Obesity and Risk for Chronic Renal Failure

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Few large-scale epidemiologic studies have quantified the possible link between obesity and chronic renal failure (CRF). This study analyzed anthropometric data from a nationwide, population-based, case-control study of incident, moderately severe CRF. Eligible as cases were all native Swedes who were aged 18 to 74 yr and had CRF and whose serum creatinine for the first time and permanently exceeded 3.4 mg/dl (men) or 2.8 mg/dl (women) during the study period. A total of 926 case patients and 998 control subjects, randomly drawn from the study base, were enrolled. Face-to-face interviews, supplemented with self-administered questionnaires, provided information about anthropometric measures and other lifestyle factors. Logistic regression models with adjustments for several co-factors estimated the relative risk for CRF in relation to body mass index (BMI). Overweight (BMI ≥ 25 kg/m²) at age 20 was associated with a significant three-fold excess risk for CRF, relative to BMI <25. Obesity (BMI ≥30) among men and morbid obesity (BMI ≥ 35) among women anytime during lifetime was linked to three- to four-fold increases in risk. The strongest association was with diabetic nephropathy, but two- to three-fold risk elevations were observed for all major subtypes of CRF. Analyses that were confined to strata without hypertension or diabetes revealed a three-fold increased risk among patients who were overweight at age 20, whereas the two-fold observed risk elevation among those who had a highest lifetime BMI of >35 was statistically nonsignificant. Obesity seems to be an important—and potentially preventable—risk factor for CRF. Although hypertension and type 2 diabetes are important mediators, additional pathways also may exist.

The number of patients with chronic renal failure (CRF) and ESRD is increasing steadily worldwide (1,2). Although the growing population with ESRD may be explained partly by more complete registration and better survival, a true rise in CRF incidence seems to be indisputable (3). This development parallels a rise in obesity prevalence of almost epidemic proportions.

Obesity has been implicated as a possible risk factor for microalbuminuria in individuals with hypertension and diabetes (4–6), and body mass index (BMI) was positively associated with progression of IgA glomerulonephritis in a cohort study (7). Studies from the general population suggest that obesity also may be harmful to the kidneys in individuals without hypertension, diabetes, or preexisting renal disease (8,9). In the Framingham Offspring cohort (10), body mass was positively related to the odds of having a GFR in the fifth or lower percentile after long-term follow-up. Similarly, follow-up among participants in health screening programs in the United States (11) and Japan (12) demonstrated a significant positive relationship between BMI and risk for ESRD, although this association seemingly was confined to men in the Japanese study.

The aim of this study was to investigate the possible effects of body mass on the incidence of moderately severe CRF overall and by subtype. We obtained detailed anthropometric information in a nationwide, population-based, case-control study of incident preuremic CRF (13).

Materials and Methods

Study Participants

The study design has been described elsewhere (13). Briefly, the Swedish National Population Register provided a well-defined source population of 5.3 million native Swedes who were aged 18 to 74 yr and lived in Sweden during the ascertainment period, May 20, 1996, through May 31, 1998.

Eligible as cases were all men and women whose serum creatinine level, for the first time and permanently, exceeded 3.4 mg/dl (300 μmol/L) and 2.8 mg/dl (250 μmol/L), respectively. For ensuring complete case ascertainment, all medical laboratories that covered inpatient and outpatient care in Sweden provided monthly lists of patients who had undergone serum creatinine testing any time during the entire study period. A second creatinine measurement, 3 mo after the first, was done to verify the chronicity. Local physicians who treat patients with renal diseases determined patients' eligibility for the study by reviewing the medical records of patients with elevated serum creatinine levels. The diagnosis of underlying disease was based on the results of routine clinical evaluation. Patients with prerenal (*e.g.*, severe heart failure) or postrenal (*e.g.*, outlet obstruction) causes or with kid-

ney transplants were ineligible. Of eligible cases, 16% refused or were too severely disabled to participate, and 6% had died, leaving 926 (78%) participants.

