidney Disease in Japanese Adults

Masahiko TOZAWA[1)], Chiho ISEKI[2)], Kaori TOKASHIKI[3)], Saori CHINEN[3)], Kentaro KOHAGURA[3)], Kozen KINJO[4)], Shuichi TAKISHITA[3)], and Kunitoshi ISEKI[2)]

Metabolic syndrome is a risk factor for the development of cardiovascular disease. Few prospective studies, however, have examined metabolic syndrome as a risk factor for chronic kidney disease (CKD) in an Asian population. We studied the occurrence of CKD in 6,371 subjects without CKD or diabetes mellitus at baseline 1997 through 2002 in Okinawa, Japan. CKD was defined as dipstick-positive proteinuria (≥1+) or a low estimated glomerular filtration rate (<60 mL/min/1.73 m^2). Metabolic syndrome was defined according to the modified criteria of the Adult Treatment Panel III in which body mass index (≥25 kg/m^2) was substituted for the waist circumference measurement. Logistic analysis was used to analyze the effect of metabolic syndrome on the development of CKD. During the 5-year follow-up, 369 (5.7%) participants developed CKD. After adjusting for age, sex, current cigarette smoking and alcohol drinking habits at baseline, the relative risk of developing CKD was 1.86 (95% confidence interval: 1.43–2.41, p<0.0001) in subjects with metabolic syndrome. Compared with those without metabolic syndrome risk components, the adjusted relative risk (95% confidence interval) was 1.49 (1.10–2.01), 1.89 (1.38–2.59), and 2.65 (1.19–3.68) in those with 1, 2, or ≥3 metabolic syndrome risk components, respectively. Metabolic syndrome is a significant risk factor for the development of CKD in the Japanese population. Detection and treatment of metabolic syndrome should be stressed as a strategy to prevent CKD. (*Hypertens Res* 2007; 30: 937–943)

***Key Words*: obesity, triglyceride, high-density lipoprotein cholesterol, blood pressure, fasting glucose**

Introduction

Metabolic syndrome is a risk factor for the development of cardiovascular disease. Lakka *et al*. reported that metabolic syndrome increased the risk of mortality from coronary heart disease in Finnish men (*1*). In Japanese men, Takeuchi *et al*. showed that subjects with metabolic syndrome had a 2.2 times greater risk of developing cardiac disease than did subjects in the non-metabolic syndrome (*2*).

The number of new dialysis patients is increasing annually, and the prevalence of dialysis patients currently is over 2,000 per million persons including those in Okinawa, Japan (*3*, *4*). In Japan, Okinawa is the area with the highest incidence and also has an increasing rate of the incidence of end-stage renal disease (*5*). The prevalence of metabolic syndrome in Okinawa is 15.1–19.1% (*6*, *7*). We and others have shown that metabolic syndrome is associated with chronic kidney disease (CKD) in cross-sectional studies (*8*, *9*).

A causal relationship between metabolic syndrome and the development of CKD, however, has not been reported. A recent longitudinal study in adults in the United States indicated that metabolic syndrome is a risk factor for CKD (*10*). The effect of obesity on glucose tolerance differs among races, but there are few published data specifically for an Asian population (*11*, *12*). Therefore, we studied whether or

From the [1)]Ikejiri-ohasi Jin Clinic, Tokyo, Japan; [2)]Dialysis Unit, University Hospital of the Ryukyus, Okinawa, Japan; [3)]Department of Cardiovascular Medicine, Nephrology, and Neurology, University of the Ryukyus, Okinawa, Japan; and [4)]Okinawa General Health Maintenance Association, Okinawa, Japan.

Address for Reprints: Kuitoshi Iseki, M.D., Dialysis Unit, University Hospital of the Ryukyus, 207 Uehara, Nishihara-cho, Okinawa 903–0125, Japan. E-mail: chihokun@med.u-ryukyu.ac.jp

Received December 21, 2006; Accepted in revised form May 18, 2007.

not metabolic syndrome contributes to the development of CKD in Japanese in Okinawa.

Methods

Study Design

All individuals between 19 and 84 years of age that participated in the 1997 health screening examination in Okinawa by the Okinawa General Health Maintenance Association (OGHMA). Subjects who developed CKD between 1997 and 2002 were identified by further OGHMA examinations. The cumulative incidence of CKD and the relative risk of developing CKD were determined based on the presence of metabolic syndrome components according to the health screening registry.

