Kidney International, Vol. 65 (2004), pp. 1870–1876

Body mass index and the risk of development of end-stage renal disease in a screened cohort

KUNITOSHI ISEKI, YOSHIHARU IKEMIYA, KOZEN KINJO, TAKU INOUE, CHIHO ISEKI, and SHUICHI TAKISHITA

Dialysis Unit and Third Department of Internal Medicine, University of The Ryukyus; and Okinawa General Health Maintenance Association, Okinawa, Japan

Body mass index and the risk of development of end-stage renal disease in a screened cohort.

Background. Obesity is associated with proteinuria and could be a risk factor for end-stage renal disease (ESRD). However, few studies have examined the significance of body mass index (BMI) as a risk factor for the development of ESRD in the general population.

Methods. We examined the relationship between BMI and the development of ESRD using data from a 1983 community-based screening in Okinawa, Japan. Screenees who developed ESRD by the end of 2000 were identified through the Okinawa Dialysis Study registry. BMI data were available for 100,753 screenees (47,504 men and 53,249 women) aged ≥20 years. The cumulative incidence of ESRD was analyzed according to the quartile of BMI: <21.0, 21.0 to 23.1, 23.2 to 25.4, and ≥25.5 kg/m^2.

Results. The mean (SD) BMI of the screenees was 23.4 (3.3) kg/m^2 (range 7.9 to 59.1 kg/m^2); the mean was 23.4 kg/m^2 for both men and women. During the follow-up period, 404 screenees (232 men and 172 women) developed ESRD. The cumulative incidences of ESRD per 1000 screenees were, from the lowest to highest BMI quartile, 2.48, 3.79, 3.86, and 5.81. The odds ratio (95% CI) of BMI for developing ESRD, after adjustment for age, sex, systolic blood pressure, and proteinuria, was 1.273 (1.121–1.446, $P = 0.0002$) for men and 0.950 (0.825–1.094, not significant) for women.

Conclusion. We found that BMI was associated with an increased risk of the development of ESRD in men in the general population in Okinawa. The maintenance of optimal body weight may reduce the risk of ESRD.

The number of patients with end-stage renal disease (ESRD) requiring chronic dialysis therapy is increasing worldwide [1–3]. The early detection and treatment of individuals at high risk may reduce the burden of ESRD. The relationships of excess body weight with all-cause and cardiovascular mortality are well established [4–7]. However, only a few studies have examined the influence of being overweight or obese on the risk of developing ESRD. Proteinuria has been found to be among the most powerful predictors of ESRD in mass screening settings [8, 9]. The relationship between body mass index (BMI) and proteinuria is therefore interesting. In a large cross-sectional population study, Ramirez et al [10] found a J-shaped relationship between BMI and the prevalence of proteinuria. We previously observed that BMI was an independent predictor of the development of proteinuria in men [11]. Donor-recipient body size mismatch is an important predictor of disease progression [12] and graft loss in renal transplantation; being overweight or obese could therefore be a significant risk factor for ESRD. Our preliminary report suggested that BMI was not a major risk factor for the development of ESRD [13]; however, the 10-year follow-up period may have been insufficient to establish any relationship between these factors. We have extended this follow-up period to 17 years; here we report our findings on the relationship between BMI and the risk of developing ESRD.

Key words: body mass index, end-stage renal disease, screening.

Received for publication September 24, 2003
and in revised form November 24, 2003
Accepted for publication December 12, 2003

METHODS

Study design

All subjects over age 20 years who participated in the 1983 mass health screening examinations in Okinawa, Japan, were eligible for the study. Okinawa consists of a number of subtropical islands in the southernmost part of Japan. The population in 1983 was approximately 1.14 million. Screening participants were excluded from the present study if their date of birth, height, or weight were not available in the registry files. In a subgroup of the screenees data for fasting blood glucose were available. Dialysis patients who were among the 1983 screening participants, and individuals who became dialysis patients between 1983 and December 2000, were identified from the Okinawa Dialysis Study (OKIDS) registry. The OKDIS registry includes information on all dialysis

patients in the Okinawa area. The identity of dialysis patients was verified through the review of medical charts in the dialysis units. The cumulative incidence of ESRD and the odds ratio (OR) for developing ESRD according to the quartile of BMI at screening were calculated. The institutional ethics committee approved the protocol for this study.

