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Paradoxical Association Between Body Mass Index and Mortality in Men With CKD Not Yet on Dialysis

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Background: Low body mass index (BMI) is associated with greater mortality in patients on dialysis therapy. This relationship is less well characterized in patients with chronic kidney disease (CKD) who are not yet on dialysis therapy.

Study Design: Historic prospective cohort.

Setting & Participants: 521 male US veterans with CKD (age, 68.8 ± 10.4 years; 21.3% black; estimated glomerular filtration rate, 37.5 ± 16.8 mL/min/1.73 m^2 [0.62 ± 0.28 mL/s/1.73 m^2]) at a single medical center.

Predictor: BMI.

Outcomes & Measurements: Associations with all-cause mortality were explored in fixed-covariate and time-dependent Cox models and sequentially adjusted for demographic characteristics (age and race), case-mix (comorbidity index, smoking, blood pressure, estimated glomerular filtration rate, and medication use), and surrogates of malnutrition and inflammation (serum albumin, cholesterol, and bicarbonate levels; white blood cell count; percentage of lymphocytes; and hemoglobin level).

Results: Patients were followed up for up to 5.5 years, and the mortality rate was 128.3 deaths/1,000 patient-years (95% confidence interval [CI], 110.5 to 149.0). Higher BMI was associated with lower mortality in the fixed-covariate Cox models, including the fully adjusted model (adjusted hazard ratios for mortality in the group with BMI in 10th to 50th, 50th to 90th, and >90th versus <10th percentiles, 0.75 [95% CI, 0.46 to 1.22], 0.56 [95% CI, 0.33 to 0.94], and 0.39 [95% CI, 0.17 to 0.87]; $P_{trend} = 0.005$). Associations were similar in a time-dependent Cox model ($P_{trend} = 0.008$ in the fully adjusted model).

Limitations: Results may not be generalizable.

Conclusions: Lower BMI is associated with greater mortality in patients with CKD not yet on dialysis therapy. Adjustment for case-mix and surrogate markers of malnutrition and inflammation attenuated, but did not reverse, this relationship.

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INDEX WORDS: Chronic kidney disease; body mass index; mortality.

Obesity has reached epidemic proportions in the developed world[1] and is implicated as a risk factor in the development of diabetes mellitus, atherosclerotic cardiovascular disease, cancer, and chronic kidney disease (CKD).[2-5] In a seemingly paradoxical manner, obesity appears associated with better survival in patients with such chronic disease states as congestive heart failure,[6] chronic obstructive pulmonary disease,[7] and rheumatoid arthritis.[8] A most prominent example for such a paradoxical association is patients with stage 5 CKD requiring maintenance hemodialysis treatment for whom higher body mass index (BMI) was associated repeatedly with better survival, even after extensive adjustment for confounding variables.[9-20] Maintenance hemodialysis patients represent a small fraction of all individuals with CKD,[21] yet much less is known about the association of BMI with outcomes in the latter group. We examined the

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association between BMI and all-cause mortality in 521 male US veterans treated at a single Veterans Affairs (VA) medical center for CKD stages 1 to 5, but not yet requiring renal replacement therapy (RRT).

METHODS

Study Population

We examined all 534 patients referred for management of CKD (excluding those on dialysis therapy and those with a kidney transplant) at Salem VA Medical Center between January 1, 2001, and June 30, 2005. Two patients (0.4%) had no BMI recorded. Of the remaining 532 patients, only 8 (1.5%) were women and only 3 (0.5%) were of a race other than white or black, and they were excluded from further analyses. Final analyses included 521 patients.

Data Collection

Baseline demographic and anthropometric information; comorbid conditions with calculation of the Charlson Comorbidity Index[22]; blood pressure measurements; use of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins), angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and aspirin; and laboratory values measured at the time of initial nephrology consultation were collected retrospectively. BMI was calculated as weight in kilograms divided by the square of height in meters.[23] Diabetes mellitus was defined as the presence of an abnormal glucose level or antidiabetic therapy, and atherosclerotic cardiovascular disease was defined as a history of cardiovascular, cerebrovascular, or peripheral vascular disease. Variables expected to change during follow-up (blood pressure, BMI, medication use, and all laboratory parameters) were collected longitudinally and averaged over periods of 6 months.

Outcomes

Patients were followed up until death or loss to follow-up or September 20, 2006, with recording of death and RRT. A patient was considered lost to follow-up if no contact with the medical center was documented for more than 6 months. Fourteen patients (2.6%) were lost to follow-up. The outcome measure of interest was all-cause mortality. Deaths were recorded from the VA computerized patient record system and cross-checked for accuracy against death-certificate–based data obtained from the National Death Index. RRT, defined as initiation of hemodialysis or peritoneal dialysis therapy, was identified from medical records at Salem VA Medical Center, including Medicare Form 2728.

