

UC Irvine

UC Irvine Previously Published Works

Title

Mortality Prediction by Surrogates of Body Composition: An Examination of the Obesity Paradox in Hemodialysis Patients Using Composite Ranking Score Analysis

Permalink

<https://escholarship.org/uc/item/6z6341dk>

Journal

American Journal of Epidemiology, 175(8)

ISSN

0002-9262

Authors

Kalantar-Zadeh, Kamyar
Streja, Elani
Molnar, Miklos Z
et al.

Publication Date

2012-04-15

DOI

10.1093/aje/kwr384

Copyright Information

This work is made available under the terms of a Creative Commons Attribution License, available at <https://creativecommons.org/licenses/by/4.0/>

Peer reviewed



Original Contribution

Mortality Prediction by Surrogates of Body Composition: An Examination of the Obesity Paradox in Hemodialysis Patients Using Composite Ranking Score Analysis

Kamyar Kalantar-Zadeh*, Elani Streja, Miklos Z. Molnar, Lilia R. Lukowsky, Mahesh Krishnan, Csaba P. Kovesdy, and Sander Greenland

* Correspondence to Dr. Kamyar Kalantar-Zadeh, David Geffen School of Medicine and UCLA School of Public Health, Harold Simmons Center for Chronic Disease Research and Epidemiology, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, 1124 West Carson Street, C1-Annex, Torrance, CA 90509-2910 (e-mail: kamkal@ucla.edu).

Initially submitted December 15, 2010; accepted for publication September 27, 2011.

In hemodialysis patients, lower body mass index and weight loss have been associated with higher mortality rates, a phenomenon sometimes called the obesity paradox. This apparent paradox might be explained by loss of muscle mass. The authors thus examined the relation to mortality of changes in dry weight and changes in serum creatinine levels (a muscle-mass surrogate) in a cohort of 121,762 hemodialysis patients who were followed for up to 5 years (2001–2006). In addition to conventional regression analyses, the authors conducted a ranking analysis of joint effects in which the sums and differences of the percentiles of change for the 2 measures in each patient were used as the regressors. Concordant with previous body mass index observations, lower body mass, lower muscle mass, weight loss, and serum creatinine decline were associated with higher death rates. Among patients with a discordant change, persons whose weight declined but whose serum creatinine levels increased had lower death rates than did those whose weight increased but whose serum creatinine level declined. A decline in serum creatinine appeared to be a stronger predictor of mortality than did weight loss. Assuming residual selection bias and confounding were not large, the present results suggest that a considerable proportion of the obesity paradox in dialysis patients might be explained by the amount of decline in muscle mass.

body mass index; muscles; obesity; renal hemodialysis

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; Kt/V, clearance effect of dialysis dose.

Overweight and obesity are risk factors for several chronic diseases, including chronic kidney disease (CKD) (1). However, many epidemiologic studies have reported an inverse association between obesity and mortality rates in patients with CKD (2, 3), with a higher body mass index (BMI, measured as weight (kg)/height (m)²) associated with lower mortality rates and a lower BMI associated with higher mortality rates (4). This obesity paradox has also been reported in patients with heart failure (5), coronary artery disease (6), and chronic lung disease (7), as well as in geriatric populations (8). Other survival paradoxes in CKD patients include the blood pressure paradox (9), the cholesterol paradox (10), and the homocysteine paradox (11); high values of these

cardiovascular risk factors have been associated with lower mortality rates in this population.

These survival paradoxes have also been referred to as reverse epidemiology of cardiovascular risk factors (12) and may have important implications for CKD patients. Over 400,000 US patients with terminal CKD require maintenance dialysis treatment at a cost of roughly \$60,000 per year per patient and have an annual mortality rate of approximately 20%, mostly due to cardiovascular or infectious diseases (13). Hence, although dialysis therapy is expected to be lifesaving, approximately 1 out of every 5 American dialysis patients dies each year, which translates to a 5-year survival rate of 33% (worse than that for most types of cancer) (13).