Control subjects, who were frequency-matched to cases according to age (±10 yr) and gender, were randomly selected from the 5.3 million Swedes in the study base, using the nationwide National Population Register. The control selection was carried out on three occasions during the ascertainment period. Of 1330 selected control subjects, 998 (75%) participated, 17% refused, 4% could not be reached, and 4% were too sick to participate. All study participants provided informed consent, and the regional ethics committees and Swedish Data Inspection Board approved the study protocol.

Data Collection

Study participants completed a mailed questionnaire about anthropometric measures (height; current weight; weight at ages 20, 40, and 60; and highest weight during lifetime), education, alcohol consumption, and tobacco use. During a subsequent face-to-face interview, professional interviewers from Statistics Sweden double-checked the questionnaires and obtained information on medical history, occupation, and analgesic use. Although blinding of the interviewers to case/control status of the participants was impossible, the interviewers were instructed to interact similarly with case patients and control subjects in a standardized manner.

Data Analyses

Relative risk for CRF among groups with different anthropometric measures was estimated by odds ratios (OR) and 95% confidence intervals (CI) that were derived from unconditional logistic regression models. We analyzed data stratified by gender throughout, except in analyses of disease-specific CRF, as a result of small sample sizes. Continuous variables (BMI [body weight divided by height raised to the second power, kg/m^2], cumulative number of cigarette pack-years, grams of alcohol per week) were categorized into quartiles according to the distribution among control subjects. In addition, BMI was categorized according to World Health Organization's (WHO's) definitions of overweight and obesity (14). Because few participants had a BMI >30 kg/m^2 at age 20, BMI at that age was dichotomized into <25 and ≥25 kg/m^2. Level of education was categorized into ≤9 yr, 10 to 12 yr, and ≥13 yr. An indicator of regular use of aspirin and paracetamol was found to control sufficiently for confounding of nonnarcotic analgesic use. Adjustment for socioeconomic status instead of number of school years did not change the risk estimates. Always included as covariates in our models were age, cumulative cigarette pack-years, grams of alcohol consumed per week, ever/never regular use of paracetamol or aspirin, and number of years of formal education. We tested for interactions but did not include any interaction terms in the final models because they were statistically insignificant. Model fit was verified with the Hosmer and Lemeshow test (15).

Results

The participating case patients are characterized with regard to renal function and underlying disease in Table 1. A majority of the patients were in the preuremic stage: 80% had a creatinine level <4.5 mg/dl (400 μmol/L); only 6% had a predicted creatinine clearance (16) <10 ml/min. Approximately one third of the patients had a diagnosis of diabetic nephropathy. The second largest group was patients with glomerulonephritis (28% of men and 16% of women), followed by renal vascular

Table 1. Participating case patients with CRF: Measures of renal function and underlying diagnosis[a]

	Men (n = 597)	Women (n = 329)
Serum creatinine at inclusion (mg/dl; median [range])[b]	3.8 (3.4 to 28)	3.2 (2.8 to 19)
Creatinine clearance (ml/min; median [range])[c]	22 (2 to 53)	19 (3 to 35)
Diagnosis group		
diabetic nephropathy (n [%])	180 (30)	106 (32)
type 1 diabetes	75	46
type 2 diabetes	97	54
unknown	8	6
glomerulonephritis (n [%])	168 (28)	54 (16)
IgA nephropathy	55	8
no renal biopsy	40	14
unclassified on biopsy	27	15
proliferative	18	8
focal segmental sclerosis	13	3
crescentic glomerulonephritis	8	4
other	7	2
renal vascular disease (n [%])	100 (17)	39 (12)
other diagnosis (n [%])	149 (25)	130 (40)
hereditary disease	58	40
systemic disease or vasculitis	40	42
other diagnosis	23	32
unknown renal disease	28	16

[a]CRF, chronic renal failure.
[b]Conversion factor for SI unit (μmol/L) is 88.4.
[c]Predicted creatinine clearance (Cockroft-Gault formula).

disease (17 and 12% of men and women, respectively). Mean age was 58 yr for men and 57 yr for women among both case patients and control subjects (Table 2). Compared with control subjects, case patients were on average less well educated, used more analgesics, and smoked more. The proportion of alcohol users was lower among case patients, but the mean consumption was somewhat higher. As expected, the prevalence of self-reported hypertension was high among case patients: 87% of men and 85% of women, compared with approximately 25% of male and female control subjects. Diabetes, present in slightly more than one third of the case patients, was reported by 7% of the control subjects (both genders). Current BMI was similar among case patients and control subjects, whereas mean of lifetime highest BMI was significantly higher among case patients, regardless of gender ($P < 0.001$).