Mass screening

The Okinawa General Health Maintenance Association (OGHMA), a nonprofit agency directed by Dr. Y. Ikemiya, performs a large community-based health examination annually [8]. OGHMA staff, doctors, and nurses visit sites accessible to Okinawa residents and daytime employees, who participate in the screening voluntarily. Screenees are interviewed and given physical examinations, a urine test, and blood tests. They are informed of the results of these tests and advised when to seek further care. During the screening, blood pressure is measured by clinical staff with a standard mercury sphygmomanometer with the screenee seated. The urine test consists of dipstick urinalysis (Ames dipstick) for proteinuria and is performed on spontaneously voided fresh urine. The urine test results are interpreted by OGHMA physicians or their assistants and are recorded as "−," "+/−," "1+," "2+," "3+," or "4+." Results recorded as "−" or "+/−" are defined as normal; others are defined as abnormal. BMI was calculated as the weight in kg divided by the square of the height in meters. Diabetes mellitus (DM) was diagnosed when the fasting blood glucose was ≥126 mg/dL. The computer-based screening data used in this study included information acquired from April 1, 1983, through to March 31, 1984. The present analysis was conducted on 100,753 screenees (47,504 men and 53,249 women), or about 13.0% of the total adult Okinawa population in 1983. Screenees who were already on chronic dialysis at the time of the screening were excluded from the study.

Dialysis registry in Okinawa

By the end of 2000, there were 46 dialysis units in Okinawa: 9 in the public sector, 17 in private hospitals, and 20 in clinics. All chronic dialysis patients residing in Okinawa who survive at least 1 month on scheduled dialysis are included in the OKIDS registry [14]. Patients dying within 1 month of the start of dialysis are not included in the registry because it is unknown whether their renal function is improving and if other medical conditions account for their rapid demise. Pertinent clinical information for the new dialysis patients, and medical events in the existing dialysis patients, was collected by the collaborating physicians acknowledged below. Records were updated at least twice a year for medical events, including death, renal transplantation, and patient transfer out of Okinawa. If necessary, other information was obtained through nurses, medical clerks, and the patients themselves. All patients were followed-up until a major medical event, or until December, 2000, whichever occurred first, and all outcomes were verified. The number of ESRD transferred outside was only 1.2% during the past 30 years [14].

Criteria for the determination of the cause of ESRD were neither simple nor standardized. Therefore, medical records were further reviewed, and patients were grouped according to one of six disease categories [14]: chronic glomerulonephritis, diagnosed when proteinuria and/or hematuria was noted before the onset of hypertension and renal failure; nephrosclerosis, diagnosed when hypertension or major vascular disease was documented before the onset of renal failure; diabetes mellitus (DM) nephropathy, diagnosed by a long history of DM, the presence of DM retinopathy, and the use of insulin; systemic lupus erythematosus, diagnosed according to the American Rheumatism Association criteria; and polycystic kidney disease, diagnosed after chart review by the presence of multiple cysts and a family history of the disease. The sixth category—"other disease"—included patients who did not fall into one of the aforementioned disease categories.

Statistical analysis

Data are expressed as mean (SD). The unpaired *t* test or chi-square test was used to analyze differences in values or ratios between groups. Trends were estimated by multivariate analysis of variance. Multivariate logistic analysis was used to examine the relationship between BMI and the development of ESRD after adjustment for age, sex, systolic blood pressure, and proteinuria. Furthermore, we performed a similar analysis in a subgroup of the screenees who had data for fasting blood glucose. All analyses were carried out with SAS (Version 6; SAS Institute, Inc., Cary, NC, USA). A result of $P < 0.05$ was considered statistically significant.

RESULTS

For both men and women, BMI was normally distributed (Fig. 1). BMI did not change significantly with age. For screenees above age 51, BMI was higher for women than men. The baseline clinical characteristics of the screened subjects are summarized in Table 1. The mean (SD) BMI was 23.4 (3.3) kg/m^2. BMI was categorized into quartiles with the following cutoff points: <21.0, 21.0 to 23.1, 23.2 to 25.4, and ≥25.5 kg/m^2. Age, systolic and diastolic blood pressure, and proteinuria increased from the lowest to highest BMI quartile (Table 2).