Although the observed survival paradoxes might be due to residual confounding or survival-selection bias, the inverse relation between indices of body mass, such as BMI, and clinical outcome in CKD patients appears to be relatively consistent, and thus the 2 may share a direct biologic explanation. Unfortunately, most studies have not examined the relative contributions of fat and muscle mass or their changes for 2 reasons: 1) Assessing muscle mass requires elaborate tests of body composition, such as dual energy x-ray absorptiometry, total body computerized tomography, or magnetic resonance imaging, and is particularly difficult in large epidemiologic studies (14) and 2) there is collinearity among surrogates of body mass and composition, and hence conventional statistical methods are difficult to use in simultaneous analyses of these surrogates. Among biomarkers for muscle mass, serum creatinine is routinely measured, but its association with kidney function and meat intake may limit its utility (15). Nonetheless, in CKD patients with minimal or no residual kidney function who undergo thrice-weekly maintenance hemodialysis treatment, serum creatinine concentration appears to be a useful surrogate for muscle mass, and changes in its moving average over time may represent parallel changes in skeletal muscle mass, assuming the patients have no changes in meat intake over time (16, 17).

We examined mortality rates among these patients in relation to BMI and serum creatinine concentrations, as well as their changes over time, in a large and nationally representative cohort of hemodialysis patients over a 5-year period (2001–2006) using ranking percentiles of BMI and serum creatinine and their changes. Given that height remains consistent, BMI change is equivalent to weight change rescaled to reflect the patient's body size (18). We hypothesized that weight gain in hemodialysis patients was associated with a reduced mortality rate, especially if it was associated with an increase in muscle mass, whereas weight loss due to sarcopenia was associated with an increased mortality rate. We used serum creatinine changes as surrogates for changes in muscle mass and analyzed BMI and creatinine using ranking scores to address concerns about the incommensurability of absolute biologic measures.

MATERIALS AND METHODS

Human subjects and data

We examined administrative data from July 1, 2001, to June 30, 2006 (for 20 consecutive calendar quarters) for all individuals with advanced renal failure who underwent hemodialysis treatment in one of the outpatient dialysis facilities of a US-based dialysis organization (DaVita Inc., El Segundo, California). The creation and analyses of this 5-year, non-concurrent dynamic cohort of hemodialysis patients have been described previously (19). To minimize measurement variability and to dilute the influence of short-term variation in dietary and fluid intakes on weight or laboratory measurements, we averaged all repeated measures for each patient during any given calendar quarter (i.e., over 13 consecutive weeks or 3 months). The study was approved by the relevant institutional review committees. The requirement for a written consent form was exempted because of the large

number and anonymity of the patients studied and the non-intrusive nature of the research.

Hemodialysis treatment

Dialysis vintage was defined as the duration of time between a patient's first day of dialysis treatment and the day that patient entered the cohort. The first (baseline) study quarter for each patient was the calendar quarter in which the patient's vintage was 90 days or longer by the middle of that quarter. The administered dialysis dose was measured by single-pooled clearance effect of dialysis dose (Kt/V) using urea kinetic modeling equations that have been described elsewhere (20).

Dry weight and BMI

We averaged up to 39 weight values measured in the dialysis clinic at the end of each thrice-weekly hemodialysis treatment using a standardized scale (Seca Digital Scale, Seca North America, Hanover, MD) to determine the post-hemodialysis dry weight for each hemodialysis patient during each calendar quarter. At least one height value during the entire follow-up period was needed to calculate the average BMI in each calendar quarter.

Laboratory values

Blood samples were collected before dialysis with the exception of postdialysis serum urea nitrogen, which was obtained to calculate urea kinetics. Blood samples were drawn using uniform techniques in all dialysis clinics and were transported within 24 hours to a single laboratory center (DaVita, Inc., Laboratory, Deland, Florida), where the laboratory values were measured using automated and standardized methods. Most laboratory values were measured monthly, including serum creatinine, urea, albumin, calcium, phosphorus, bicarbonate, alkaline phosphatase, and total iron binding capacity. Serum ferritin and intact parathyroid hormone levels were measured at least quarterly. Hemoglobin was measured weekly to biweekly in most patients.