Screened Cohort

The subjects in our current study were participants in the human dry dock program, which was reported previously (*13*, *14*). The program, run by OGHMA, involved a thorough physical examination of 9,914 participants in 1997. Among them, 8,151 subjects (82.2%) participated in the program more than once during the following 5 years (1998 through 2002). From these 8,151 subjects, we excluded 728 subjects who had CKD and 3 who did not receive a urinalysis in 1997 were excluded. In addition, those undergoing medical treatment for hypertension, diabetes, or treatment of hyperlipidemia (n=769), those with fasting blood glucose ≥126 mg/dL, or hemoglobin A1c >7.0% (n=243), and those missing data for cigarette smoking or alcohol drinking habits (n=37) were excluded. Finally, in the present study, we analyzed 6,371 subjects that were free from CKD at baseline (1997). The present study was conducted in accordance with the principles set out in the Declaration of Helsinki 1975, as revised in 1993. The study design was approved by the ethics committee of OGHMA. Only the field data set, which excluded private information such as name and address, was used for this study. All participants were informed of the nature of the screening and all signed a consent for the questionnaire.

Each subject's medical history and current medical condition were recorded on a self-administered, standardized questionnaire. To corroborate the collected information, a physician also interviewed every subject. Dipstick urinalysis (Ames dipstick) was performed on fresh, mid-stream urine collected in the morning. The results of the urine test were interpreted as: (–), (±), (1+), (2+), (3+), or (4+). Height, body weight, blood pressure, fasting glucose, serum urea nitrogen, serum creatinine, serum albumin, triglyceride, total cholesterol, and high-density lipoprotein (HDL) cholesterol were measured in all subjects. All subjects fasted overnight before blood sampling. Serum creatinine was measured using an enzyme-based method. It was calibrated using the following formula to the value of the Jaffe method: serum creatinine (Jaffe method) = 0.194 + 1.079 × serum creatinine (enzyme method) (*6*). After the subjects sat for 15 min, blood pressure was measured twice by a trained nurse using a standard sphygmomanometer. The lower value of two blood pressure measurements was used for this study.

Table 1. Baseline Characteristics of Subjects Who Were Dropped Out and Those That Were Followed

Variables	Dropped out (n=1,763)	Followed (n=8,151)
Age (year)	50±12	49±9*
Male (%)	53	64*
BMI (kg/m^2)	23±3	24±3*
SBP (mmHg)	123±18	122±17*
DBP (mmHg)	75±11	75±11
Serum albumin (g/dL)	4.45±0.2	4.47±0.2*
Serum urea nitrogen (mg/dL)	14±4	14±3
Serum creatinine (mg/dL)	0.98±0.22	1.00±0.19*
Total cholesterol (mg/dL)	208±37	207±35
Triglyceride (mg/dL)	141±124	145±127
HDL cholesterol (mg/dL)	57±14	55±14*
Fasting glucose (mg/dL)	104±27	102±20*
Current smoking (%)	27	28
Alcohol drinking habits (%)	60	65*

Values are expressed as mean±SD, except where otherwise indicated. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein. *p<0.05 *vs*. subjects that dropped out.

Metabolic syndrome was defined by the modified criteria of ATP III (*15*) in which body mass index (BMI) (≥25 kg/m^2) was substituted for the waist circumference measurement. Waist circumference was not measured in the present study. Specifically, metabolic syndrome was defined as the presence of three or more of the following components: 1) obesity: BMI ≥25 kg/m^2; 2) high serum triglyceride: ≥1.69 mmol/L (150 mg/dL); 3) low HDL cholesterol: <1.03 mmol/L (40 mg/dL) in men or <1.29 mmol/L (50 mg/dL) in women; 4) high blood pressure: systolic ≥130 mmHg or diastolic ≥85 mmHg; 5) high fasting plasma glucose: ≥6.10 mmol/L (110 mg/dL).

The glomerular filtration rate was estimated from a formula by the Modification of Diet in Renal Disease study using calibrated serum creatinine measurements (*16*). CKD was defined as a glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m^2 or dipstick proteinuria (≥1+) (*17*).