OR for overall CRF in relation to BMI are presented sepa-rately for men and women (Table 3), although no statistically significant effect modification by gender could be confirmed, neither when using quartiles as cut points for BMI categories nor when using the WHO's cut points for overweight and obesity ($P = 0.35$ and $P = 0.25$, respectively). We found a positive association of highest lifetime BMI with overall CRF risk, particularly among men (Table 3). Men in the highest quartile had a 2.3-fold increased risk (95% CI 1.6 to 3.3) com-pared with those in the lowest quartile. The corresponding OR was modest and statistically nonsignificant among women, but when using WHO's cut points (14), clear excesses of three-fold or greater were seen for BMI ≥ 35 kg/m^2 in both genders. Men and women who reported a BMI ≥ 25 kg/m^2 at age 20 had a significant three-fold elevated risk for CRF compared with patients with BMI <25 kg/m^2. BMI at age 40 and at age 60 showed similar relationships with CRF risk as did highest

Table 2. Selected characteristics of case patients and control subjects[a]

	Men		Women	
	Case Patients ($n = 597$)	Control Subjects ($n = 653$)	Case Patients ($n = 329$)	Control Subjects ($n = 345$)
Age at interview (yr; n [%])				
18 to 24	5 (1)	14 (2)	5 (2)	6 (2)
25 to 34	34 (6)	32 (5)	29 (9)	26 (8)
35 to 44	59 (10)	62 (9)	36 (11)	35 (10)
45 to 54	131 (22)	116 (18)	62 (19)	70 (20)
55 to 64	124 (21)	134 (21)	62 (19)	70 (20)
65 to 74	244 (41)	295 (45)	135 (41)	138 (40)
Education (yr; n [%])				
≤9	350 (59)	355 (54)	187 (57)	170 (49)
10 to 12	129 (22)	150 (23)	80 (24)	96 (28)
>12	109 (18)	142 (22)	59 (18)	78 (23)
missing	9 (2)	6 (1)	3 (1)	1 (0)
Smoking (pack-years; n [%])				
never regular smokers[b]	216 (36)	252 (39)	156 (47)	188 (54)
≤6.6	61 (10)	94 (14)	18 (5)	44 (13)
6.7 to 15.9	86 (14)	85 (13)	55 (17)	47 (14)
16.0 to 27.3	96 (16)	101 (15)	60 (18)	41 (12)
>27.3	130 (22)	117 (18)	37 (11)	24 (7)
missing	8 (1)	4 (1)	3 (1)	1 (0)
Diabetes (n [%])				
yes	206 (35)	45 (7)	123 (37)	23 (7)
no	391 (65)	608 (93)	206 (63)	322 (93)
missing	0 (0)	0 (0)	0 (0)	0 (0)
Hypertension (n [%])				
yes	518 (87)	160 (25)	279 (85)	88 (26)
no	77 (13)	488 (75)	49 (15)	257 (74)
missing	2 (0)	5 (1)	1 (0)	0 (0)
Height (cm; mean [SD])	176.9 (7.3)	177.7 (7.0)	163.8 (6.4)	164.4 (5.7)
Current BMI (kg/m^2; mean [SD])	25.6 (4.2)	25.8 (3.5)	25.0 (5.0)	25.3 (4.1)
Highest BMI[c] (kg/m^2; mean [SD])	28.5 (4.9)	26.8 (3.9)	28.3 (5.9)	26.7 (4.6)

[a]BMI, body mass index.
[b]Less than 6 mo of daily smoking in lifetime.
[c]Highest BMI in lifetime.