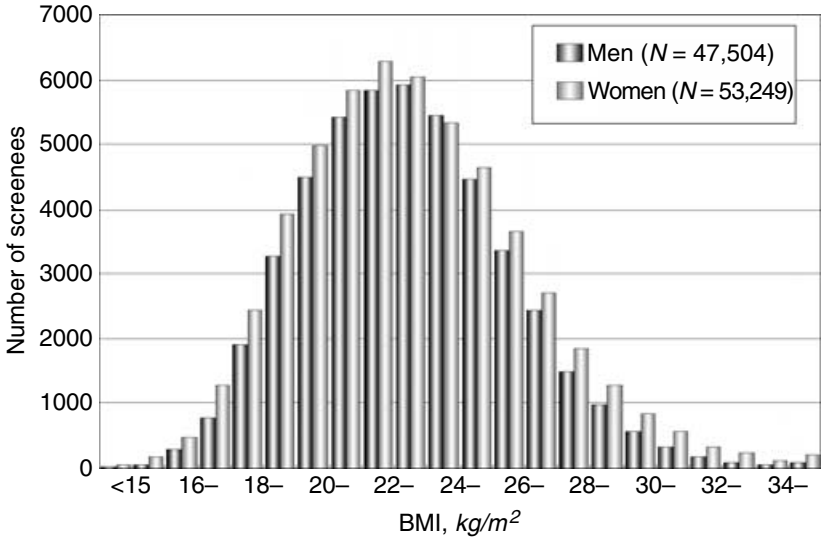


Fig. 1. Distribution of body mass index in men and women at the time of screening. Screening was completed between April 1, 1983, and March 31, 1984.

Table 1. Baseline clinical characteristics of screened subjects for who body mass index (BMI) data were available ($N = 100,753$)

Men (%)	47,504 (47.1%)
Age at screening *years*	49.6 (16.2)
Height *cm*	154.1 (9.1)
Weight *kg*	55.9 (10.3)
Body mass index *kg/m²*	23.4 (3.3)
Systolic blood pressure *mm Hg*	130.3 (19.4)
Diastolic blood pressure *mm Hg*	78.7 (11.4)
Proteinuria	5291 (5.3%)

Data are expressed as mean (SD). Screening was performed in Okinawa, Japan, from April 1, 1983, to March 31, 1984. Data for blood pressure and proteinuria were available for more than 98% of screenees. Proteinuria denotes dipstick positive (≥1+).

Table 2. Baseline clinical characteristics of the screenees by the quartiles of body mass index

	BMI*kg/m²*			
	<21.0	21.0–23.1	23.2–25.4	≥25.5
N	24,155	25,826	25,130	25,642
Mean BMI	19.4 (1.2)	22.1 (0.6)	24.2 (0.7)	27.8 (2.2)
Men %	44.8%	48.3%	50.0%	45.4%
Age at screening *years*	48.7 (19.3)	49.1 (16.6)	50.1 (14.9)	50.3 (13.6)
SBP *mm Hg*	123.6 (18.8)	128.0 (18.7)	131.9 (18.6)	137.2 (19.1)
DBP *mm Hg*	73.8 (10.5)	76.9 (10.5)	79.9 (10.6)	84.0 (11.2)
Proteinuria %	4.5%	4.5%	4.9%	7.5%

Abbreviations are: SBP, systolic blood pressure; DBP, diastolic blood pressure. Data are expressed as mean (SD). Trends were all significant, $P < 0.0001$, by quartile of BMI.

During the follow-up period, 404 screenees (232 men and 172 women) required scheduled dialysis. Baseline data for these screenees is summarized in Table 3. The mean (SD) BMI for these subjects was 24.4 (3.4) kg/m^2. At the time of start of dialysis, it was 22.3 (3.0) kg/m^2, $P < 0.0001$ by paired t test. The 17-year cumulative incidence of ESRD by BMI quartile is shown in Figure 2. The mean

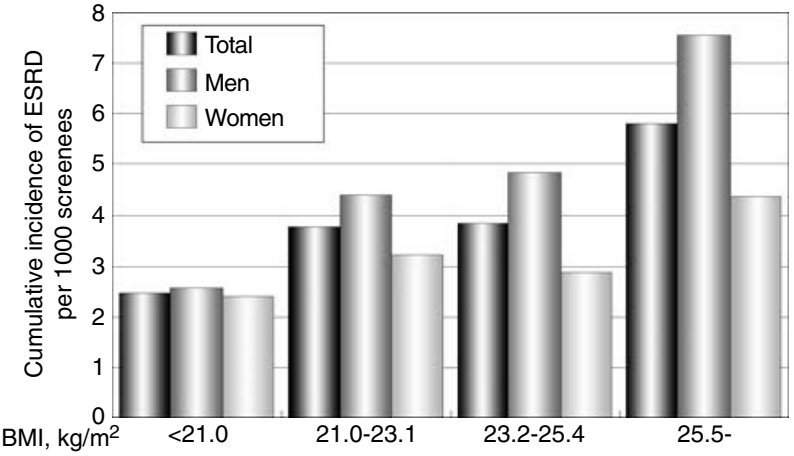
Table 3. Baseline clinical characteristics of the screenees who developed end-stage renal disease (ESRD) during the study period ($N = 404$)

