Associations of Body Size with Metabolic Syndrome and Mortality in Moderate Chronic Kidney Disease

Bonnie C.H. Kwan,* Maureen A. Murtaugh,† and Srinivasan Beddhu*‡

*Division of Nephrology & Hypertension and †Department of Family Practice and Preventive Medicine, University of Utah School of Medicine, and ‡Medical Service, Salt Lake Veterans Affairs Healthcare System, Salt Lake City, Utah

Background and Objectives: Obesity is associated with metabolic syndrome and poor outcomes in those with normal kidney function but better survival in dialysis patients. We examined whether chronic kidney disease (CKD) modifies the association of obesity with metabolic syndrome and mortality.

Design, Setting, Participants, & Measurements: Analyses of 15,355 participants in limited access, public use Atherosclerosis Risk in Communities Study database.

Results: The prevalence of metabolic syndrome in (BMI) groups <20, 20 to 24.9, 25 to 29.9, 30 to 34.9, and ≥35 kg/m^2 were 1, 6, 17, 28, and 35% and 9, 15, 32, 46, and 58% in participants without (n = 14,894) and with CKD (n = 461), respectively. Using BMI 20 to 24.9 kg/m^2 as the reference, there was a U-shaped association of BMI with mortality in a parametric survival model of death. An interaction term of BMI and CKD added to the model was significant. In participants with (BMI) ≥25 kg/m^2, each 1-kg/m^2 increase in BMI was associated with increased hazard of death only in those without CKD. Adjustment for components of metabolic syndrome, markers of inflammation, and cardiovascular conditions abolished these associations in participants without CKD but became protective in participants with CKD.

Conclusions: The prevalence of obesity parallels metabolic syndrome in popultions with and without CKD. However, the presence of CKD modifies the associations of obesity with mortality.

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Adipose tissue is not a mere storage depot of fat. It is metabolically active and produces adipokines such as TNF-α, IL-6, plasminogen activator inhibitor, leptin, angiotensinogen, and adiponectin (1–15). Alterations in production of these adipokines in obesity result in metabolic derangements that cause insulin resistance, dyslipidemia, hypertension, and inflammation (1–15). Hence, higher body size in the general population has been associated with increased mortality (16). On the contrary, higher body size in the dialysis population has been consistently associated with lower mortality (17–19). Furthermore, in a recent study, higher fat mass as directly measured by dual-energy x-ray absorptiometry in dialysis patients was associated with lower mortality (20).

These observations raise very interesting questions: Does kidney disease modify the metabolic effects of adipocytes and the associations of obesity with diabetes, hypertension, dyslipidemia, and markers of inflammation? If not, then does kidney disease modify the associations of obesity with mortality?

We hypothesized that in chronic kidney disease (CKD), the metabolic effects of obesity are not diminished but obesity exerts dual competing effects on survival: An increased risk for death mediated through metabolic effects such as insulin resistance, hypertension, dyslipidemia, and inflammation and a decreased risk for death mediated through nutrition. Thus, kidney disease does not reverse the associations of obesity with its metabolic effects, but it does modify the associations of obesity with death. To test this hypothesis, we examined the associations of body mass index (BMI) with insulin resistance, hypertension, dyslipidemia, inflammation, and mortality in the moderate CKD cohort in the Atherosclerosis Risk in Communities (ARIC) Study.

Materials and Methods

Study Population

The ARIC Study is a large-scale, National Heart, Lung, and Blood Institute (NHLBI)-sponsored, long-term, prospective study that measured the associations of established and suspected coronary heart disease risk factors with atherosclerosis in a cohort of men and women who were aged 45 to 64 yr in four US communities.