Serum creatinine as a muscle-mass surrogate

As described recently in the Appendix of our earlier study (19), to validate the association between serum creatinine concentration and lean body mass (which includes skeletal muscle), we carried out a substudy within the Nutritional and Inflammatory Evaluation in Dialysis Study (21, 22). A total of 747 randomly selected hemodialysis patients from 8 dialysis clinics in the Los Angeles South Bay area underwent body composition assessment tests via near-infrared interactance and dual energy x-ray absorptiometry (14) (see Nutritional and Inflammatory Evaluation in Dialysis Study website at <http://www.NIEDstudy.org> and prior studies (21, 22) for more details). To mitigate the influence of Kt/V variation on prehemodialysis creatinine concentrations, we adjusted serum creatinine values for Kt/V using a Kt/V value of 1.5 (mean Kt/V in our cohort) via the following equation

Table 1. Examples of Ranking Scores of Change in Body Mass Index and Muscle Mass (Reflected by Change in Serum Creatinine Level) Over 6 Months, Their Interpretations, and the Resultant Composite Ranking Scores, 2001–2006

Case	Individual Ranking Scores of Change Over Time ^a		Interpretation	Composite Ranking Scores ^a (Muscle Change ± Weight Change)	
	Change in Muscle Mass (Creatinine) Percentile	Change in Body Mass Index Percentile		Sum of the Scores	Difference of the Scores
A	80	90	Equally substantial muscle and fat gain	170	–10
B	40	70	Gained more fat than muscle	110	–30
C	20	10	Minimal gain in muscle or fat	30	10
D	80	–10	Gained enormous muscle with almost no change in fat	70	90
E	40	–70	Gained moderate muscle and lost more fat	–30	110
F	20	–90	Mild gain in muscle with enormous fat loss	–70	110
G	–20	90	Mild muscle loss but enormous fat gain	70	–110
H	–40	70	Moderate muscle loss but large fat gain	30	–110
I	–80	10	Enormous muscle loss with minimal fat gain	–70	–90
J	–20	–10	Minimal muscle and fat loss	–30	–10
K	–40	–70	Moderate muscle loss but larger fat loss	–110	30
L	–80	–90	Equally substantial muscle and fat loss	–170	10

^a Rankings are according to the changes over 2 consecutive calendar quarters in body mass index and in 3-month averaged serum creatinine values adjusted for the clearance effect of dialysis dose. These change values were ranked as –100th to 0th percentiles for declines and 0th to 100th percentiles for increases over time. We then added and subtracted these change scores to create change sums and differences between –200 and 200 for each patient.

(using serum creatinine and Kt/V values from the same monthly blood draw in each patient):

$$\text{adjusted creatinine} = \text{creatinine} + \text{creatinine} \\ \times (\text{Kt/V} - 1.5) / 1.5.$$

Composite ranking scores

We ranked patients over 2 consecutive calendar quarters with respect to: 1) change in BMI determined using weight from quarterly averages of up to 39 thrice-weekly measured postdialysis dry weights and 2) change in 3-month averaged Kt/V-adjusted serum creatinine values. The 2 change values were ranked as –100th to 0th percentiles for declines and 0th to 100th percentiles for increases. We then added and subtracted (creatinine plus/minus BMI) these 2 change scores for each patient to create 2 composite scores (a number between –200 and 200 for each subject). Our goal was to create simple, nearly uncorrelated rankings of body-composition change that could be examined simultaneously to distinguish influences of concordant and discordant changes in the surrogate body-composition measures. The sum reflects mostly joint declines below –100 and joint increases above 100, and thus its coefficient is most heavily influenced by patients with concordant changes. In reverse, the difference score reflects mostly discordant changes, with creatinine changes indicative of muscle loss predominant below –100 and weight increases predominant above 100. Table 1 shows selected examples of the change scores in weight and creatinine over time, their interpretations, and the derived composite scores.

Statistical methods

Using proportional hazards regression models with restricted cubic splines, we examined the relation to mortality of baseline BMI and Kt/V-adjusted serum creatinine. Such analyses assume that the variables have a multiplicative joint relation to the mortality rate. In an attempt to mitigate the impact of the regression to the mean for analyses of change in time, all models that examined change as a mortality predictor were also adjusted for baseline BMI or creatinine values. Because of the complexity of interpreting spline products and the high collinearity of our surrogates, we relied on our composite ranking analysis to examine joint changes in the latter surrogates. To get a simple initial idea of joint change effects, we also dichotomized changes in weight and serum creatinine values into decline versus increase, which produced 2 concordant groups (both decline or both increase) and 2 discordant groups (one declines, the other increases).