Statistical Methods

The unpaired t-test or χ^2 test was used to analyze differences in values or ratios between groups. The χ^2 test for trend and analysis of variance were used to test linearity across years or a number of components (*18*). The relative risk of developing CKD was estimated with the use of multiple logistic regres-

Table 2. Baseline Characteristics of the Subjects Included in the Analysis Stratified by Whether or Not They Had Metabolic Syndrome

Variables	All (n=6,371)	Metabolic syndrome	
		Absence (n=5,487)	Presence (n=884)
Age (years)	47±9	47±9	49±9 *
Male (%)	63	60	80*
BMI (kg/m^2)	23±3	23±2	26±2*
SBP (mmHg)	118±15	116±14	130±14*
DBP (mmHg)	73±10	72±9	80±9*
Serum albumin (g/dL)	4.4±0.2	4.4±0.2	4.5±0.2*
Serum urea nitrogen (mg/dL)	14±3	14±3	14±3
Serum creatinine (mg/dL)	0.9±0.1	0.9±0.1	1.0±0.1*
GFR (mL/min/1.73 m^2)	82±12	83±12	81±11*
Total cholesterol (mg/dL)	205±34	203±34	213±36*
Triglyceride (mg/dL)	137±101	120±77	245±155*
HDL cholesterol (mg/dL)	56±14	58±14	44±10*
Fasting glucose (mg/dL)	98±8	97±7	105±9*
Hemoglobin A1c (%)	4.8±0.3	4.7±0.3	4.9±0.4*
Current smoking (%)	29	28	34*
Current drinking (%)	66	64	77*

Values are expressed as mean±SD except where otherwise indicated. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; GFR, glomerular filtration rate; HDL, high-density lipoprotein. *p<0.05 *vs*. absence of metabolic syndrome.

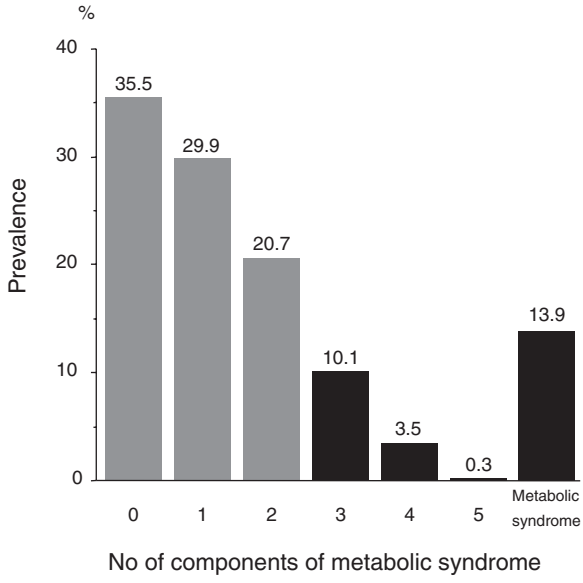

Fig. 1. *Prevalence of screened subjects by the number of components of metabolic syndrome.*

sion models (StatView 5.0, SAS Institute, Cary, USA). A p value of less than 0.05 was considered significant.

Results

Table 1 shows the baseline (1997) characteristics of subjects who dropped out of the study and of subjects who completed the study. Age, systolic blood pressure, HDL cholesterol, and fasting glucose were significantly lower in subjects who completed the study than in those who did not. Body mass index, serum albumin, and serum creatinine were higher in subjects completing the study than in those who did not. The percentage of males and the percentage of subjects with an alcohol drinking habit were both higher in subjects completing the study than those who did not. There were no differences in diastolic blood pressure, serum urea nitrogen, total cholesterol, triglyceride levels, or prevalence of current smoking habit.

Age, percentage of males, BMI, systolic blood pressure, diastolic blood pressure, serum albumin, serum creatinine, total cholesterol, triglyceride, hemoglobin A1c, prevalence of cigarette smoking, and prevalence of an alcohol drinking habit were higher (p<0.05) in subjects with metabolic syndrome (Table 2). The GFR and HDL cholesterol were lower in subjects with metabolic syndrome. Overall, 13.9% of the subjects (n=884) had metabolic syndrome. The prevalence of varying numbers of metabolic syndrome components in the subject population is shown in Fig. 1.