Statistical Analyses

Continuous variables were expressed as mean ± SD or geometric mean (95% confidence interval [CI]), and categorical variables were expressed as proportions. Continuous variables with skewed distribution (cholesterol level, white blood cell [WBC] count, and 24 hour urine protein excretion) were natural log-transformed. BMI was analyzed as both a categorical variable and continuous measure. The National Institutes of Health classifies nutritional status by BMI as undernutrition (BMI < 18.5 kg/m^2), normal (BMI, 18.5 to 24.9 kg/m^2), overweight (BMI, 25 to 29.9 kg/m^2), and obese (BMI ≥ 30 kg/m^2).[24] Only 7 patients in our cohort (1.3%) had a BMI less than 18.5 kg/m^2; hence, BMI groups were defined as less than the 10th percentile (<22.2 kg/m^2), 10th to 50th percentile (22.2 to 28 kg/m^2), 50th to 90th percentile (28.1 to 36.7 kg/m^2), and greater than 90th percentile (>36.7 kg/m^2), as recently proposed by Kwan et al.[25] Kidney function was explored as both a continuous and categorical measure after glomerular filtration rate (GFR) was estimated by using the 4-variable equation developed for the Modification of Diet in Renal Disease Study,[26] and patients were classified according to the Kidney Dialysis Outcome Quality Initiative Clinical Practice Guidelines for CKD: Evaluation, classification, and stratification,[27] with dialysis added as a separate time-dependent variable in patients initiating RRT. Missing values were substituted by using the last-value-carried-forward method. Missing variables with no previously recorded values (3% for phosphorus level, 1% for albumin level, 2% for cholesterol level, 1.8% for WBC count, 1.8% for percentage of lymphocytes in WBC count, and 2.6% for proteinuria) were imputed by means of linear regression using all other characteristics as independent variables. Smoking status was missing in 1.8% of patients; these were analyzed by adding a dummy category incorporating the missing values.

Event rates were calculated using the person-years approach. Associations between BMI and all-cause mortality were examined in fixed-covariate and time-dependent Cox models, with blood pressure, BMI, medication use, dialysis, and all laboratory parameters included as time-dependent variables. Multivariable models were created after a priori adjustment for age and race (model 1), additional case-mix excluding surrogates of the malnutrition-inflammation-cachexia syndrome (MICS; comorbidity index, smoking, blood pressure, kidney function, proteinuria, and medication use; model 2), and after adjustment for all these plus markers associated with MICS (serum albumin, cholesterol, and bicarbonate levels, blood WBC count, hemoglobin level, and percentage of lymphocytes in WBC count; model 3). Nonlinear associations were explored by inclusion of quadratic terms. Effect modification was explored by performing subgroup analyses by race, smoking status, diabetes, and stages of CKD. Because lower BMI is associated with greater mortality in older individuals,[28] we performed separate analyses in subgroups dichotomized by median age to determine whether the inverse association between BMI and mortality also holds true in younger individuals. Similar analyses were performed in subgroups divided according to median follow-up to determine whether the inverse association between BMI and mortality also is present in patients with longer follow-up. The association between BMI and mortality also was examined in subgroups with and without the presence of markers of MICS, defined as patients with 1 or more of the following: serum albumin level less than 10th percentile, WBC count greater than 90th percentile, or percentage of lymphocytes in WBC count less than 10th percentile. All analyses were repeated with BMI categorized by quartiles (<25, 25 to 27.9, 28 to 33, and >33 kg/m^2). The proportionality assumption in the fixed-covariate Cox mod-

els was tested by using plots of log (−log [survival rate]) against log (survival time) and comparing predicted with actual survival curves. *P* less than 0.05 is considered significant. Statistical analyses were performed using Stata statistical software, version 8 (Stata Corp, College Station, TX). The study protocol was approved by the Research and Development Committee at the Salem VA Medical Center.

RESULTS

Mean age of the 521 patients was 68.8 ± 10.4 years, 111 (21.3%) were black, and 305 (58.5%) had diabetes mellitus. Mean estimated GFR was 37.5 ± 16.8 mL/min/1.73 m^2. Baseline characteristics for patient groups divided by categories of BMI are listed in Table 1. Patients with BMI less than the 10th percentile were older; less likely to have diabetes and use angiotensin-converting enzyme inhibitors/angiotensin receptor blockers or statins; more likely to be active smokers, and had lower estimated GFRs, blood hemoglobin levels, and percentages of lymphocytes in WBC counts. Characteristics of the 14 patients lost to follow-up were not significantly different (data not shown). One hundred seventy-two patients (33.0%) died during a median follow-up of 2.3 years (interquartile range, 1.6 to 3.6 years; total time at risk, 1,340 patient-years); the overall mortality rate was 128.3 deaths/1,000 patient-years (95% CI, 110.5 to 149.0). Distributions of event rates (deaths, dialysis, and loss to follow-up) by categories of BMI are listed in Table 2.