For each analysis, 3 models were examined based on the level of multivariate adjustment: 1) a minimally adjusted model that included death as the outcome, surrogates of body mass or composition (in either continuous or ordinal format), patient height, and entry calendar quarter (quarter 1 through quarter 20) as covariates; 2) case-mix adjusted models that included all of the above plus age, sex, diabetes mellitus, dialysis vintage, primary insurance, marital status, dialysis dose, and residual renal function during the entry quarter; and 3) malnutrition-inflammation-complex syndrome-adjusted models that included all of the covariates in the case-mix model as well as 10 surrogates of nutritional status and inflammation. These surrogates were serum albumin, serum total iron binding capacity, serum ferritin, serum phosphorus,

Table 2. Baseline Calendar Quarter Data for 121,762 Patients Undergoing Maintenance Hemodialysis, 2001

Variable	Total (n = 121,762)		Body Mass Index ^a									
			<20 (n = 14,088)		20–24.9 (n = 42,444)		25–29.9 (n = 34,502)		30–34.9 (n = 17,333)		≥35 (n = 13,395)	
	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)
Age		62 (15)		63 (18)		63 (16)		62 (14)		60 (14)		57 (13)
Female sex	45		52		40		41		50		59	
Diabetes mellitus	47		30		39		48		55		59	
Race/ethnicity												
White	43		42		44		43		43		43	
Black	32		32		29		31		35		40	
Hispanic	14		11		15		16		14		11	
Asian	3		6		4		2		1		1	
Other	7		7		7		7		6		5	
Dialysis vintage												
<6 months	14		19		15		13		13		12	
6–23 months	31		31		31		31		30		31	
2–4 years	33		28		32		35		36		36	
≥5 years	22		21		22		22		22		21	
Primary insurance												
Medicare	63		64		63		63		63		61	
Medicaid	5		6		6		5		4		5	
Private insurance	10		9		10		10		10		9	
Other	14		11		13		14		16		18	
Marital status												
Married	40		33		39		42		42		40	
Divorced	7		6		6		7		7		8	
Single	23		25		23		21		23		26	
Widowed	13		17		13		13		12		10	
Dialysis dose		1.53 (0.36)		1.64 (0.36)		1.56 (0.36)		1.51 (0.35)		1.47 (0.34)		1.39 (0.36)
Comorbid conditions												
Acquired immunodeficiency syndrome	1		1		1		1		1		1	
Cancer	4		5		4		5		3		2	
Heart failure	27		26		26		27		28		29	
Peripheral vascular disease	11		12		11		11		10		10	
Ischemic heart disease	18		17		19		19		19		14	
Myocardial infarction	6		5		6		6		6		4	
Nonambulatory	3		3		2		2		2		3	
Pulmonary disease	5		7		5		5		5		6	
Smoking	5		7		5		4		4		4	

Serum or blood levels						
Albumin, g/dL	3.67 (0.47)	3.54 (0.53)	3.67 (0.48)	3.72 (0.45)	3.72 (0.43)	3.68 (0.41)
Creatinine, mg/dL	8.0 (3.3)	7.2 (3.0)	8.0 (3.3)	8.2 (3.3)	8.3 (3.4)	8.3 (3.4)
Adjusted creatinine, mg/dL	8.1 (3.5)	7.4 (3.5)	8.2 (3.5)	8.2 (3.7)	8.1 (3.5)	8.1 (3.4)
Total iron binding capacity, mg/dL	208 (46)	192 (48)	204 (45)	211 (45)	216 (45)	218 (46)
Bicarbonate, mg/dL	22.3 (3.0)	22.4 (3.3)	22.3 (3.0)	22.2 (3.0)	22.2 (2.9)	22.2 (2.9)
Phosphorus, mg/dL	5.6 (1.5)	5.4 (1.6)	5.5 (1.5)	5.6 (1.5)	5.7 (1.5)	5.8 (1.5)
Calcium, mg/dL	9.2 (0.7)	9.1 (0.8)	9.2 (0.7)	9.2 (0.7)	9.2 (0.7)	9.2 (0.7)
Ferritin, ng/mL	520 (493)	610 (614)	538 (510)	502 (468)	482 (432)	456 (408)
Intact parathyroid hormone, pg/mL	343 (362)	325 (378)	329 (356)	341 (353)	361 (359)	398 (387)
Hemoglobin, g/dL	12.0 (1.4)	12.0 (1.4)	12.0 (1.4)	12.0 (1.4)	12.0 (1.3)	11.9 (1.3)
White blood cell count $\times 10^3/\mu\text{L}$	7.5 (2.6)	7.6 (3.1)	7.3 (2.6)	7.4 (2.4)	7.5 (2.4)	7.9 (2.3)
Lymphocytes, % of white blood cells	21 (8)	19 (8)	20 (8)	21 (8)	21 (8)	21 (8)
Normalized protein catabolic rate, g/kg/day	0.95 (0.26)	0.93 (0.27)	0.95 (0.26)	0.95 (0.25)	0.95 (0.25)	0.94 (0.25)
Dry weight, kg	75.4 (21.1)	51.4 (8.1)	64.4 (9.1)	77.3 (10.7)	90.2 (12.8)	111.9 (24.6)
Height, m	1.68 (0.11)	1.67 (0.11)	1.68 (0.11)	1.68 (0.11)	1.67 (0.11)	1.65 (0.13)
Body mass index ^a	26.8 (7.0)	18.3 (1.5)	22.6 (1.4)	27.3 (1.4)	32.2 (1.4)	40.9 (7.6)