Men (%)	232 (57.4%)
Age at screening *years*	53.1 (13.0)
Height *cm*	154.4 (8.5)
Weight *kg*	58.6 (10.6)
Body mass index *kg/m²*	24.4 (3.4)
Systolic blood pressure *mm Hg*	144.2 (22.1)
Diastolic blood pressure *mm Hg*	86.7 (12.8)
Proteinuria %	44.8 %
Cause of ESRD	
Chronic glomerulonephritis	198 (49.0%)
Diabetes mellitus	98 (24.3%)
Polycystic kidney disease	10 (2.5%)
Systemic lupus erythematosus	6 (1.5%)
Nephrosclerosis	51 (12.6%)
Other	41 (10.1%)

Data are expressed as mean (SD).

time from the screening to the start of dialysis was 109.6 months in those with BMI <21.0 kg/m^2, 122.2 months in those with BMI 21.0 to 23.1 kg/m^2, 132.2 months in those with BMI 23.2 to 25.4 kg/m^2, and 139.2 months in those with BMI ≥25.5 kg/m^2. Twelve out of 404 screenees (2.97%) entered ESRD program within 24 months after screening. Their mean (SD) BMI was 23.6 (2.6) kg/m^2, which was slightly lower than the mean (SD) of screenees who entered ESRD 24 months later of 24.5 (3.4) kg/m^2 ($N = 392$, not significant).

The contribution of BMI to the risk of developing ESRD was evaluated by multivariate logistic analysis. The adjusted odds ratio (95% CI) was 1.111 (1.012–1.220, $P = 0.0274$) for BMI categorized into quartiles (Table 4). Quartile BMI was a significant predictor of ESRD in men, for whom the adjusted odds ratio was 1.273 (1.121–1.446, $P = 0.0002$). However, this was not true for women, for whom the adjusted odds ratio was 0.950 (0.825–1.094,



BMI, kg/m^2	<21.0	21.0-23.1	23.2-25.4	25.5-
N of screenees	24,155	25,826	25,130	25,642
(Men/women)	(10,810/13,345)	(12,473/13,353)	(12,575/12,555)	(11,646/13,996)
N of ESRD	60	98	97	149
(Men/women)	(28/32)	(55/43)	(61/36)	(88/61)

Fig. 2. Cumulative incidence of end-stage renal disease according to quartile of body mass index at the time of screening.

not significant). When BMI was considered as a continuous variable, the adjusted odds ratio for men was 1.063 (1.023–1.104, $P = 0.0020$), and for women was 0.988 (0.948–1.031, not significant).

Similar results were obtained even after excluding the screenees with BMI <15 kg/m^2 ($N = 78$). Because the impact of the presence of proteinuria is strong, we reevaluated the contribution of BMI in both the screened subjects with proteinuria and those without proteinuria at the baseline. In the screenees with proteinuria, the OR (95% CI) of BMI was 1.020 (0.851–1.222, not significant) for men and 0.945 (0.764–1.170, not significant) for women. However, in the screenees without proteinuria, the OR (95% CI) of BMI was 1.516 (1.270–1.809, $P < 0.0001$) for men and 0.940 (0.780–1.132, not significant) for women. In a subgroup of the screened cohort ($N = 14,094$, 14% of the total), the prevalence of DM was 5.4% ($N = 761$). The prevalence of DM was 4.0% in the screenees with BMI <21.0 kg/m^2, 4.8% in those with BMI 21.0 to 23.1 kg/m^2, 5.0% in those with BMI 23.2 to 25.4 kg/m^2, and 7.3% in those BMI 25.5 kg/m^2. The mean BMI was significantly higher in the screenees with DM (24.7 kg/m^2) than that of non-DM screenees (23.8 kg/m^2, $P < 0.0001$). Significance of BMI on the risk of developing ESRD was lost in men ($N = 7323$) after including the presence of DM in addition to variables in Table 4 (the adjusted OR 0.988, 95% CI 0.735–1.327). Even in non-DM screenees ($N = 6943$), the significance of BMI was not clear (the adjusted OR of 0.933, 95% CI 0.697–1.250).