Figure 1 shows hazard ratios and 95% CIs for all-cause mortality by categories of BMI in fixed-covariate Cox models, with sequential adjustments for age and race (model 1); age, race,

Table 1. Baseline Characteristics of Individuals Stratified by BMI Categories

	BMI (kg/m^2)				
	<22.2; <10th Percentile (N = 53)	22.2-28.0; 10th-50th Percentile (N = 208)	28.1-36.7; 50th-90th Percentile (N = 209)	>36.7; >90th Percentile (N = 51)	*P*
Age (y)	67.5 ± 11.8	71.6 ± 9.7	67.9 ± 10.4	61.9 ± 8.1	<0.0001
Race (black)	13 (24.5)	39 (18.7)	51 (24.4)	8 (15.7)	0.3
BMI (kg/m^2)	20.7 ± 1.6	25.6 ± 1.5	31.8 ± 2.3	40.8 ± 3.9	
Diabetes mellitus	19 (35.8)	103 (49.5)	142 (67.9)	41 (80.4)	<0.001
Atherosclerotic cardiovascular disease	30 (56.6)	131 (63.0)	128 (61.2)	29 (56.9)	0.7
Comorbidity index	2.7 ± 1.8	2.6 ± 1.8	2.8 ± 1.8	2.3 ± 1.9	0.3
Smoking	24 (46.1)	48 (23.8)	42 (20.3)	8 (15.7)	0.001
Aspirin	18 (34.0)	93 (44.7)	102 (48.8)	23 (45.1)	0.28
ACE inhibitors/ARBs	37 (69.8)	150 (72.1)	174 (83.2)	46 (90.2)	0.003
Statin	17 (32.1)	124 (59.6)	135 (64.6)	38 (74.5)	<0.001
Systolic blood pressure (mm Hg)	140 ± 30	150 ± 29	148 ± 26	145 ± 25	0.15
Diastolic blood pressure (mm Hg)	70 ± 17	70 ± 15	73 ± 16	74 ± 16	0.12
GFR (mL/min/1.73 m^2)	33.6 ± 19.5	35.4 ± 14.8	39.4 ± 16.8	42.1 ± 19.2	0.005
CKD stage					
1	1 (1.9)	2 (0.9)	5 (2.4)	2 (3.9)	
2	3 (5.7)	8 (3.8)	15 (7.2)	4 (7.8)	
3	22 (41.5)	130 (62.5)	130 (62.2)	33 (64.7)	
4	22 (41.5)	54 (25.9)	54 (25.8)	12 (23.5)	
5	5 (9.4)	14 (6.7)	5 (2.4)	0 (0.0)	0.037
Albumin (g/dL)	3.4 ± 0.6	3.5 ± 0.5	3.6 ± 0.5	3.5 ± 0.4	0.15
Cholesterol (mg/dL)	167 (154-182)	176 (171-183)	178 (172-185)	179 (169-190)	0.48
Bicarbonate (mmol/L)	25.1 ± 4.3	25.7 ± 3.6	26.1 ± 3.3	26.2 ± 2.5	0.18
Hemoglobin (g/dL)	11.9 ± 2.0	12.5 ± 1.9	12.8 ± 1.8	12.9 ± 2.0	0.007
WBC (1,000/μL)	7.3 (6.5-8.2)	6.9 (6.6-7.3)	6.9 (6.6-7.2)	7.4 (6.9-7.9)	0.47
Lymphocytes (% WBC)	19.6 ± 7.6	23.2 ± 9.5	23.6 ± 8.3	22.8 ± 8.3	0.03
Proteinuria (mg/24 h)	820 (552-1,224)	544 (450-658)	561 (450-692)	804 (518-1,248)	0.13

Note: Values expressed as mean ± SD, number (percent of total), or geometric mean (95% CI). Comparisons were made using analysis of variance or chi-square test. To convert GFR in mL/min/1.73 m^2 to mL/s/1.73 m^2, multiply by 0.01667; serum albumin in g/dL to g/L, multiply by 10; serum total cholesterol in mg/dL to mmol/L, multiply by 0.02586; hemoglobin in g/dL to g/L, multiply by 10; proteinuria in mg/24 h to g/24 h, multiply by 1,000.