During the follow-up period, 369 subjects (5.7%) developed CKD. According to the staging of CKD by Kidney Disease: Improving Global Outcomes, the distribution of subjects by stage was: 2,781 in Stage 1, 3,465 in Stage 2, 125 in Stage 3, and none in Stages 4 and 5 (*19*).The cumulative incidence of CKD during the follow-up period according to the presence or absence of metabolic syndrome is shown in Fig. 2. The percentage of subjects who developed CKD was higher in the presence of metabolic syndrome (p<0.005).

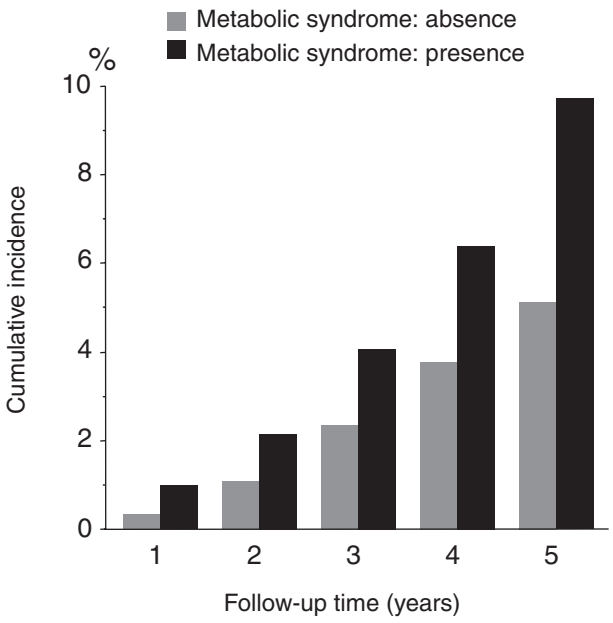

Fig. 2. *Cumulative incidence of chronic kidney disease (CKD) in 6,614 screened subjects, according to the absence or presence of metabolic syndrome. p values were calculated using a test for linearity across years (χ^2 test for trend of CKD incidence). p = 0.14 for the absence of metabolic syndrome and p = 0.01 for the presence of metabolic syndrome.*

The relative risk of developing CKD based on the presence or absence of metabolic syndrome or on the number of metabolic syndrome components is shown in Table 3. Compared to the absence of metabolic syndrome, the presence of metabolic syndrome was associated with a significantly higher risk for CKD ($p<0.0001$). The risk did not significantly differ by sex ($p=0.5$). The risk increased with age (relative risk: 1.04; 95% confidence interval: 1.03–1.05; $p<0.0001$). Relative to those with no metabolic syndrome risk components, the risk for CKD in subjects with ≥3 components was significant ($p<0.0001$).

The risk of developing lower GFR (GFR < 60 mL/min/1.73 m^2) or proteinuria is shown in Table 3. Compared to the absence of metabolic syndrome, the presence of metabolic syndrome was not associated with a significantly higher risk for lower GFR ($p=0.1$). Relative to those with no metabolic syndrome risk components, the risk for lower GFR in subjects with ≥3 components was not significant ($p=0.07$). Compared to the absence of metabolic syndrome, the presence of metabolic syndrome was associated with a significantly higher risk for proteinuria ($p<0.0001$). Relative to those with no metabolic syndrome risk components, the risk for proteinuria in subjects with ≥3 components was significant ($p<0.0001$).

The relative risks for CKD by individual components of metabolic syndrome are shown in Table 4. Among these components, obesity and high systolic blood pressure (≥130 mmHg) were significant risk factors for developing CKD in the adjusted model (obesity $p=0.01$, systolic blood pressure $p=0.0002$).

Discussion

The major findings of this study are that metabolic syndrome was an independent risk factor for the development of CKD in a screened cohort of 6,371 subjects in Okinawa, Japan, who did not have diabetes mellitus or hypertension at baseline. Our results validate the usefulness of the modified ATP III guideline for the diagnosis of metabolic syndrome when predicting the incidence of CKD.