The adjusted odds ratio for men in the highest compared with the lowest quartile of BMI was 2.389 (1.529–3.735, $P = 0.0001$) and for women was 0.8430 (0.604–1.510, not significant) (Table 5).

DISCUSSION

Obesity is known to have a negative impact on renal disease, and it is closely associated with hypertension, hyperlipidemia, and microalbuminuria [15, 16]. A significant correlation between obesity and urinary albumin excretion has been reported in a large cross-sectional study of middle-aged men and women [17]. Weight loss and a decrease in proteinuria have also been found to be significantly correlated [18]. The contribution of obesity to the risk of ESRD has not been adequately studied in a large population. Our data suggest that the maintenance of an optimal body weight may reduce the risk of ESRD, independent of the effect of blood pressure [19] and proteinuria [8].

The mean BMI of the general population in the United States is 26.3 kg/m^2 [20]; we found that the corresponding figure in Okinawa was 23.4 kg/m^2. Our results show that the prevalence of obesity, defined as BMI 30.0 kg/m^2, in Okinawa was 3.5% in 1983 and 4.8% in 1993; this is slightly lower than the prevalence of 5.7% in Singapore [10]. Okinawa was under U.S. control from the end of World War II until 1972. Since the return to Japanese control, the lifestyle on the islands has changed, because Okinawa has become more a part of the industrialized world. Individuals now do less walking and are more likely to become overweight [21].

There are several plausible mechanisms for the association between BMI and ESRD. High BMI is a risk factor for hypertension, DM, and hyperlipidemia, all of which increase the risk of ESRD. The number of glomeruli is dependent on birth weight, and does not increase after birth. Patients with hypertension [22] or low birth weight have been observed to have a low number of nephrons. The incidence of low birth weight (defined as weight less

Table 4. Results of univariate and multivariate logistic analyses for the development of end-stage renal disease

	Univariate		Multivariate	
Variable	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Men and women				
Age	1.013 (1.007–1.020)	<0.0001	1.000 (0.993–1.007)	NS
Sex vs. women	1.514 (1.243–1.845)	<0.0001	1.510 (1.225–1.861)	0.0001
SBP *mm Hg*	1.029 (1.025–1.033)	<0.0001	1.018 (1.013–1.023)	<0.0001
BMI[a]	1.293 (1.181–1.415)	<0.0001	1.111 (1.012–1.220)	0.0274
Proteinuria	3.073 (2.868–3.294)	<0.0001	2.835 (2.637–3.048)	<0.0001
Men				
Age	1.016 (1.008–1.024)	<0.0001	1.006 (0.997–1.015)	NS
SBP *mm Hg*	1.030 (1.024–1.035)	<0.0001	1.018 (1.011–1.024)	<0.0001
BMI[a]	1.383 (1.222–1.564)	<0.0001	1.273 (1.121–1.446)	0.0002
Proteinuria	3.075 (2.804–3.373)	<0.0001	2.858 (2.598–3.145)	<0.0001
Women				
Age	1.016 (1.006–1.025)	0.0012	0.995 (0.984–1.006)	NS
SBP *mm Hg*	1.029 (1.023–1.035)	<0.0001	1.019 (1.012–1.027)	<0.0001
BMI[a]	1.192 (1.042–1.364)	0.0103	0.950 (0.825–1.094)	NS
Proteinuria	3.064 (2.757–3.404)	<0.0001	2.825 (2.528–3.158)	<0.0001

NS, not significant; SBP, systolic blood pressure. Proteinuria was categorized as: "−," "+/−," "1+," "2+," "3+," or "4+" by dipstick test. Multivariate analyses were done after including variables such as age, gender, SBP, and proteinuria.

[a]BMI, body mass index, in quartiles: <21.0, 21.0–23.1, 23.2–25.4, and ≥ 25.5 kg/m^2.