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

Table 2. Distribution of Events by BMI Category

	BMI (kg/m^2)				
	<22.2; <10th Percentile (N = 53)	22.2-28.0; 10th-50th Percentile (N = 208)	28.1-36.7; 50th-90th Percentile (N = 209)	>36.7; >90th Percentile (N = 51)	*P*
Death rate	255.4 (177.5-367.6)	148.3 (118.8-185.2)	99.6 (76.7-129.5)	64.8 (33.7-124.4)	<0.0001
Dialysis initiation rate	110.2 (61.1-199.1)	54.1 (36.8-79.5)	54.1 (37.4-78.4)	30.9 (11.6-82.2)	0.07
Loss of follow-up rate	26.4 (8.5-81.9)	7.6 (2.8-20.2)	10.7 (4.8-23.7)	7.2 (1.0-51.0)	0.36

Note: Values represent number of events/1,000 patient-years (95% CI). Comparisons were made by means of log-rank test for equality of survivor functions.

comorbidity index, blood pressure, smoking status, kidney function, proteinuria, and medication use (model 2); and albumin level, WBC count, hemoglobin level, percentage of lymphocytes in WBC count, cholesterol level, and bicarbonate level in addition to the listed variables (model 3). Higher BMI was associated with lower all-cause mortality in all 3 models, but this association was weakened by the adjustments applied (hazard ratios in groups with BMI > 90th percentile versus <10th percentile in models 1, 2, and 3, 0.28 [95% CI, 0.13 to 0.61]; $P = 0.001$; 0.35 [95% CI, 0.16 to 0.78]; $P = 0.01$; and 0.39 [95% CI, 0.17 to 0.87]; $P = 0.022$). Analyzing BMI as a continuous variable yielded similar findings, a 5.8-kg/m^2 (1 SD) higher BMI was associated with hazard ratios for all-cause mortality of 0.72 (95% CI, 0.60 to 0.87) in model 1, 0.77 (95% CI, 0.63 to 0.93) in model 2, and 0.78 (95% CI, 0.65 to 0.95) in model 3. Inclusion of the quadratic term for BMI did not indicate the presence of a significant nonlinear association ($P = 0.19$ for the quadratic term in model 3). Table 3 lists hazard ratios and 95% CIs for all-cause mortality associated with all variables included in the fixed-effect multivariable Cox models for models 1, 2, and 3.

Higher BMI similarly was associated with lower all-cause mortality in the time-dependent Cox models (hazard ratios in groups with BMI > 90th percentile versus <10th percentile in models 1, 2, and 3, 0.41 [95% CI, 0.21 to 0.80]; $P = 0.009$; 0.47 [95% CI, 0.23 to 0.95]; $P = 0.036$; and 0.53 [95% CI, 0.26 to 1.09]; $P = 0.08$). Analyzing BMI as a continuous variable also yielded similar findings: a 5.8-kg/m^2 (1 SD) higher BMI was associated with hazard ratios for all-cause mortality of 0.69 (95% CI, 0.58 to 0.83) in model 1, 0.72 (95% CI, 0.59 to 0.88) in model 2; and 0.77 (95% CI, 0.64 to 0.94) in model 3.

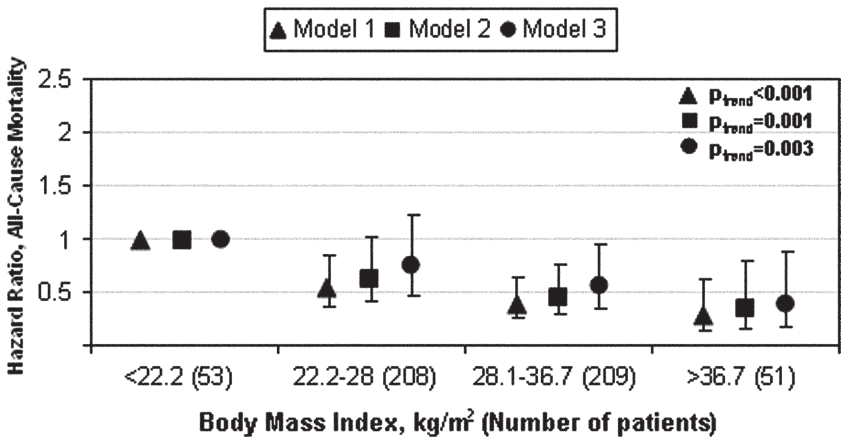

Figure 1. Hazard ratios and 95% CIs for all-cause mortality associated with different levels of BMI in a fixed-covariate Cox model. Adjustments were made for age and race (model 1); age, race, comorbidity index, smoking, blood pressure, kidney function, proteinuria, and medication use (model 2); and age, race, comorbidity index, smoking, blood pressure, kidney function, proteinuria, medication use, albumin level, WBC count, hemoglobin level, percentage of lymphocytes in WBC count, cholesterol level, and bicarbonate level (model 3). The group with BMI less than 22.2 kg/m^2 served as reference.