Metabolic syndrome is associated with an increased risk of CKD in cross-sectional and longitudinal studies in the United States (*6*, *10*). We previously examined 6,980 screened subjects in a cross-sectional study using another registry in Okinawa and determined that metabolic syndrome was significantly associated with CKD (*9*). Ninomiya *et al*. followed up 1,440 community-dwelling individuals in the Hisayama study, Japan, without CKD for 5 years and found that metabolic syndrome remained an independent risk factor for the occurrence of CKD (odds ratio: 2.08; 95% confidence interval: 1.23–3.52) even after adjustment for multiple factors including hyperinsulinemia (*12*). The results of the present longitudinal study also suggest that metabolic syndrome is a risk factor for developing CKD in the Japanese.

Metabolic syndrome was an independent risk factor for the development of proteinuria, but not for the decrease in GFR in the present study. In the early stage of diabetes mellitus, GFR becomes elevated above baseline. This phenomenon may bias the result.

Obesity is a significant risk factor for developing proteinuria (*13*, *20*, *21*). Body mass index at the first renal biopsy is an independent risk factor for developing chronic renal failure in IgA nephropathy and is significantly associated with an increased risk for CKD (*22–24*). The mechanism by which obesity induces renal injury, however, is poorly understood. A clinical study suggests that obesity is associated with renal hyperfiltration and hyperperfusion (*25*). Kidneys from obese subjects exhibit focal glomerulosclerosis and other histologic changes similar to those observed in diabetic nephropathy (*26*). An experimental study in dogs showed that a high-fat diet causes obesity, increased arterial pressure, hyperinsulinemia, activation of the renin-angiotensin system, glomerular hyperfiltration, and structural changes in the kidney (*27*). A high-fat diet in dogs is also associated with marked changes in renal cytokine gene expression profiles (*28*).

High triglyceride levels are a risk factor for developing proteinuria, and high triglyceride levels in women as well as low HDL cholesterol levels in men predict a decline in renal function (*14*). In a prospective study of 12,728 subjects, high triglycerides and low HDL cholesterol were significant risk factors for increasing serum creatinine (*29*). Thus, high triglyceride levels and low HDL cholesterol levels are probably

Table 3. Relative Risk (95% Confidence Interval) of Developing Chronic Kidney Disease, Decreasing GFR, and Developing Proteinuria

Dependent variables and independent variables	Model 1		Model 2	
	RR (95% CI)	*p*	RR (95% CI)	*p*
CKD (GFR<60 mL/min or proteinuria) (*n*=369)				
Metabolic syndrome				
Absence	1.00		1.00	
Presence	1.98 (1.53–2.55)	<0.0001	1.86 (1.43–2.41)	<0.0001
Number of components				
0	1.00		1.00	
1	1.63 (1.21–2.19)	0.0011	1.49 (1.10–2.01)	0.009
2	2.11 (1.55–2.86)	<0.0001	1.89 (1.38–2.59)	<0.0001
≥3	2.93 (2.14–4.02)	<0.0001	2.65 (1.91–3.68)	<0.0001
GFR<60 mL/min				
Metabolic syndrome				
Absence	1.00		1.00	
Presence	1.41 (0.89–2.23)	0.1	1.36 (0.84–2.18)	0.1
Number of components				
0	1.00		1.00	
1	1.47 (0.90–2.38)	0.1	1.18 (0.71–1.94)	0.5
2	2.02 (1.23–3.30)	0.005	1.56 (0.93–2.60)	0.08
≥3	1.98 (1.14–3.43)	0.01	1.67 (0.94–2.97)	0.07
Proteinuria				
Metabolic syndrome				
Absence	1.00		1.00	
Presence	2.24 (1.68–3.01)	<0.0001	2.09 (1.55–2.81)	<0.0001
Number of components				
0	1.00		1.00	
1	1.72 (1.19–2.47)	0.003	1.64 (1.13–2.37)	0.008
2	2.16 (1.48–3.15)	<0.0001	2.02 (1.37–2.97)	0.0003
≥3	3.43 (2.36–5.00)	<0.0001	3.16 (2.14–4.67)	<0.0001

Model 1: unadjusted analysis. Model 2: adjusted for age, sex, current cigarette smoking and alcohol drinking habits. RR, relative risk; CI, confidence interval; CKD, chronic kidney disease; GFR, glomerular filtration rate.