Table 5. Adjusted odds ratio (95% CI) for developing ESRD by BMI quartile

BMI *kg/m^2*	Adjusted odds ratio	95% CI	*P* value
Men and women			
<21.0	1		
21.0–23.1	1.486	1.070–2.062	0.0181
23.2–25.4	1.338	0.960–1.864	0.0854
≥25.5	1.483	1.083–2.031	0.0140
Men			
<21.0	1		
21.0–23.1	1.788	1.123–2.846	0.0142
23.2–25.4	1.950	1.230–3.090	0.0045
≥25.5	2.389	1.529–3.735	0.0001
Women			
<21.0	1		
21.0–23.1	1.249	0.780–1.996	0.3536
23.2–25.4	0.879	0.535–1.445	0.6118
≥25.5	0.955	0.604–1.510	0.8430

Adjusted for age, systolic blood pressure, and proteinuria.

than 2500 g) in Okinawa is 7.4% to 9.3%, and is higher than the national average of 5.7% [14]. Low birth weight has been linked to the subsequent development of hypertension and renal failure [23]. This would be more evident in Okinawa because the prevalence of obesity has increased recently. Actually, the incidence of ESRD is highest in Okinawa among Japanese [24]. Interestingly, although the number of glomeruli is different for each individual, the average number of glomeruli per person does not differ by gender [25].

Gender differences in the progression of various renal diseases have been reported. Men are at higher risk of developing ESRD, and tend to develop ESRD earlier in life, than women [26–28]. This may in part be caused by the influence testosterone and other sex hormones have on gender differences in the risk of proteinuria and glomerular sclerosis [29]. In addition, differences in the risk conferred by being overweight or obese may be important to the gender differences in ESRD risk.

Recently, we showed that smoking and obesity were significant predictors of proteinuria and, therefore, the development of ESRD [11]. In Okinawa, the prevalence of smoking is 43.0% in men and 4.5% in women [11]. It is likely that smoking alters the effect of BMI on the risk of death from many diseases, including smoking-related cancers. Smoking has been reported to be associated with microalbuminuria independently of blood pressure in a cross-sectional study of the general population [30] and in DM patients [31, 32]. Furthermore, Orth et al [33] showed that smoking increased the risk of ESRD in men diagnosed with IgA nephropathy or autosomal-dominant polycystic kidney disease.

In our study, as BMI decreased, the incidence of ESRD also decreased. However, this does not necessarily imply that low BMI confers a low risk of ESRD. In fact, Ramirez et al [10] reported that their graph of proteinuria versus BMI was J-shaped, so that patients at a very low BMI had an increased risk of proteinuria. However, they showed racial difference in the relationship between BMI and proteinuria. Factors related to these racial differences need to be determined. Our study has several limitations. First, although all new ESRD patients were accounted for, subjects who died were not; deceased patients, therefore, were not excluded from the logistic analysis. Given the increased morbidity and mortality of obese patients, our data might underestimate the true importance of BMI to the risk of ESRD. In the 1980s, the incidence of DM in ESRD was low, as in other parts of Japan [1]. The annual incidence increased from 35.0 per million populations in 1990 to 99.1 per million populations in 2002 in Japan. Such trends may be explained by increasing prevalence of DM associated with obesity in the general population in Japan. The acceptance policy for ESRD has been quite open since 1972 in Japan.

Second, BMI was measured on only one occasion. We therefore cannot determine the effects of weight loss or gain in this study. Body weight may be related to current health status or health practices. For example, smoking or chronic disease may lead to weight loss. In patients with chronic kidney disease, the absorption of dietary protein and energy, and serum and anthropometric measures of protein-energy nutritional status progressively decline with the glomerular filtration rate (GFR) [34, 35]. A higher GFR has been associated with a higher BMI in men, but not in women [35]. Unfortunately, in our study, data on serum creatinine was available in only 13.7% of the screened subjects [36].

Third, subjects who chose to participate in the screening were generally healthy individuals who were interested in their health. Individuals who were already diagnosed with renal failure or cancer may have been less likely to participate in the screening.

Fourth, the incidences of primary renal diseases in the screened ESRD patients were slightly different than in the entire ESRD Okinawa population during the study period. ESRD was caused by DM in 24.3% of screened ESRD patients but 33.7% of ESRD patients in the general Okinawa population during this study period.

Fifth, our database did not include information on other risk factors related to ESRD risk, including hematocrit, hyperlipidemia, DM, and smoking. In particular, the relationship between overweight and obesity on the risk of developing proteinuria [11] and DM should be examined further in larger population. Low income and education, potential risk factors for the development of chronic kidney disease [35, 36], were also not measured in this study. Finally, regional variations in the prevalence of obesity and the incidence of ESRD are being identified with increasing frequency; therefore, our results should be confirmed in other regions or countries.

CONCLUSION

We found that increasing BMI was associated with an increased risk of the development of ESRD in men even after adjustment for blood pressure and proteinuria. The prevention and treatment of obesity, at least in men, is an important strategy for reducing the burden of ESRD.