Table 3. Hazard Ratios for All-Cause Mortality for Variables Included in Different Multivariable Fixed-Effect Cox Models

	Model 1		Model 2		Model 3	
	Hazard Ratio	95% CI	Hazard Ratio	95% CI	Hazard Ratio	95% CI
BMI	0.72	0.60-0.87	0.76	0.63-0.92	0.77	0.64-0.93
Age	1.20	1.02-1.42	1.18	0.97-1.44	1.12	0.92-1.37
Black race (referent, white race)	0.87	0.59-1.29	0.89	0.59-1.35	0.96	0.62-1.46
Comorbidity index			1.22	1.05-1.42	1.16	0.99-1.35
Active smoking (referent, nonsmoking)			1.11	0.75-1.64	1.11	0.75-1.65
Systolic blood pressure			0.89	0.74-1.08	0.97	0.79-1.17
Diastolic blood pressure			0.81	0.65-1.01	0.78	0.62-0.99
Statin use (referent, no statin use)			0.67	0.48-0.93	0.75	0.53-1.07
Aspirin use (referent, no aspirin use)			1.17	0.84-1.62	1.10	0.79-1.53
ACE inhibitor/ARB use (referent, no ACE inhibitor/ARB use)			1.59	1.08-2.36	1.52	1.02-2.28
Estimated GFR			0.68	0.55-0.85	0.61	0.48-0.77
24-H urine protein			1.08	0.91-1.29	0.96	0.79-1.18
Serum albumin					0.68	0.56-0.82
Serum cholesterol					0.87	0.74-1.02
WBC count					0.93	0.79-1.10
Percent lymphocytes in WBC					0.84	0.70-1.01
Blood hemoglobin					1.12	0.93-1.35
Serum bicarbonate					1.14	0.97-1.34

Note: Shown for all continuous variables are hazard ratios and 95% CIs associated with a 1-SD higher level of the variable.
Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

Results remained consistent in subgroup analyses performed in categories divided according to race, smoking status, estimated GFR, and patients with or without the presence of MICS (data not shown). However, results were discrepant in patients with and without diabetes, as shown in Fig 2. There was no significant association between BMI and all-cause mortality in patients with diabetes in the fixed-covariate Cox models (adjusted hazard ratio for 5.8-kg/m^2 higher BMI in patients with diabetes, 0.93 [95% CI, 0.75 to 1.16]; $P = 0.5$) compared with significantly lower mortality associated with higher BMI in patients without diabetes (adjusted hazard ratio for 5.8-kg/m^2 higher BMI in patients without diabetes, 0.46 [95% CI, 0.30 to 0.69]; $P < 0.001$). Formal testing of the interaction with diabetes supported these findings ($P = 0.004$ for the interaction term). The same interaction with diabetes mellitus also was detected in the time-dependent Cox models (results not shown). Lower BMI remained associated with higher all-cause mortality in patients younger than 70 years, but showed a nonlinear U-shaped association with mortality in those older than 70 years ($P = 0.022$ for the quadratic term), as shown in Fig 3 for fixed-effect Cox models. No statistically significant interaction was present between age and BMI ($P = 0.22$ for the interaction term).

Results of the time-dependent Cox models were similar. In subgroups divided according to length of follow-up, the inverse association between BMI and mortality remained present in those with follow-up longer than the median follow-up of 2.3 years (mortality rate, 51.4 deaths/1,000 patient-years [95% CI, 39.5 to 66.7]) and was similar, but less pronounced, in patients with follow-up less than 2.3 years in whom adjustment for case-mix attenuated this association more significantly (mortality rate, 463.3 deaths/1,000 patient-years [95% CI, 386.2 to 555.7]), as shown in Fig 4 for the fixed-effect Cox models. Time-dependent models showed similar results. Results remained consistent when performing analyses after dividing BMI by quartiles.

DISCUSSION

We examined the association between BMI and all-cause mortality in a 5-year nonconcurrent contemporary cohort of unselected male US veterans with CKD stages 1 to 5 not yet on RRT at a single medical center. We found that higher BMI was associated with lower all-cause mortality.