Abbreviation: SD, standard deviation.

^a Weight (kg)/height (m)².

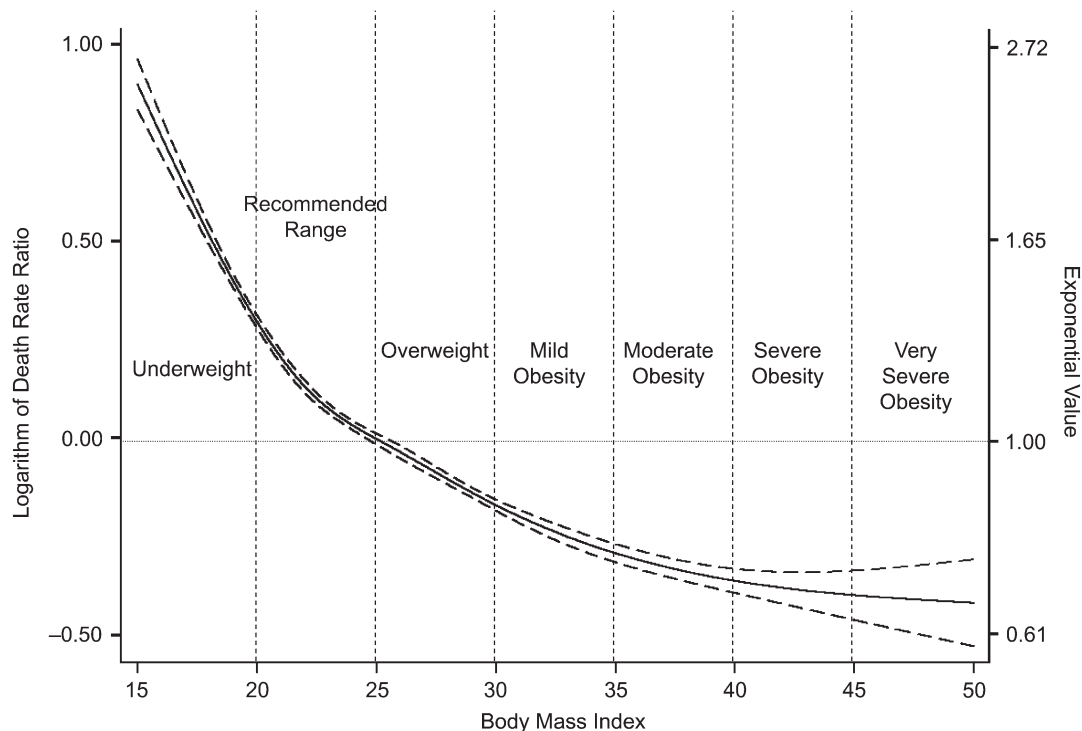


Figure 1. Association of baseline body mass index (BMI, measured as weight (kg)/height (m)² and derived from 3-month averaged dry weight) with mortality in 121,762 hemodialysis patients over 5 years (July 2001–June 2006). The y-axes show the rate ratios of all-cause mortality over 5 years based on the spline model, adjusted for case mix and malnutrition-inflammation-complex syndrome. Models were adjusted for age, sex, diabetes mellitus, dialysis vintage, primary insurance, marital status dialysis dose, residual renal function, serum albumin, transferrin, ferritin, phosphorus, calcium, bicarbonate, peripheral white blood cell count, lymphocyte percentage, hemoglobin, and daily protein intake. Dashed lines are 95% pointwise confidence bands.

serum calcium, serum bicarbonate, peripheral white blood cell count, lymphocyte percentage, hemoglobin, and normalized protein catabolic rate, which was an indicator of daily protein intake, also known as the normalized protein nitrogen appearance (23).