ACKNOWLEDGMENTS

Parts of this study were supported by grants from the Ministry of Health and Welfare of Japan. We are indebted to the staff of the Okinawa General Health Maintenance Association, in particular to Mr. M. Itokazu and Mr. K. Shiroma, for retrieving data files from the 1983 health check. The authors are grateful for the collaboration with the physicians and co-medical staff working at all the dialysis units in Okinawa. The following doctors gave us invaluable advice, support, and encouragement: Drs. T. Minei, T. Kowatari, K. Nishime, H. Ogimi, T. Yonaha, C. Mekaru, K. Kinjo, M. Nakayama, H. Uehara, H. Sunagawa, S. Nakasato, Y. Oshiro, N. Kuwae, T. Wake, M. Arakaki, S. Yoshi, S. Miyagi, K. Tokuyama, I. Kyan, Y. Uezu, T. Hokama, S. Kiyuna, H. Henzan, T. Asato, Y. Nakasone, Y. Shiohira, K. Higa, T. Miyagi, H. Afuso, F. Miyasato, S. Maeshiro, T. Sakuda, H. Momozono, T. Asato, M. Ikemura, T. Taminato, Y. Oshiro, M. Yamasato, T. Izumi, T. Oura, S. Toma, T. Sunagawa, T. Funakoshi, S. Terukina, T. Oyama, Y. Tinen, Y. Oshiro, K. Nakama, K. Nakao, O. Shiranezawa, K. Nagasawa, H. Uchima, T. Higa, A. Higa, K. Yoshihara, M. Maeshiro, S. Miyagi, T. Kinjo, M. Ishu, H. Yoshimura, Y. Arakaki, N. Nakamura, H. Kinjo, O. Shinjo, T. Nakanishi, I. Shiroma, S. Shiroma, K. Ishikawa, K. Nagata, K. Akamine, T. Tana, S. Oshiro, N. Tomiyama, K. Kohagura, H. Muratani, Professor Y. Ogawa, ex-Prof. A. Osawa, and ex-Prof. K. Fukiyama. The authors are grateful to Dr. O. Morita for helping with the data processing and statistical analyses.

Reprint requests to Dr. Kunitoshi Iseki, M.D., Dialysis Unit, University of The Ryukyus, 207 Uehara, Okinawa 903–0215, Japan.
E-mail: chihokun@med.u-ryukyu.ac.jp

REFERENCES

1. Nakai S, Shinzato T, Sanaka T, *et al*: The current state of chronic dialysis treatment in Japan (as of December 31, 2000). *J Jpn Soc Dial Ther* 35:1155–1184, 2002
2. US Renal Data System: Excerpts from the USRDS 2001 Annual Data Report: Atlas of end-stage renal disease in the United States. *Am J Kidney Dis* 38(Suppl 3): S1–S248, 2001
3. Schena FP: Epidemiology of end-stage renal disease: International comparisons of renal replacement therapy. *Kidney Int* 57(Suppl 74): S39–S45, 2000
4. Kenchaiah S, Evans JC, Levy D, *et al*: Obesity and the risk of heart failure. *N Engl J Med* 347:305–313, 2002
5. Calle EE, Rodriguuez C, Thurmond KW, Thun MJ: Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med* 348:1625–1638, 2003
6. Manson JE, Willett WC, Stampfer MJ, *et al*: Body weight and mortality among women. *N Engl J Med* 333:677–685, 1995
7. Must A, Spadano J, Coakley EH, Field AE: The disease burden associated with overweight and obesity. *JAMA* 282:1523–1529, 1999
8. Iseki K, Ikemiya Y, Iseki C, Takishita S: Proteinuria and the risk of developing end-stage renal disease. *Kidney Int* 63:1468–1474, 2003
9. Iseki K: The Okinawa Screening Program. *J Am Soc Nephrol* 14:S127–S130, 2003
10. Ramirez SP, McClellan W, Port FK, Hsu SIH: Risk factors for proteinuria in a large, multiracial, southeast Asian population. *J Am Soc Nephrol* 13:1907–1917, 2002
11. Tozawa M, Iseki K, Iseki C, *et al*: Influence of smoking and obesity on the development of proteinuria. *Kidney Int* 62:956–962, 2002
12. Brenner BM, Chertow GM: Congenital oligonephropathy and the etiology of adult hypertension and progressive renal injury. *Am J Kidney Dis* 23:171–175, 1994
13. Iseki K, Ikemiya Y, Fukiyama K: Predictors of end-stage renal disease and body mass index in a screened cohort. *Kidney Int* 52(Suppl 63):S169–S170, 1997
14. Iseki K, Tozawa M, Iseki C, *et al*: Demographic trends in the Okinawa Dialysis Study (OKIDS) registry (1971–2000). *Kidney Int* 61:668–675, 2002
15. Spangler JG, Konen JC: Hypertension, hyperlipidemia, and abdominal obesity and the development of microalbuminuria in patients with non–insulin-dependent diabetes mellitus. *J Am Board Fam Pract* 9:1–6, 1996
16. Reid M, Bennett F, Wilks R, Forrester T: Microalbuminuria, renal function and waist: Hip ratio in black hypertensive Jamaicans. *J Hum Hypertens* 12:221–227, 1998
17. Metcalf P, Baker J, Scott A, *et al*: Albuminuria in people at least 40 years old: Effect of obesity, hypertension, and hyperlipidemia. *Clin Chem* 38:1802–1808, 1992
18. Praga M, Hernandez E, Andres A, *et al*: Effects of body-weight loss and captopril treatment on proteinuria associated with obesity. *Nephron* 70:35–41, 1995
19. Tozawa M, Iseki K, Iseki C, *et al*: Blood pressure predicts risk of developing end-stage renal disease in men and women. *Hypertension* 41:1341–1345, 2003