Table 3. OR for CRF associated with BMI[a]

	Men		Women	
	No. of Case Patients/Control Subjects	OR[b] (95% CI)	No. of Case Patients/Control Subjects	OR[b] (95% CI)
Highest BMI (kg/m2)[c]				
gender-specific quartiles[d]				
Q1 (lowest quartile)	101/158	1.0 (referent)	64/81	1.0 (referent)
Q2	113/160	1.1 (0.8 to 1.6)	56/85	0.8 (0.5 to 1.3)
Q3	136/158	1.4 (1.0 to 2.0)	81/82	1.2 (0.7 to 1.9)
Q4 (highest quartile)	230/157	2.3 (1.6 to 3.3)	107/84	1.3 (0.8 to 2.1)
cut points in accordance with WHO's definition of overweight and obesity				
<25.00	129/213	1.0 (referent)	96/136	1.0 (referent)
25.00 to 29.9	265/323	1.4 (1.0 to 1.9)	115/133	1.2 (0.8 to 1.8)
30.0 to 34.9	130/79	2.7 (1.9 to 4.0)	49/46	1.4 (0.8 to 2.4)
≥35.00	56/18	4.4 (2.4 to 8.2)	48/17	3.1 (1.6 to 6.1)
BMI at age 20 (kg/m^2)[e]				
gender-specific quartiles[f]				
Q1 (lowest quartile)	94/136	1.0 (referent)	55/68	1.0 (referent)
Q2	75/130	0.9 (0.6 to 1.4)	52/75	0.9 (0.5 to 1.5)
Q3	125/142	1.3 (0.9 to 1.9)	48/72	0.8 (0.5 to 1.5)
Q4 (highest quartile)	175/138	1.9 (1.3 to 2.8)	86/72	1.4 (0.8 to 2.3)
cut points in accordance with the WHO definition of overweight				
<25.0	377/506	1.0 (referent)	211/274	1.0 (referent)
≥25.0	92/40	3.1 (2.1 to 4.8)	30/13	3.0 (1.4 to 6.1)

[a]CI, confidence interval; OR, odds ratio; Q, quartile; WHO, World Health Organization.
[b]Adjusted for age, education, smoking, alcohol, and use of paracetamol and salicylates.
[c]Highest BMI during lifetime. Because of missing information on ≥1 covariate, 46 case patients and 53 control subjects were excluded from analyses.
[d]Q1: Men <24.4, women <23.6; Q2: men 24.4 to 26.4, women 23.6 to 25.8; Q3: men 26.5 to 28.8, women 25.9 to 28.9; Q4: men >28.8, women >28.9.
[e]Because of missing information on ≥1 covariate, 222 case patients and 183 control subjects were excluded from analyses
[f]Q1: men <20.5, women <19.0; Q2: men 20.6 to 21.7, women 19.1 to 20.5; Q3: men 21.8 to 23.4, women 20.6 to 21.9; Q4: men >23.4, women >21.9.

lifetime BMI, but the relative risk estimates were less precise as a result of the smaller number of patients who had attained these ages (data not shown). However, BMI at time of interview was not significantly associated with CRF risk: Men and women with BMI of 35 kg/m^2 or more had adjusted OR of 1.9 (95% CI 0.8 to 4.6) and 1.2 (95% CI 0.5 to 3.3), respectively, relative to patients with BMI <25.

In analyses stratified by the presence or absence of self-reported diabetes, the elevated CRF risk with increasing maximum BMI was more pronounced among individuals with than without diabetes. However, even for men and women without diabetes, a lifetime highest BMI of 35 kg/m^2 or more entailed a significant OR of 2.2, relative to those with BMI <25 kg/m^2 (Table 4). Likewise, obesity was associated with CRF also among patients who self-reported that they had no history of clinically known hypertension. The OR for CRF among these presumably nonhypertensive patients with highest BMI ≥35 kg/m^2 was 2.8 (95% CI 1.0 to 8.1), relative to patients with BMI

<25 kg/m^2. Analyses that were confined to individuals who reported neither diabetes nor hypertension produced point estimates of similar magnitude, albeit without statistical significance (Table 4). In contrast, a statistically significant three-fold risk increase was observed among those who did not have diabetes and hypertension and who reported overweight at age 20 (Table 4).