Patients who received kidney transplants, switched to peritoneal dialysis, or left DaVita clinics were censored at the time of the event. Missing covariate data (under 1% for most laboratory and demographic variables) were imputed as means or medians of recorded values. Most analyses were carried out using SAS, version 9.1 (SAS Institute, Inc., Cary, North Carolina). Survival analyses with cubic splines were carried out using Stata, version 10.1 (Stata Corporation LP, College Station, Texas).

RESULTS

The national cohort of the hemodialysis patients included 164,801 adult subjects. After we deleted those patients who did not maintain at least 45 days of thrice-weekly hemodialysis treatment during the base calendar quarter or those for whom we were missing core values (age, dialysis vintage, averaged dry weight, and at least 1 height value), 121,762 hemodialysis patients remained. These patients had a median follow-up time

of 738 days. Table 2 shows the relevant demographic, clinical, and laboratory data of the studied patients according to the 5 categories of BMI: <20, 20–24.9, 25–29.9, 30–34.9, and ≥35. Older age was associated with a lower BMI. Black and Asian patients were overrepresented in the highest and lowest BMI groups, respectively. Baseline serum creatinine levels were incrementally higher across higher BMI groups, but this gradient was reduced after serum creatinine values were adjusted for Kt/V.

Figure 1 shows that association of 3-month averaged baseline BMI and mortality rates in the 121,762 studied patients over 5 years using cubic splines. BMI exhibited a fairly monotonic association with reduced mortality rates, although the advantage of high BMI was reduced in ranges above 40. Nonetheless, no association of high BMI with increased mortality was observed. Figure 2 shows the association between the Kt/V-adjusted 3-month averaged predialysis creatinine level as the muscle-mass surrogate and 5-year mortality rates in 107,082 patients whose creatinine and Kt/V values for the entire first 3 months of the cohort were available. In sensitivity analyses, inclusion of the term created by multiplying BMI and creatinine resulted in similar associations with mortality for BMI and serum creatinine, even though the term had a significance of $P < 0.001$. Separate analyses of creatinine–death associations across BMI increments