Assessment of Baseline Characteristics in the ARIC Study

Information on age, gender, and race was based on self-report. Prevalent coronary heart disease was defined as a reported history of physician-diagnosed heart attack, cardiovascular surgery, coronary angioplasty, or evidence of previous myocardial infarction on electrocardiogram. Congestive heart failure was defined as history of leg swelling associated with either orthopnea or paroxysmal nocturnal dyspnea. Peripheral vascular disease was defined as presence of intermittent claudication or absence of posterior tibialis pulse. History of physician-diagnosed stroke, chronic lung disease, and malignancy was defined as prevalent stroke, chronic lung disease, and malignancy, respectively. Smoking was categorized as never, past, and current. Trained techni-

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Correspondence: Dr. Srinivasan Beddhu, 85 North Medical Drive East, Room 201, Salt Lake City, UT 84112. Phone: 801-585-3810; Fax: 801-581-4750; E-mail: srinivasan.beddhu@hsc.utah.edu

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cians measured BP in the sitting position thrice by using a random-zero sphygmomanometer, and the average of last two readings was used.

Anthropometry Measures

Height was measured to the nearest centimeter using a metal rule attached to a wall and a standard triangular headboard. Weight was measured in pounds using a beam balance with the individual standing in a scrub suit and no shoes. BMI was calculated as weight in kilograms divided by height in meters squared.

Laboratory Data

Participants were asked to fast for 12 h before the clinical examination. Fasting blood samples were drawn and processed following standardized protocols (21). The sample aliquots were quickly frozen at −70°C until analysis, which was performed within a few weeks. Serum glucose, lipid profile, and albumin and plasma fibrinogen were measured at ARIC Central Laboratories following standard protocols (21). Laboratories in each study community performed leukocyte cell counts (white blood cell [WBC]) by using cell counters.

Follow-Up of Mortality

Participants underwent a baseline examination in 1987 to 1989. Follow-up included annual telephone interviews (to identify hospitalizations and deaths); examinations every 3 yr in 1990 to 1992, 1993 to 1995, and 1996 to 1998; and survey of death certificates and discharge lists from local hospitals. Out-of-hospital deaths were traced by using death certificate data and, in most cases, an interview with next-of-kin and questionnaires completed by the patients' physicians. Coroner reports and autopsy reports were obtained, when available, for use in validation.

Definition of CKD

GFR was estimated from the four-variable Modification of Diet in Renal Disease (MDRD) equation: GFR = $186.3 \times \text{serum creatinine}^{-1.154} \times \text{age}^{-0.203} \times 0.742$ if female $\times$ 1.21 if black (22). Serum creatinine concentration was calibrated with Cleveland Clinic measurement standards by subtraction of 0.24 mg/dl (23). Those with calculated GFR >150 ml/min per 1.73 m^2 were excluded (23). CKD was defined as GFR <60 ml/min per 1.73 m^2 and non-CKD defined as GFR ≥60 ml/min per 1.73 m^2.

Definition of BMI Groups

The NHLBI classification defines BMI <18.5 kg/m^2 as undernutrition, 18.5 to 24.9 kg/m^2 as normal, 25 to 29.9 kg/m^2 as overweight, 30 to 34.9 kg/m^2 as obesity 1, and ≥35 kg/m^2 as obesity 2 or 3 (24). Only five participants with CKD defined by the MDRD formula had BMI <18.5 kg/m^2. Therefore, in this analysis, the BMI groups were defined as <20, 20 to 24.9, 25 to 29.9, 30 to 34.9, and ≥35 kg/m^2.

Definition of Metabolic Syndrome

The National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) considered metabolic syndrome present when any three of the following five conditions were present (25): Abdominal obesity (waist circumference ≥102 cm in men and 88 cm in women), elevated serum triglycerides (≥150 mg/dl after 12-h fasting), reduced levels of serum HDL cholesterol (<40 mg/dl in men and <50 mg/dl in women), hypertension (systolic BP ≥130 mmHg or diastolic BP ≥85 mmHg or use of antihypertensive medications or a self-reported history of hypertension), and insulin resistance (fasting glucose ≥110 mg/dl or use of antidiabetic agents or self-reported history of diabetes). Because BMI also accounts for abdominal obesity, we defined metabolic syndrome as the presence of any three of insulin resistance, hypertension, low HDL cholesterol, or hypertriglyceridemia.

Statistical Analyses

Baseline characteristics in CKD and non-CKD groups were examined using χ^2 test for categorical variables and Kruskal-Wallis test for continuous variables. The associations of BMI groups in CKD and non-CKD participants with metabolic syndrome and its components and markers of inflammation were also examined with χ^2 test for categorical variables and Kruskal-Wallis test for continuous variables.