Table 4. Individual Metabolic Syndrome Components and Relative Risk (95% Confidence Interval) of Developing Chronic Kidney Disease

Variables	Model 1		Model 2	
	RR (95% CI)	*p*	RR (95% CI)	*p*
Obesity	1.27 (1.02–1.59)	0.03	1.31 (1.04–1.64)	0.01
High triglycerides	1.09 (0.86–1.38)	0.45	1.17 (0.91–1.49)	0.2
Low HDL cholesterol	1.16 (0.88–1.55)	0.28	1.10 (0.82–1.47)	0.5
High blood pressure				
SBP≥130 mmHg	2.06 (1.60–2.60)	<0.0001	1.64 (1.26–2.14)	0.0002
DBP≥85 mmHg	0.93 (0.68–1.27)	0.6	1.05 (0.76–1.43)	0.7
High fasting glucose	1.28 (0.94–1.75)	0.11	1.22 (0.89–1.07)	0.2

Model 1: unadjusted analysis. Model 2: adjusted for age, sex, current cigarette smoking and alcohol drinking habits. RR, relative risk; CI, confidence interval; HDL, high-density lipoprotein; SBP, systolic blood pressure; DBP, diastolic blood pressure.

risk factors for developing CKD. The mechanisms whereby lipids contribute to renal injury are not completely understood. Several cytokines might be involved in renal injury. The secretion of interleukin-6, platelet-derived growth factor, transforming growth factor-β, and tumor necrosis factor-α by mesangial cells is enhanced when mesangial cells are exposed

to lipids (*30*). In mesangial cells, lipoproteins stimulate the production of fibronectin and monocyte chemoattractant protein-1 expression (*31*). Insulin-like growth factor-1 induces lipid accumulation in mesangial cells, and this impairs their ability to respond to specific migratory and contractile stimuli (*32*). Increased expression of sterol regulatory element–binding proteins might also have an important role in renal lipid accumulation, glomerulosclerosis, tubulointerstitial fibrosis, and proteinuria in mice with type 2 diabetes (*33*).

Hypertension is a well-described risk factor for renal injury. High blood pressure is a strong independent risk factor for developing end-stage renal disease (*34–37*). Even a high-normal level of blood pressure predicted the development of renal disease in these studies (*34–37*). In the present study, high systolic blood pressure was also a significant risk factor for developing CKD.

Obesity induces glucose intolerance and hyperinsulinemia, as well as diabetes mellitus. Ethnic differences in the genetic predisposition to diabetes mellitus do exist, however, and diabetes mellitus tends to develop more in Asians than in Caucasians, even in those with a smaller BMI (*11*). In Japan, diabetes mellitus has become the leading cause of new onset dialysis since 1998, affecting 13,920 patients (41.3%) in 2004 (*38*). Furthermore, in Japan, obesity increases health care costs, all causes of mortality, and the risk of cancer (*39*). Obesity is a great problem in Japan now and will be in the future.

There are potential limitations to the interpretations of this study. First, the measurement of waist circumference was not commonly performed in the OGHMA screening in 1997. Therefore, metabolic syndrome was defined based on the modified criteria of the ATP III, in which BMI ($\geq$25 kg/m^2) was substituted for the waist circumference measurement. Both waist circumference and BMI are accurate predictors of total body fat, however, in the Asian population (*40*). Furthermore, the present study suggests that the modified ATP III criteria are useful for detecting the risk for developing CKD. Second, a selection bias of subjects might exist. Our subjects were able to pay the fee to participate in the screening program, and they were mainly employees of local companies. This might be one reason why more men than women participated. Also, some baseline characteristics were different between the subjects that were followed and those that dropped out. Third, serum creatinine levels and calculated GFR have been used to define CKD (*17*). Although inulin or iothalamate clearance techniques might provide a more sensitive estimate of renal function, serum creatinine is widely used in large epidemiologic studies and clinical practice for estimating renal function. Therefore, our findings are applicable to clinical and public health practice settings. We chose estimated GFR calculated by the Modification of Diet in Renal Disease formula, which is more accurate for predicting GFR than is measuring the creatinine clearance or other commonly used equations (*16*). Fourth, in the present study, we did not measure the reproducibility of proteinuria and GFR, because only one set of data for proteinuria and GFR were available at each examination. Fifth, the possible effect of hypertension or diabetes mellitus developed during the follow-up period on the development of CKD could not be excluded in the present study.