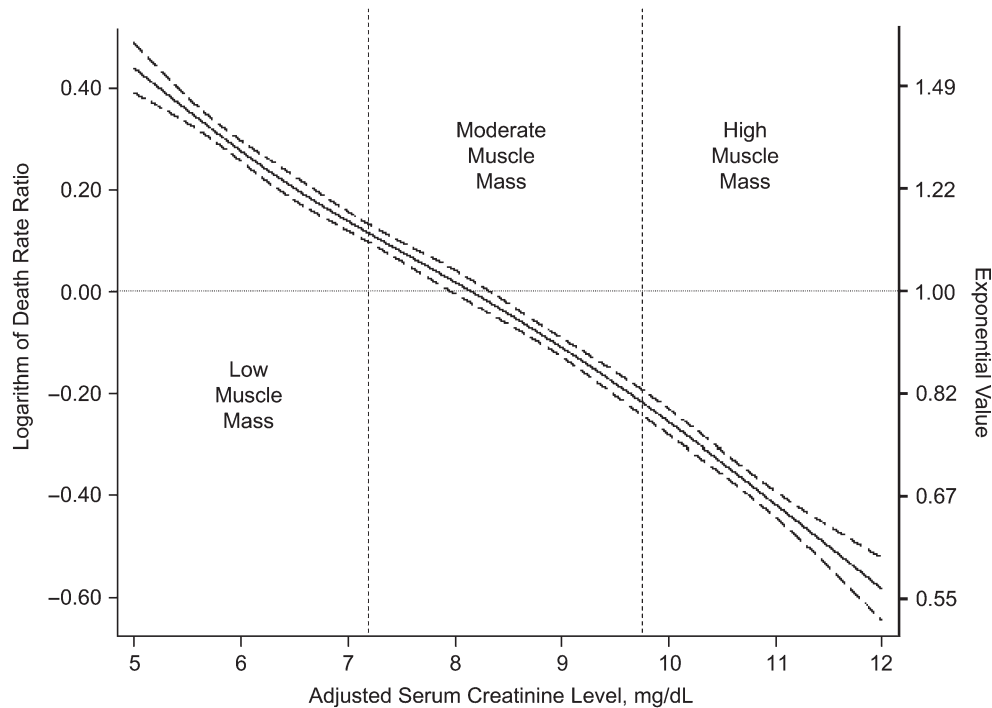


Figure 2. Association of 3-month averaged prehemodialysis serum creatinine levels with mortality in 107,082 hemodialysis patients, 2001–2006. The y-axes show the rate ratios of all-cause mortality over 5 years based on the spline model, adjusted for case mix and malnutrition-inflammation-complex syndrome. Models were adjusted for age, sex, diabetes mellitus, dialysis vintage, primary insurance, marital status dialysis dose, residual renal function, serum albumin, transferrin, ferritin, phosphorus, calcium, bicarbonate, peripheral white blood cell count, lymphocyte percentage, hemoglobin, and daily protein intake. Dashed lines are 95% pointwise confidence bands.

showed relations similar to those in Figure 2 (Web Figure 1, available at <http://aje.oxfordjournals.org/>).

Figures 3 and 4 show mortality rates by changes in BMI and serum creatinine level over the first 6 months of the cohort in 57,247 hemodialysis patients who survived through the first 2 calendar quarters of the study and for whom we had dry weight, creatinine, and Kt/V values for the 6 consecutive months after dialysis began. The demographic, clinical, and laboratory characteristics of this subcohort were similar to those of the parent cohort (data not shown). As shown in Figure 3, weight loss, as reflected by a score away from the 0th percentile and toward the 100th percentile, was associated with higher death rates. A moderate gain in weight up to the 50th percentile, but not higher gains, tended to predict lower death rates. Changes in averaged serum creatinine levels appeared to have more symmetrical and monotonic associations with mortality, such that a decline or rise in creatinine level was associated with higher or lower risks of death, respectively, as shown in Figure 4.

To further study the combined impact of changes in weight and creatinine, we examined the composite scores (Figure 5). The correlation of the composite scores was 0.01 compared with a correlation of 0.28 for the original change scores from which they were computed. For the sums, the mortality rate was the highest among patients with the most extreme concurrent declines in both weight and serum creatinine and was lowest among patients with the most extreme concurrent

increases (Figure 5A). Mortality consistently increased as the difference of changes declined below zero (representing a decline in creatinine not offset by weight gain; Figure 5B). In contrast, the mortality rate appeared to have no consistent relation to the difference of changes as the latter increased above zero (representing a weight loss not offset by a creatinine gain; Figure 5B).

DISCUSSION

In a large cohort of hemodialysis patients treated thrice weekly for up to 5 years in a large US-based dialysis organization, we confirmed that body mass (measured as 3-month averaged BMI) and creatinine levels (3-month averaged dialysis dose-adjusted creatinine concentrations, a surrogate for muscle mass) simultaneously predicted lower mortality rates even after extensive multivariate adjustment (including for measures of nutritional status and inflammation). In a subcohort of patients in whom change could be examined, weight decline and creatinine decline were both associated with an increased risk of death, and creatinine increase was associated with a reduced risk of death. Concordant changes in these 2 body composition surrogates also predicted mortality, but analyses of discordant combinations indicated that creatinine (and thus presumably muscle mass) had more impact on mortality in this cohort.