Because BMI violated the proportionality assumption of Cox models, parametric proportional hazards model (26) were used to examine the associations of body size with mortality. The proportional-hazards multivariable model with one internal knot was the most parsimonious model and was used in these analyses.

We examined whether the associations of BMI with mortality were modified by the presence or absence of CKD by examining for significance of interaction term and formal test of interaction by likelihood ratio test. First, the associations of GFR and BMI groups with time to all-cause death were examined in the entire cohort. This model was adjusted for age, gender, race, chronic lung disease, malignancy, smoking, and alcohol use. If CKD modifies the associations of BMI with mortality, then a multiplicative interaction term of BMI and CKD will be statistically significant and hence that interactive term was added to the model. Likelihood ratio test of models that included the interaction term of BMI and CKD adjusted for the mentioned covariates *versus* that excluded the interaction term adjusted for the covariates was examined as a formal test of interaction.

To examine further the effect modification of CKD on the associations of BMI with death, we examined these associations in subgroup analyses of those with and without CKD in parametric proportional hazards models. Because BMI has a known U-shaped association with death (27), the associations of BMI as a continuous variable with mortality were examined separately in those with BMI ≥25 kg/m^2 (above the upper limit of normal BMI [24]) and <25 kg/m^2 in CKD and non-CKD participants. In these analyses, associations of BMI with mortality were first examined adjusted for demographics (age, gender, and race), chronic lung disease, malignancy, smoking, and alcohol use. If adiposity leads to insulin resistance, dyslipidemia, hypertension, inflammation, and cardiovascular disease, then the associations of obesity with mortality will be attenuated or nullified when adjusted for these. This was tested by adding insulin resistance, systolic and diastolic BP, serum HDL cholesterol, LDL cholesterol, triglycerides, markers of inflammation (WBC count, plasma fibrinogen, and serum albumin), and baseline prevalence of atherosclerotic conditions (coronary artery disease, cerebrovascular disease, and peripheral vascular disease) and congestive heart failure to the models. The significance of the interaction term of BMI with GFR and formal test of interaction (the likelihood ratio test) was examined in the subgroups of BMI <25 and ≥25 kg/m^2 to examine whether the effects of increasing BMI on mortality were modified by the level of GFR in the normal BMI and overweight/obese subgroups.

Results

ARIC public limited access data set contained data on 15,732 of the 15,792 ARIC participants. Data were available to calculate GFR in 15,582. Those with missing data on BMI (n = 11) and estimated GFR >150 ml/min per 1.73 m^2 (n = 216) were excluded. Hence 15,355 ARIC participants were included, 461 of whom had CKD (GFR <60 ml/min per 1.73 m^2). The vast

majority with CKD was in stage 3 ($n = 429$) with few ARIC participants in stage 4 CKD ($n = 32$).

Table 1 summarizes the baseline characteristics of those with and without CKD. Those with CKD were older, had higher prevalence of atherosclerotic conditions and congestive heart failure, and had lower prevalence of smoking or alcohol use.

Within both CKD and non-CKD groups, higher body size was strongly associated with metabolic syndrome (Figure 1) as well as markers of inflammation (Table 2). These data indicate that the associations of obesity with its metabolic effects in the CKD population parallel those of the non-CKD population, and the presence of CKD did not reverse the associations of body size with metabolic syndrome and markers of inflammation.

In the entire cohort, there were 9.3 deaths per 1000 patient-years (1420 deaths over 152,604 patient-years of follow-up). The mean duration of follow-up was 9.9 ± 1.8 yr. There was a U-shaped association of BMI with death in the entire cohort as the unadjusted incidence of death in BMI groups <20, 20 to 24.9, 25 to 29.9, 30 to 34.9, and ≥35 kg/m^2 were 16.7, 8.0, 8.9, 10.2, and 11.0 deaths per 1000 patient-years, respectively. In parametric proportional-hazards survival models of the entire cohort, with further adjustments, the U-shaped association of BMI with mortality persisted (Table 3). A multiplicative interaction term of BMI with the presence of CKD added to the model was significant ($P < 0.001$), suggesting that the associations of body size with mortality differ on the basis of the presence or absence of CKD. Likelihood ratio test (a formal test of interaction) of the models with and without the interaction term was significant ($P < 0.001$).