20. Kuczmarski RJ, Flegal KM, Campbell SM, Johnson CL: Increasing prevalence of overweight among US adults. *JAMA* 272:205–211, 1994
21. Iseki K, Oshiro S, Tozawa M, *et al*: Prevalence and correlates of diabetes mellitus in a screened cohort in Okinawa, Japan. *Hypertens Res* 25:185–190, 2002
22. Keller G, Zimner G, Mall G, *et al*: Nephron number in patients with primary hypertension. *N Engl J Med* 348:101–108, 2003
23. Luft FC: Food intake and the kidney: The right amounts at the right times. *Am J Kidney Dis* 37:629–631, 2000
24. Usami T, Koyama K, Takeuchi O, *et al*: Regional variation in the incidence of end-stage renal failure in Japan. *JAMA* 284:2622–2624, 2000
25. Merlet-Benichou C, Gilbert T, Vilar J, *et al*: Nephron number: Variability is the rule. Causes and consequences. *Lab Invest* 79:515–527, 1999
26. Hopper J, Jr, Trew PA, Biava CG: Membranous nephropathy: Its relative benignity in women. *Nephron* 29:18–24, 1981
27. Donadio JV, Jr, Torres VE, Velosa JA, *et al*: Idiopathic membranous nephropathy: The natural history of untreated patients. *Kidney Int* 33:708–715, 1988
28. Gretz N, Zeier M, Gerberth S, *et al*: Is gender a determinant for evolution of renal disease? A study in autosomal dominant polycystic kidney disease. *Am J Kidney Dis* 14:178–183, 1989
29. Sakemi T, Toyoshima H, Morito F: Testosterone eliminates the attenuating effect of castration on the progressive glomerular injury in hypercholesterolemic male Imai rats. *Nephron* 67:469–476, 1994
30. Horner D, Fliser D, Klimm HP, Ritz E: Albuminuria in normotensive and hypertensive individuals attending offices of general practitioners. *J Hypertens* 14:655–660, 1996
31. Stegmayr B, Lithner F: Tobacco and end stage diabetic nephropathy. *BMJ* 295:581–582, 1987
32. Olivarius NDF, Andersen AH, Keiding N, Mogensen CE: Epidemiology of renal involvement in newly-diagnosed middle-aged and elderly diabetic patients. Cross-sectional data from the population-based study "Diabetes Care in General Practice," Denmark. *Diabetologia* 36:1007–1016, 1993
33. Orth SR, Stockmann A, Conradt C, *et al*: Smoking as a risk factor for end-stage renal disease in men with primary renal disease. *Kidney Int* 54:926–931, 1998
34. Kopple JD, Greene T, Chumlea C, *et al*: Relationship between nutritional status and the glomerular filtration rate: Results from the MDRD study. *Kidney Int* 57:1688–1703, 2000
35. National Kidney Foundation: K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification and stratification. *Am J Kidney Dis* 39(Suppl 1):S1–S266, 2002
36. Iseki K, Ikemiya Y, Fukiyama K. Risk factors of end-stage renal disease and serum creatinine in a community-based mass screening. *Kidney Int* 51:850–854, 1997