Lifetime highest BMI was dose-dependently associated with risk for all major CRF subtypes (Table 5). The highest risk was found for diabetic nephropathy: Having a BMI of 35 kg/m^2 or more entailed a more than seven-fold increase in risk relative to having a BMI <25 kg/m^2. The association was restricted essentially to nephropathy caused by type 2 diabetes, for which the OR was 6.4 (95% CI 3.5 to 11.7) among patients with a BMI of 30 to 34.9 kg/m^2 and 17.7 (95% CI 8.8 to 35.4) among those with a BMI of 35 kg/m^2 or more compared with nonoverweight individuals. A BMI of 30 kg/m^2 or more was associated with a significant 2.4-fold excess in risk also for nephrosclerosis and a

Table 4. OR for CRF associated with BMI[a]

	No Diabetes		No Hypertension		No Diabetes or Hypertension	
	No. of Case Patients/Control Subjects	OR[b] (95% CI)	No. of Case Patients/Control Subjects	OR[b] (95% CI)	No. of Case Patients/Control Subjects	OR[b] (95% CI)
Highest BMI in lifetime (kg/m^2)[c]						
<25	159/336	1.0 (referent)	37/293	1.0 (referent)	31/281	1.0 (referent)
25 to 29.9	274/434	1.3 (1.0 to 1.7)	58/347	1.3 (0.8 to 2.0)	44/335	1.1 (0.6 to 1.8)
30 to 34.9	104/105	2.0 (1.4 to 2.8)	19/72	1.8 (1.0 to 3.5)	10/65	1.2 (0.5 to 2.6)
≥35.0	37/28	2.2 (1.3 to 3.8)	7/13	2.8 (1.0 to 8.1)	4/11	2.1 (0.6 to 7.6)
BMI at age 20 (kg/m^2)[d]						
<25.0	413/728	1.0 (referent)	81/588	1.0 (referent)	62/559	1.0 (referent)
≥25.0	64/51	2.4 (1.6 to 3.6)	17/33	3.6 (1.8 to 7.1)	12/33	3.0 (1.4 to 6.4)

[a]Analyses are restricted to participants without self-reported diabetes and/or hypertension.
[b]Adjusted for age, gender, education, smoking, alcohol, and use of paracetamol and salicylates.
[c]Cut points in accordance with the WHO definition of overweight and obesity.
[d]Cut points in accordance with the WHO definition of overweight.

Table 5. OR among men and women for various subtypes of CRF associated with BMI

	No. of Control Subjects	Diabetic Nephropathy		Nephrosclerosis		Glomerulonephritis		Other	
		No. of Case Patients	OR[a] (95% CI)	No. of Case Patients	OR[a] (95% CI)	No. of Case Patients	OR[a] (95% CI)	No. of Case Patients	OR[a] (95% CI)
Highest BMI in lifetime (kg/m^2)[b]									
<25	349	59	1.0 (referent)	30	1.0 (referent)	58	1.0 (referent)	78	1.0 (referent)
25 to 29.9	456	90	1.2 (0.8 to 1.7)	61	1.4 (0.8 to 2.2)	99	1.3 (0.9 to 1.9)	130	1.3 (1.0 to 1.9)
30 to 34.9	125	65	2.8 (1.8 to 4.4)	32	2.4 (1.4 to 4.3)	43	2.0 (1.2 to 3.2)	39	1.5 (0.9 to 2.4)
≥35.0	35	56	7.4 (4.2 to 13.0)	12	2.8 (1.2 to 6.2)	14	2.0 (1.0 to 4.2)	22	2.0 (1.1 to 3.9)
BMI at age 20 (kg/m^2)[c]									
<25.00	780	149	1.0 (referent)	95	1.0 (referent)	154	1.0 (referent)	190	1.0 (referent)
≥25.00	53	49	5.2 (3.2 to 8.4)	18	3.0 (1.6 to 5.5)	30	3.0 (1.8 to 4.9)	25	2.1 (1.2 to 3.6)

[a]Adjusted for age, gender, education, smoking, alcohol, and use of paracetamol and salicylates.
[b]Cut points in accordance with the WHO definition of overweight and obesity.
[c]Cut points in accordance with the WHO definition of overweight.

two-fold increase in risk for glomerulonephritis and "other renal disease." Likewise, elevated BMI at age 20 yielded increases in risk for all major types of CRF (Table 5).