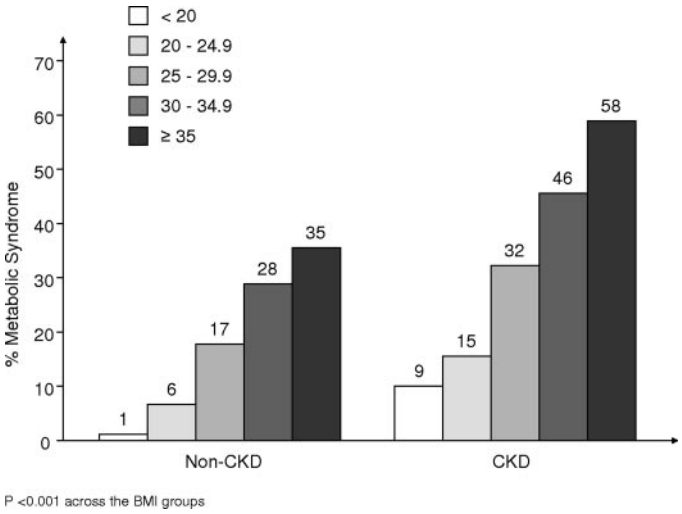

Figure 1. Prevalence of metabolic syndrome by body mass index (BMI) groups in cohorts with and without chronic kidney disease (CKD).

Table 1. Baseline characteristics of ARIC study participants ($n = 15,355$)[a]

Characteristic	Non-CKD (GFR ≥60 ml/min per 1.73 m^2; $n = 14,894$)	CKD (GFR <60 ml/min per 1.73 m^2; $n = 461$)
Demographics		
age (yr; mean ± SD)	54 ± 6	57 ± 6
male (%)	45	36
black (%)[b]	26	26
Clinical features		
BMI (kg/m^2; mean ± SD)	28 ± 5	29 ± 5
GFR (ml/min per 1.73 m^2; mean ± SD)	87 ± 16	48 ± 12
coronary artery disease (%)	5	11
cerebrovascular accident (%)	5	10
heart failure (%)	9	20
peripheral vascular disease (%)	2	6
insulin resistance (%)	22	37
hypertension (%)	43	65
hypertriglyceridemia (%)	28	39
low HDL cholesterol (%)	39	50
Smoking (%)[c]		
never	42	41
former	32	38
current	26	21
Alcohol consumption (%)	56	46
Laboratory data (mean ± SD)		
WBC count (×10^3 cells/mm^3)	6.1 ± 1.9	6.7 ± 3.7
plasma fibrinogen (mg/dl)	302 ± 64	337 ± 84
serum albumin (g/dl)	3.9 ± 0.3	3.8 ± 0.4

[a]ARIC, Atherosclerosis Risk in Communities; BMI, body mass index; CKD, chronic kidney disease; WBC, white blood cell.
[b]$P = 0.82$, [c]$P = 0.02$; all other $P < 0.001$.

Table 2. Mean values of markers of inflammation by category of BMI in CKD and non-CKD groups ($n = 15,355$)[a]

Parameter	BMI					P[b]
	<20	20 to 24.9	25 to 29.9	30 to 34.9	≥35	
Without CKD ($n = 14894$)	$n = 485$	$n = 4496$	$n = 5877$	$n = 2713$	$n = 1323$	
WBC count ($\times 10^3$ cells/mm^3)	6.3 ± 2.1	6.0 ± 2.0	6.1 ± 1.9	6.2 ± 1.9	6.5 ± 1.9	<0.001
plasma fibrinogen (mg/dl)	293 ± 65	291 ± 62	300 ± 62	312 ± 64	338 ± 68	<0.001
serum albumin (g/dl)	3.9 ± 2.8	3.9 ± 0.3	3.9 ± 0.3	3.9 ± 0.3	3.7 ± 0.3	<0.001
With CKD ($n = 461$)	$n = 12$	$n = 102$	$n = 181$	$n = 113$	$n = 53$	
WBC count ($\times 10^3$ cells/mm^3)	5.9 ± 1.9	6.0 ± 2.0	6.5 ± 2.2	7.5 ± 6.3	6.8 ± 2.3	0.001
plasma fibrinogen (mg/dl)	341 ± 123	323 ± 84	331 ± 78.4	343 ± 70	373 ± 105	0.002
serum albumin (g/dl)	3.6 ± 0.4	3.9 ± 0.3	3.8 ± 0.3	3.8 ± 0.4	3.7 ± 0.4	0.002