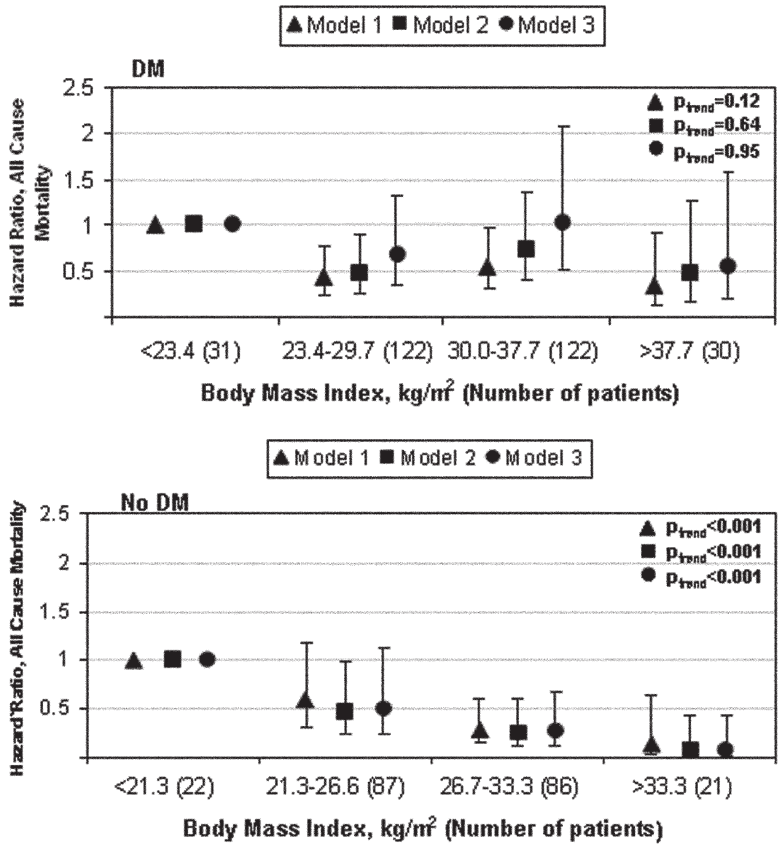

Figure 2. Adjusted hazard ratios for all-cause mortality associated with categories of less than 10th, 10th to 50th, 50th to 90th and greater than 90th percentiles of BMI in a fixed-covariate Cox model in 305 patients with diabetes mellitus and 216 patients with no diabetes mellitus. Adjustments were made for age and race (model 1); age, race, comorbidity index, smoking, blood pressure, kidney function, proteinuria, and medication use (model 2); and age, race, comorbidity index, smoking, blood pressure, kidney function, proteinuria, medication use, albumin level, WBC count, hemoglobin level, percentage of lymphocytes in WBC count, cholesterol level, and bicarbonate level (model 3). Groups with BMI less than the 10th percentile served as reference.

Although these associations were attenuated after adjustments for potential confounders (including surrogate markers of MICS), the overall tendency of a higher BMI being associated with lower mortality remained present. These results did not vary in subgroups divided according to race, kidney function, or presence of MICS, but seemed to be restricted to patients without diabetes mellitus. The inverse association between BMI and mortality was present even in subgroups of patients of younger age and with longer follow-up.

An inverse association between body size and risk of death is well documented in patients on maintenance hemodialysis therapy,[9-20] with the benefit of larger body size extending linearly into the range of morbid obesity (BMI $>$ 35 kg/m^2). Some,[29-33] but not all,[34-36] studies of patients receiving peritoneal dialysis described a similar association. Other populations with an inverse relationship between BMI and mortality include patients with congestive heart failure,[6] chronic obstructive pulmonary disease,[7] rheumatoid arthritis,[8] and older (octogenarian and nonagenarian) individuals.[28]

Our findings in general are concordant with those from studies of patients on dialysis therapy. We also found an inverse association between BMI and mortality. Although this association was partially attributable to confounding effects of case-mix and MICS, adjustment for these characteristics did not result in its reversal. Furthermore, the inverse association between BMI and mortality remained strong in subgroups for