Discussion

In this population-based, case-control study of preuremic CRF, being overweight at age 20 or obese (for women being morbidly obese) at any later time was linked with an increased risk for CRF. In contrast, BMI at time of interview was not significantly related to CRF. The latter finding may be explained by weight loss among case patients as a consequence of morbidity related to the renal failure itself.

There is an accumulating body of clinical and experimental data implicating obesity as an important causative factor in renal disease (17,18), but epidemiologic data linking obesity to CRF have been scarce so far. Some studies have investigated the association between obesity and proteinuria in the general population (8,9); however, few epidemiologic studies have quantified the possible link between obesity and established renal failure in population-based settings. Our study is one of the first large-scale, population-based investigations to identify obesity as an important risk factor in the development of renal failure. Relative risk estimates that were consistent with ours were reported in a cohort study with a smaller number of incident CRF cases (19). In a Japanese cohort that was assembled during a mass screening project in 1983, high BMI was associated with an increased risk for ESRD 17 yr later but only among men (12). There, the excess risk was comparable or slightly higher than in our study. A similar US cohort study among individuals who participated in a health testing program reported an even stronger and monotonic trend of increasing ESRD risk with increasing BMI among both men and women (11). Another US cohort study among men and women who were free of kidney disease at baseline noted a 23% in-

crease per unit BMI in the odds of falling below the fifth percentile of GFR after 18.5 yr of follow-up (10).

It is widely known that obesity markedly increases risk for diabetes and hypertension (20) and that both diabetes and hypertension are important contributors to ESRD (21,22). Not surprising, in analyses that estimated risks for specific renal diseases, we found the strongest positive association of high BMI with risk for diabetic nephropathy (related to type 2 diabetes) and the second strongest relationship with nephrosclerosis (almost all patients were reported to have hypertension as the underlying cause of this diagnosis). Nevertheless, two- to three-fold risk elevations also were observed for glomerulonephritis and "other renal diseases," although we cannot exclude some degree of misclassification because the renal diagnoses were based on biopsies in only 30%. As hypertension accompanies virtually all types of renal disease not only as a cause but also frequently as a consequence of the renal failure and because both hypertension and mild to moderate renal failure can pass unnoticed for several years, it is a limitation of our study that we were unable to establish whether any hypertension preceded the onset of the kidney disease. Specifically, we cannot exclude that some patients with glomerulonephritis and "other renal diseases" also had previous hypertension, potentially related to obesity. We chose not to adjust for hypertension in our modeling because hypertension frequently is a secondary effect of CRF, but in an attempt to elucidate further the effect of BMI on CRF risk, independent of hypertension and diabetes, we conducted analyses that were stratified on these conditions. We observed stronger associations among individuals with hypertension and/or diabetes, but excesses in risks also were seen among overweight individuals with a negative self-reported history of these conditions, at least among individuals who reported overweight at age 20. However, these analyses were based on small numbers, and the results must be interpreted cautiously. In addition, some of the patients may have had undiagnosed hypertension or diabetes.

We did not take preexisting proteinuria into consideration in this study, because confounding by proteinuria seems unlikely. It seems well established that leakage of proteins through the glomeruli, regardless of the cause, is harmful to the kidney (23,24). As obesity is the cause of glomerular leakage of proteins, proteinuria must be a link in one of the causal chains between obesity and CRF. Hence, proteinuria could be a true confounding factor only if it would be associated with obesity without being a consequence of it. It is conceivable that massive proteinuria of other causes than obesity could be associated with fluid retention, but it is inconceivable that such retention could result in BMI values of 30 or more. If proteinuria of other causes than obesity would result in reduced physical activity without a corresponding reduction in energy intake, then some weight gain also would be expected, but BMI values in excess of 30 seem implausible. Therefore, in our opinion, proteinuria is in the causal pathway between obesity and CRF and does not act as a confounder.

Focal segmental glomerulosclerosis (FSGS) and/or glomerulomegaly is seen commonly in renal biopsies from morbidly obese patients (25–27), and the development of these conditions seems to be independent of hypertension and diabetes. The proportion of all renal biopsies that exhibited obesity-related FSGS or glomerulomegaly increased 10-fold from 1986 to 2000 in a New York clinicopathologic study (27). Although a low rate of renal biopsy may have entailed underascertainment, only 16 of our case patients had received a diagnosis of FSGS, and only one had a lifetime highest BMI that exceeded 35 kg/m^2.