[a]Data are means ± SD of continuous variables presented.
[b]Kruskal-Wallis test; P value is that for the trend across the groups.

This effect modification of CKD on the associations of BMI with mortality is evident with further subgroup analyses of those with and without CKD. For each 1-kg/m^2 increase in BMI, the hazard for death decreased in both CKD and non-CKD participants with BMI <25 kg/m^2 (Table 4). However, these associations were much stronger in the CKD cohort. In this subgroup with BMI <25 kg/m^2, a multiplicative interaction term of BMI and CKD was significant ($P < 0.001$), and the likelihood ratio test was significant ($P < 0.001$).

In non-CKD participants with BMI ≥25 kg/m^2, adjusted for demographics and comorbidity, the hazard for death increased for each 1-kg/m^2 increase in BMI (Table 5). This was attenuated by adjustment for insulin resistance, BP, lipids, markers of inflammation, and cardiovascular disease. In contrast, in CKD participants, each 1-kg/m^2 increase in BMI in was not associated with mortality (Table 5). With adjustment for the previously mentioned variables, increase in BMI was associated with lower mortality in the CKD cohort (Table 5). In this subgroup with BMI ≥25 kg/m^2, a multiplicative interaction term of BMI and CKD was significant ($P < 0.001$), and the likelihood ratio test was significant ($P < 0.001$).

Discussion

The associations of obesity with its metabolic effects in the CKD population parallel that of the non-CKD population (Figure 1, Table 2). However, the interaction term of BMI and presence of CKD and the likelihood ratio test were significant for mortality in the entire cohort and BMI subgroups (<25 and ≥25 kg/m^2). Thus, the associations of obesity with mortality differed by the presence or absence of CKD in the entire cohort and the subgroups with BMI <25 and ≥25 kg/m^2. Taken together, these data suggest that kidney disease modifies the mortality effects and does not reverse the metabolic effects of obesity.

High BMI is consistently associated with decreased mortality in dialysis patients (17–19), and our earlier analyses indicated that even within high-BMI groups, body composition influences survival (18) (*i.e.*, patients who had high BMI and inferred high muscle mass had better survival than patients who had high BMI and inferred high fat mass). Furthermore, in recent studies, high body fat mass as well as high lean body mass as measured by dual energy x-ray absorptiometry scans or bioimpedance analysis in hemodialysis patients were associated with better survival (20,28). Even though measured high body fat was associated with better survival in these studies, visceral adiposity in dialysis patients is associated with insulin resistance (29), inflammation (30), and carotid atherosclerosis (31). Furthermore, high BMI in dialysis patients is associated with higher prevalence of diabetes (29) and coronary calcification (32,33).

These seemingly perplexing associations might be explained if (*1*) adiposity has dual competing effects on survival, a pro-

Table 3. Associations of BMI groups with all-cause mortality in parametric survival models in the entire cohort ($n = 15,355$)[a]

BMI (kg/m^2)	Model A (HR [95% CI])[b]	Model B (HR [95% CI])[c]
<20 ($n = 497$)	2.15 (1.69 to 2.74)	1.92 (1.51 to 2.46)
20 to 24.9 ($n = 4598$)	Reference	Reference
25 to 29.9 ($n = 6058$)	1.10 (0.97 to 1.26)	1.03 (0.90 to 1.18)
30 to 34.9 ($n = 2826$)	1.26 (1.08 to 1.47)	1.22 (1.04 to 1.43)
≥35 ($n = 1376$)	1.41 (1.17 to 1.71)	1.56 (1.28 to 1.90)

[a]HR, hazard ratio; CI, confidence interval.
[b]Unadjusted.
[c]Adjusted for age, gender, race, chronic lung disease, malignancy, smoking, alcohol use, and GFR.