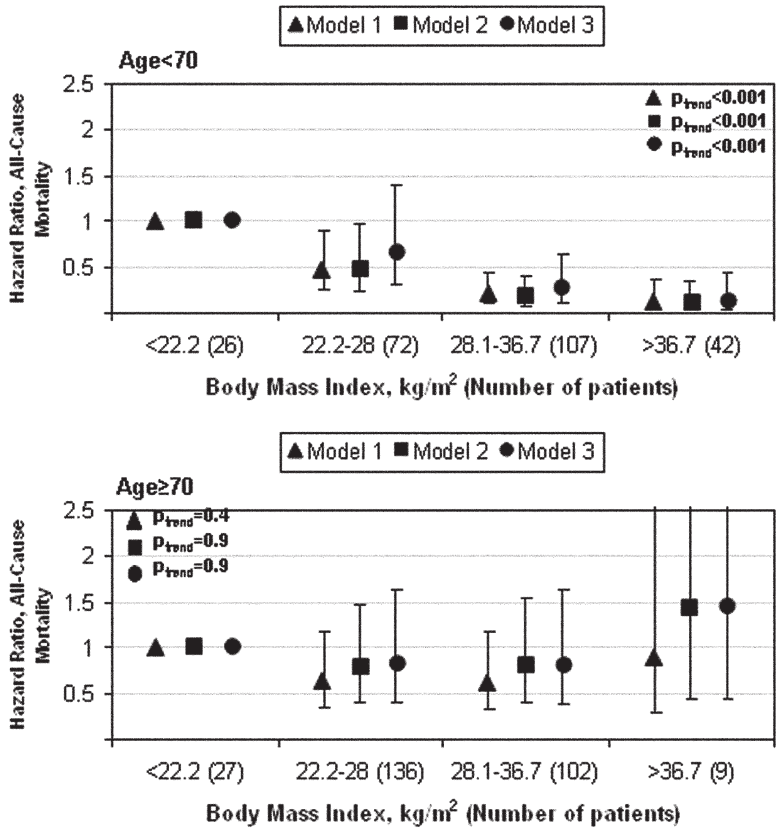

Figure 3. Hazard ratios and 95% CIs for all-cause mortality associated with different levels of BMI in a fixed-covariate Cox model in patient groups divided according to median age. Adjustments were made for age and race (model 1); age, race, comorbidity index, smoking, blood pressure, kidney function, proteinuria, and medication use (model 2); and age, race, comorbidity index, smoking, blood pressure, kidney function, proteinuria, medication use, albumin level, WBC count, hemoglobin level, percentage of lymphocytes in WBC count, cholesterol level, and bicarbonate level (model 3). Groups with BMI less than 22.2 kg/m^2 served as reference. Upper limits of 95% CIs for hazard ratios in the subgroup with BMI greater than 36.7 kg/m^2 for the patient group older than 70 years were 2.76 (model 1), 4.61 (model 2), and 4.81 (model 3).

which reverse causation by a state of more advanced illness was less likely (younger patients and those with lower mortality rates), hence strengthening the case for a truly beneficial effect of a higher BMI in patients with CKD. In addition to studies that examined the association between baseline BMI values and mortality, we also tried to account for temporal changes in BMI and several potential confounders especially important in a patient population showing a progressive disease course, such as CKD. Time-dependent analyses showed results similar to those detected in fixed-covariate Cox models.

In a study describing the association between BMI and mortality in patients with advanced CKD that examined 920 Swedish patients with serum creatinine levels greater than 3.4 mg/dL (>300 μmol/L) for men and greater than 2.8 mg/dL (>247 μmol/L) for women, lower BMI was associated with greater mortality.[37] An inverse association between BMI and mortality also was reported in 714 patients with less advanced CKD drawn from the Atherosclerosis Risk in Community Study[25] and 33,474 participants at high risk of kidney disease enrolled in the National Kidney Foundation Kidney Early Evaluation Program.[38] Conversely, in a study of 1,795 patients screened for the Modification of Diet in Renal Disease Study, BMI was not an independent predictor of mortality,[39] and higher BMI was associated with increased mortality in a large number of individuals with underlying CKD enrolled in a managed care organization.[3] Reasons behind the discrepancies among these studies are unclear because results of most of these studies are available in only abstract form.

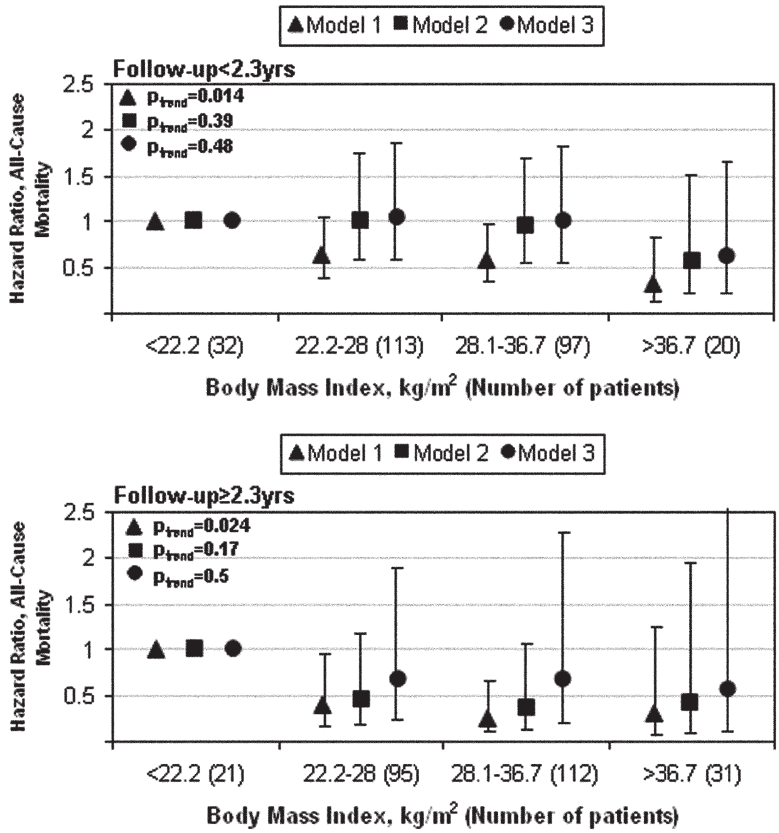

Figure 4. Hazard ratios and 95% CIs for all-cause mortality associated with different levels of BMI in a fixed-covariate Cox model in patient groups divided according to length of follow-up. Adjustments were made for age and race (model 1); age, race, comorbidity index, smoking, blood pressure, kidney function, proteinuria, and medication use (model 2); and age, race, comorbidity index, smoking, blood pressure, kidney function, proteinuria, medication use, albumin level, WBC count, hemoglobin level, percentage of lymphocytes in WBC count, cholesterol level, and bicarbonate level (model 3). Groups with BMI less than 22.2 kg/m^2 served as reference. The upper limit of the 95% CI for hazard ratios in the subgroup with BMI greater than 36.7 kg/m^2 for the patient group with follow-up of 2.3 years or longer was 2.78.