Our finding that obesity was independently associated with increased risks for all major types of CRF agrees with the "multi-hit" hypothesis (28); that is, obesity entails an extra burden on the nephrons, which promotes the progression of renal failure. Obesity previously has been linked to the progression of existing renal disease, independent of other risk factors, but it also is an independent risk factor for proteinuria in the general population (8,9). In the latter case, obesity would act as an initiator of the process, although a preceding state of reduced number of nephrons as a result of congenital or unknown environmental and lifestyle factors cannot be excluded. Obese individuals, compared with lean, are at higher risk for developing proteinuria and CRF after unilateral nephrectomy (29). This supports the view that the coexistence of obesity and reduced number of functioning nephrons increases risk for CRF.

The BMI–CRF risk relationship seemed to be somewhat stronger—and evident in a lower BMI range—in men than in women. However, no BMI*gender interactions attained statistical significance. Therefore, the observed difference is likely to be a chance finding. However, the previous literature has provided some weak indications that a true gender difference might exist (11,12). The definition of ESRD in these studies was based mainly on the occurrence of renal replacement therapy (or death as a result of ESRD), so gender differences with regard to medical management could have introduced bias. In our study, the outcome classification was based on serum creatinine measurements in combination with evaluations by local specialists. Although different cut points were used for men and women, the inherent association among body weight, muscle mass, and serum creatinine warrants cautious interpretation of gender differences. In general, however, it seems that men have a more rapid progression rate of renal failure than women (30), possibly mediated by sex hormones, but one could speculate that differences in risk that is conferred by being overweight also may be important to this gender difference in progression rate.

The mechanisms that lead to renal damage in obesity are not completely understood. Suggested contributing factors include hyperlipidemia, hyperleptinemia, a state of low-grade inflammation, hyperfiltration caused by insulin resistance, increased sympathetic activity, and activated renin-angiotensin system (17,31).

The major strengths of our study include its population-based design deriving from a well-defined and continuously enumerated source population, the complete ascertainment of all incident CRF cases, and the relatively large sample size. Moreover, the vast majority of case patients had moderately severe renal failure, thus allaying some concern about recall

bias, reverse causation, and/or selective loss of cases with rapid disease progression. Important selection bias is unlikely owing to the fairly high and equal participation rates among case patients and control subjects. However, obese individuals, who experience considerable morbidity of various kinds, may undergo serum creatinine testing more often than the average person, raising some concern about possible detection bias. The creatinine levels that were chosen for our case definition are typically symptomatic. Therefore, the pool of asymptomatic prevalent cases that potentially could be recruited through more zealous creatinine testing is likely to be small.

Misclassification of the self-reported anthropometric measures could have influenced our results. Although self-reported information on height, current weight, weight at age 20, and birth weight is known to be relatively accurate overall (32–34), there is a systematic tendency for overweight individuals to underestimate their body size; conversely, very lean individuals tend to overestimate (35). Such misclassification of exposure, if nondifferential between case patients and control subjects, would bias estimates of associations toward null. The absence of any widespread preconceptions among the public about links between anthropometric measures and CRF lessens concern about reporting bias.

Conclusion

Taking experimental, clinical, and epidemiologic data together, obesity seems to be causally linked, directly or indirectly, to the development of CRF. Our results support that obesity contributes to the rapidly increasing burden of CRF in both men and women. The excess risk for CRF among obese people seems to be driven mainly by a high prevalence of hypertension and/or type 2 diabetes, but additional pathways cannot be ruled out. According to our data, the etiologic fraction (36) of all CRF that is attributable to obesity in the comparably lean Swedish population is 16% among men and 11% among women. This fraction is likely to be greater in the United States, where the general prevalence of obesity is higher. Hence, obesity probably should be put high on the list of potentially preventable causes of CRF. Moreover, promising results of weight reduction in patients with early-stage renal disease raise hopes for future secondary prevention (37).

Acknowledgments

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