In summary, we investigated the effects of metabolic syndrome on the incidence of CKD in a large screened cohort of Japanese. Metabolic syndrome was an independent predictor for developing CKD. Early detection and treatment of those with metabolic syndrome are essential as continuing strategies to prevent CKD.

Acknowledgements

The authors thank Mr. Masanori Itokazu and Mr. Kaoru Shiroma of the Okinawa General Health Maintenance Association for technical assistance.

References

1. Lakka HM, Laalsonen DE, Lakka TA, *et al*: The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *JAMA* 2002; **288**: 2709–2716.
2. Takeuchi H, Saitoh S, Takagi S, *et al*: Metabolic syndrome and cardiac disease in Japanese men: applicability of the concept of metabolic syndrome defined by the National Cholesterol Education Program–Adult Treatment Panel III to Japanese men—the Tanno and Sobetsu Study. *Hypertens Res* 2005; **28**: 203–208.
3. Japanese Society for Dialysis Therapy: An overview of regular dialysis treatment in Japan: as of December 21, 2005. http://www.jsdt.or.jp
4. Iseki K, Tozawa M, Iseki C, Takishita S, Ogawa Y: Demographic trends in the Okinawa Dialysis Study (OKIDS) registry (1971–2000). *Kidney Int* 2002; **61**: 668–675.
5. Usami T, Koyama K, Takeuchi O, Morozumi K, Kimura G: Regional variations in the incidence of end-stage renal failure in Japan. *JAMA* 2000; **284**: 2622–2624.
6. Tanaka H, Shimabukuro T, Shimabukuro M: High prevalence of metabolic syndrome among men in Okinawa. *J Atheroscler Thromb* 2005; **12**: 284–288.
7. Iseki K, Kohagura K, Sakima A, *et al*: Changes in the demographic and prevalence of chronic kidney disease in Okinawa, Japan (1993 to 2002). *Hypertens Res* 2007; **30**: 55–62.
8. Chen J, Muntner P, Hamm LL, *et al*: The metabolic syndrome and chronic kidney disease in U.S. adults. *Ann Intern Med* 2004; **140**: 167–174.
9. Tanaka H, Shiohira Y, Uezu Y, Higa A, Iseki K: Metabolic syndrome and chronic kidney disease in Okinawa, Japan. *Kidney Int* 2006; **69**: 369–374.
10. Kurella M, Lo JC, Chertow GM: Metabolic syndrome and the risk for chronic kidney disease among nondiabetic adults. *J Am Soc Nephrol* 2005; **16**: 2134–2140.
11. Mandavilli A, Cyranoski D: Asia's big problem. *Nat Med* 2004; **10**: 325–327.
12. Ninomiya T, Kiyohara Y, Kubo M, *et al*: Metabolic syndrome and CKD in a general Japanese population: the Hisayama Study. *Am J Kidney Dis* 2006; **48**: 383–391.
13. Tozawa M, Iseki K, Iseki C, Oshiro S, Ikemiya Y, Takishita