Exact reasons for the seemingly paradoxical inverse association between BMI and mortality are unclear. Possible explanations include reverse causation and residual confounding, known sources of bias in observational studies.[40] Comorbid states with high mortality also could induce a state of malnutrition, hence generating an association between lower BMI and greater mortality. In such a case scenario, lower BMI would be merely a surrogate of the higher burden of comorbidity, rather than a causal factor in the path to increased death risk. This explanation appears less plausible considering that most patients in our and other studies had BMIs that would not be regarded as "low" (only 7 of our 521 patients would have qualified as undernourished), and the lower mortality associated with higher BMI was linear and extended well into the ranges of BMI increase that would be considered pathologically "high" in the general population. We also found that the inverse association between BMI and mortality remained pronounced in subgroups who were younger and had lower mortality rates, which also lessens the possibility of reverse causation alone being the reason behind the observed results. Confounders, such as chronic inflammation, also could be responsible for the seemingly inverse association between lower BMI and greater mortality. We tried to account for this by adjusting for surrogate markers of MICS and examining subgroups with and without the presence of such markers and found the inverse association to hold even in patients who did not have evidence of MICS.

Another possibility is a true protective effect conferred by increased body size. Patients with

CKD, whether on dialysis therapy or not, have very high mortality rates compared with the general population.[41-43] It is conceivable that such pathophysiological states as obesity, which would increase the risk of mortality during the longer life span of a relatively healthy population, may have shorter term benefits. Such temporary survival advantage may be materialized in patients with high short-term death risk, such as patients with CKD.[41-43] This hypothesis may hold true in our cohort despite our observation that even patients with lower mortality rates showed an inverse association between BMI and mortality because even these patients had greater mortality rates than those observed in the general population. Several hypotheses exist about how obesity might be beneficial in the short term. Obesity may be associated with a more stable hemodynamic status, and it may mitigate stress responses and heightened sympathetic and renin-angiotensin activity.[44] The altered cytokine and neuroendocrine profiles of obesity could also confer a relative survival advantage; increased production of adiponectins[45] and soluble tumor necrosis factor α receptors[46] by adipose tissue may neutralize adverse effects of tumor necrosis factor α. Additionally, higher cholesterol levels that are associated with obesity could result in enhanced binding of circulating endotoxins and thus alleviate the inflammation associated with them,[47] and uremic toxins may be sequestered by adipose tissue.[48]

We detected a significant interaction with diabetes mellitus for the association between BMI and mortality, with the inverse association present only in patients without diabetes. Patients with diabetes had significantly higher BMIs compared with those without diabetes in our study (30.4 ± 5.9 versus 27.2 ± 5.0 kg/m^2; $P < 0.0001$). Hence, a true protective effect of higher BMI should have been magnified in this subgroup. We speculate that the deleterious and potentially beneficial effects of obesity may cancel each other out in patients with diabetes, thus resulting in an overall neutral association between BMI and mortality in this subgroup. One explanation could be a worsening of diabetes control in obese patients with diabetes, potentially resulting in increased mortality.

Several limitations of our study have to be acknowledged. We examined exclusively male patients from a single medical center; hence, our results may not apply to other patient populations, especially females. Data used in our study originally were measured for clinical purposes; hence, results may be subject to imprecise ascertainment of comorbidities. The observational nature of our study does not allow us to make inferences about causation, but merely the description of associations. Although we attempted to correct for major confounders, we cannot rule out the effect of residual confounding. This may be especially important because we examined patients (US veterans) who were not the subject of prior studies in this field; hence, certain characteristics inherent of this group and potentially meaningful for the studied outcome, but not available for our analyses (eg, socioeconomic status and dietary habits), may have had a confounding role. We used surrogate markers of MICS, but direct measurements of inflammation (C-reactive protein and interleukin 6) were not available to us. We speculated that worsened diabetes control could explain the discrepant results in patients with diabetes, but we did not have measures of such control available to test this hypothesis.

In conclusion, higher BMI is associated with lower all-cause mortality in patients with moderate to advanced CKD who are not yet on dialysis therapy, especially those without diabetes. This association is explained only partially by case-mix characteristics and the presence of MICS. Extrapolations from the general population about what constitutes an "ideal" BMI may not apply to patients with CKD. Although we caution about making causal inferences based on observational data, the wealth and consistency of observations indicating a potential benefit of higher BMI in patients with CKD is emphasizing the need to prospectively study of this matter.

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