Table 4. Hazard for death for each 1-kg/m^2 increase in BMI in non-CKD and CKD participants with BMI <25 kg/m^2

Parameter	Non-CKD (n = 4981)	CKD (n = 114)
Deaths per 1000 patient-years	8.5 (419 deaths/49,666 yr)	26.9 (27 deaths/1001 yr)
Model A (HR [95% CI])[a]	0.90 (0.85 to 0.94)	0.70 (0.56 to 0.86)
Model B (HR [95% CI])[b]	0.88 (0.83 to 0.93)	0.60 (0.41 to 0.86)

[a]Adjusted for age, gender, race, non-skin cancer, smoking, and alcohol use.
[b]Adjusted for model A plus cardiovascular conditions (coronary artery disease, cerebrovascular disease, peripheral vascular disease, and congestive heart failure), insulin resistance, systolic and diastolic BP, serum LDL cholesterol, serum HDL cholesterol, serum triglycerides, serum albumin, WBC count, and plasma fibrinogen.

Table 5. Hazard for death for each 1-kg/m^2 increase in BMI in non-CKD and CKD participants with BMI ≥25 kg/m^2

Parameter	Non-CKD (n = 9913)	CKD (n = 347)
Deaths per 1000 patient years	8.8 (873 deaths/99,012 yr)	32.9 (100 deaths/3036 yr)
Model A (HR [95% CI])[a]	1.03 (1.02 to 1.04)	1.01 (0.96 to 1.05)
Model B (HR [95% CI])[b]	0.99 (0.97 to 1.01)	0.94 (0.89 to 0.99)

[a]Adjusted for age, gender, race, non-skin cancer, smoking, and alcohol use.
[b]Adjusted for model A plus cardiovascular conditions (coronary artery disease, cerebrovascular disease, peripheral vascular disease, and congestive heart failure), insulin resistance, systolic and diastolic BP, serum LDL cholesterol, serum HDL cholesterol, serum triglycerides, serum albumin, WBC count, and plasma fibrinogen.

tective nutritional effect and a deleterious metabolic effect resulting in insulin resistance, dyslipidemia, hypertension, and inflammation, and (2) the level of kidney function modifies the relative importance of these effects. In this paradigm, the deleterious metabolic effects of obesity outweigh its protective nutritional effects in the non-CKD population, the deleterious metabolic effects of obesity are neutralized by its protective nutritional effects in the moderate CKD population, and the deleterious metabolic effects of obesity are outweighed by its protective nutritional effects in patients who have stage 5 CKD and are on dialysis. In other words, the overall effects of obesity on survival vary according to the level of kidney function, and there is an interaction of body size and presence or absence of CKD on survival.

Several theories for the survival benefit associated with high BMI in dialysis patients have been proposed, including "competing risk factors" theory (17–19). The results of our study indicate that obesity has metabolic consequences in CKD even though it might exert competing protective nutritional effects. Hence, strategies that minimize the negative effects without abolishing the protective effects associated with high BMI should be tested in interventional studies in the CKD population.

This study has several strengths. The data were carefully collected. The study population includes a large sample of participants with moderate CKD. However, there are several limitations to this study. First, data on C-reactive protein are not available. We used other markers of inflammation (WBC, plasma fibrinogen, and serum albumin), and all show the same trend of increased inflammation (higher WBC, higher plasma fibrinogen, and lower serum albumin) as BMI increased. Second, data on albuminuria and hematuria are unavailable; therefore, ARIC participants with GFR ≥60 ml/min per 1.73 m^2 and kidney damage evidenced by hematuria and proteinuria are classified in the non-CKD group in this analysis. Thus, inferences on whether stages 1 and 2 CKD modify the mortality effects of obesity could not be drawn from the results of this study; nonetheless, these results indicate such effect modification occurs in stages 3 and 4 of CKD.

Conclusions

In moderate CKD, a higher body size is associated with increased prevalence of metabolic syndrome and inflammation. However, when adjusted for these metabolic effects of obesity, a higher body size is associated with better overall survival in CKD.

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Disclosures

None.

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