S: Influence of smoking and obesity on the development of proteinuria. *Kidney Int* 2002; **62**: 956–962.
14. Tozawa M, Iseki K, Iseki C, Oshiro S, Ikemiya Y, Takishita S: Triglyceride, but not total cholesterol or low-density lipoprotein cholesterol levels, predict development of proteinuria. *Kidney Int* 2002; **62**: 1743–1749.
15. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults: Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 2001; **285**: 2486–2497.
16. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D, Modification of Diet in Renal Disease Study Group: A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. *Ann Intern Med* 1999; **130**: 461–470.
17. Kopple JD: National kidney foundation K/DOQI clinical practice guidelines for nutrition in chronic renal failure. *Am J Kidney Dis* 2001; **37** (1 Suppl 2): S66–S70.
18. Petrie A, Sabin C: Medical Statistics at a Glance. Oxford, Blackwell Science, Ltd, 2000, pp 64–66.
19. Levey AS, Eckardt KU, Tsukamoto Y, *et al*: Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2005; **67**: 2089–2100.
20. Kramer H, Luke A, Bidani A, Cao G, Cooper R, McGee D: Obesity and prevalent and incident CKD: the Hypertension Detection and Follow-Up Program. *Am J Kidney Dis* 2005; **46**: 587–594.
21. Ejerblad E, Fored CM, Lindblad P, Fryzek J, McLaughlin JK, Nyren O: Obesity and risk for chronic renal failure. *J Am Soc Nephrol* 2006; **17**: 1695–1702.
22. Bonnet F, Deprele C, Sassolas A, *et al*: Excessive body weight as a new independent risk factor for clinical and pathological progression in primary IgA nephritis. *Am J Kidney Dis* 2001; **37**: 720–727.
23. Gelber RP, Kurth T, Kausz AT, *et al*: Association between body mass index and CKD in apparently healthy men. *Am J Kidney Dis* 2005; **46**: 871–880.
24. Hsu CY, McCulloch CE, Iribarren C, Darbinian J, Go AS: Body mass index and risk for end-stage renal disease. *Ann Intern Med* 2006; **144**: 21–28.
25. Ribstein J, du Cailar G, Mimran A: Combined renal effects of overweight and hypertension. *Hypertension* 1995; **26**: 610–615.
26. Kasiske BL, Crosson JT: Renal disease in patients with massive obesity. *Arch Intern Med* 1986; **146**: 1105–1109.
27. Henegar JR, Bigler SA, Henegar LK, Tyagi SC, Hall JE: Functional and structural changes in the kidney in the early stages of obesity. *J Am Soc Nephrol* 2001; **12**: 1211–1217.
28. Gu JW, Wang J, Stockton A, Lokitz B, Henegar L, Hall JE: Cytokine gene expression profiles in kidney medulla and cortex of obese hypertensive dogs. *Kidney Int* 2004; **66**: 713–721.
29. Muntner P, Coresh J, Smith JC, Eckfeldt J, Klag MJ: Plasma lipids and risk of developing renal dysfunction: the atherosclerosis risk in communities study. *Kidney Int* 2000: **58**: 293–301.
30. Keane WF, O'Donnell MP, Kasiske BL, Kim Y: Oxidative modification of low-density lipoproteins by mesangial cells. *J Am Soc Nephrol* 1993; **4**: 187–194.
31. Nishida Y, Yorioka N, Oda H, Yamakido M: Effect of lipoproteins on cultured human mesangial cells. *Am J Kidney Dis* 1997; **29**: 919–930.
32. Berfield AK, Andress DL, Abrass CK: IGF-1–induced lipid accumulation impairs mesangial cell migration and contractile function. *Kidney Int* 2002; **62**: 1229–1237.
33. Wang Z, Jiang T, Li J, *et al*: Regulation of renal lipid metabolism, lipid accumulation, and glomerulosclerosis in FVBdb/db mice with type 2 diabetes. *Diabetes* 2005; **54**: 2328–2335.
34. Klag MJ, Whelton PK, Randall BL, *et al*: Blood pressure and end-stage renal disease in men. *N Engl J Med* 1996; **334**: 13–18.
35. Tozawa M, Iseki K, Iseki C, Kinjo K, Ikemiya Y, Takishita S: Blood pressure predicts risk of developing end-stage renal disease in men and women. *Hypertension* 2003; **41**: 1341–1345.
36. Hsu CY, McCulloch CE, Darbinian J, Go AS, Iribarren C: Elevated blood pressure and risk of end-stage renal disease in subjects without baseline kidney disease. *Arch Intern Med* 2005; **165**: 923–928.
37. Segura J, Campo C, Gil P, *et al*: Development of chronic kidney disease and cardiovascular prognosis in essential hypertensive patients. *J Am Soc Nephrol* 2004; **15**: 1616–1622.
38. Nakai S, Wada A, Kitaoka T, *et al*: An overview of dialysis treatment in Japan (as of Dec. 31, 2004). *J Jpn Soc Dial Ther* 2006; **39**: 1–22.
39. Kuriyama S: Impact of overweight and obesity on medical care costs, all-cause mortality, and the risk of cancer in Japan. *J Epidemiol* 2006; **16**: 139–144.
40. Chen YM, Ho SC, Lam SS, Chan SS: Validity of body mass index and waist circumference in the classification of obesity as compared to percent body fat in Chinese middle-aged women. *Int J Obes* (*Lond*) 2006; **30**: 918–925.