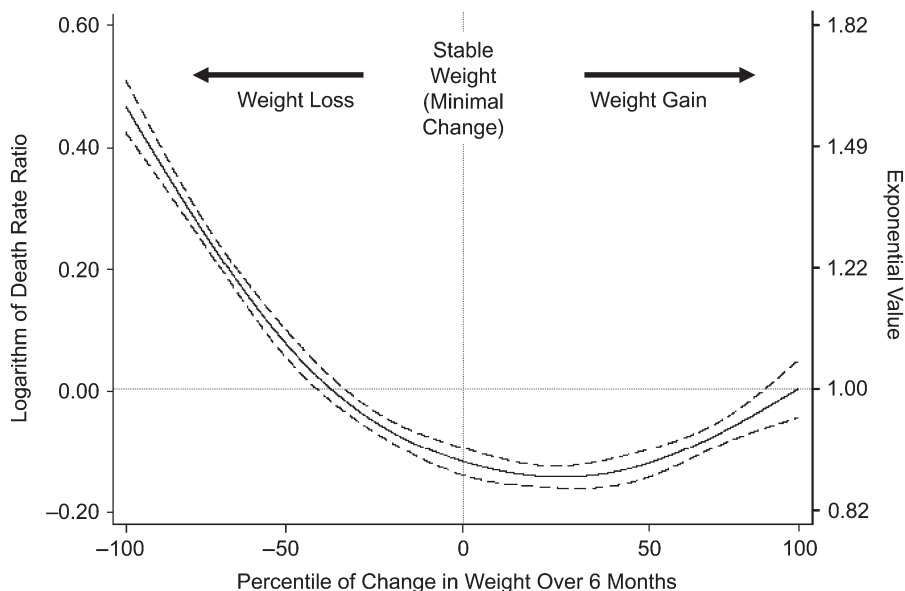


Figure 3. Association between mortality and change in dry weight (measured using body mass index (weight (kg)/height (m)²) over the first 6 months of the study in 57,247 hemodialysis patients who survived through the first 2 calendar quarters of the study and for whom posthemodialysis dry weight values for 6 consecutive months were available, 2001–2006. The y-axes show the rate ratios of all-cause mortality over 5 years based on the spline model, adjusted for case mix and malnutrition-inflammation-complex syndrome. Models were adjusted for age, sex, diabetes mellitus, dialysis vintage, primary insurance, marital status, dialysis dose, residual renal function, serum albumin, transferrin, ferritin, phosphorus, calcium, bicarbonate, peripheral white blood cell count, lymphocyte percentage, hemoglobin, and daily protein intake. Changes are ranked as –100th to 0th percentiles for decline and 0th to 100th percentiles for increases. Dashed lines are 95% pointwise confidence bands.

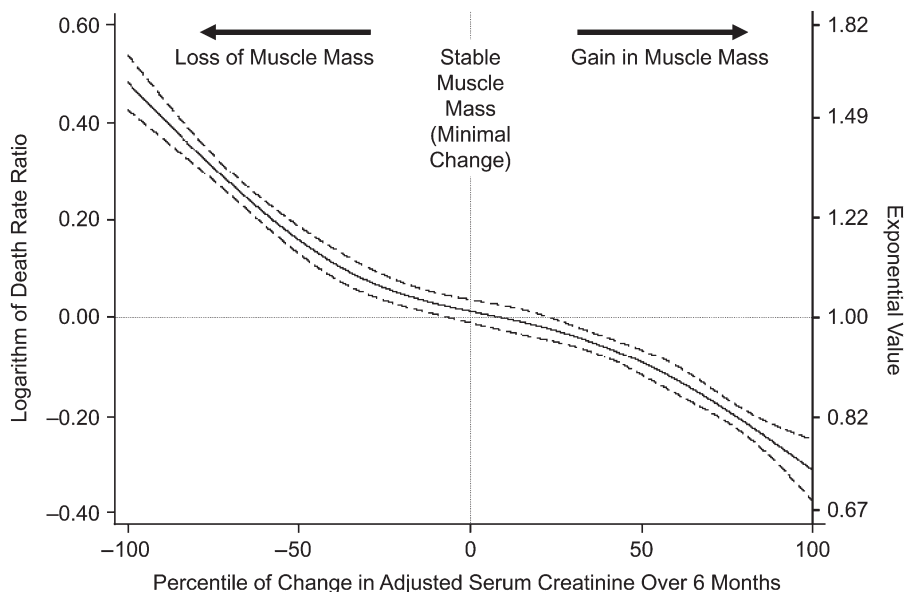


Figure 4. Association between mortality and changes in serum creatinine over the patients' first 6 months in the study in 58,201 hemodialysis patients who survived through the first 2 calendar quarters and for whom prehemodialysis serum creatinine values for 6 consecutive months were available, 2001–2006. The y-axes show the rate ratios of all-cause mortality over 5 years based on the spline model, adjusted for case mix and malnutrition-inflammation-complex syndrome. Models were adjusted for age, sex, diabetes mellitus, dialysis vintage, primary insurance, marital status, dialysis dose, residual renal function, serum albumin, transferrin, ferritin, phosphorus, calcium, bicarbonate, peripheral white blood cell count, lymphocyte percentage, hemoglobin, and daily protein intake. Changes are ranked as –100th to 0th percentiles for decline and 0th to 100th percentiles for increases. Dashed lines are 95% pointwise confidence bands.

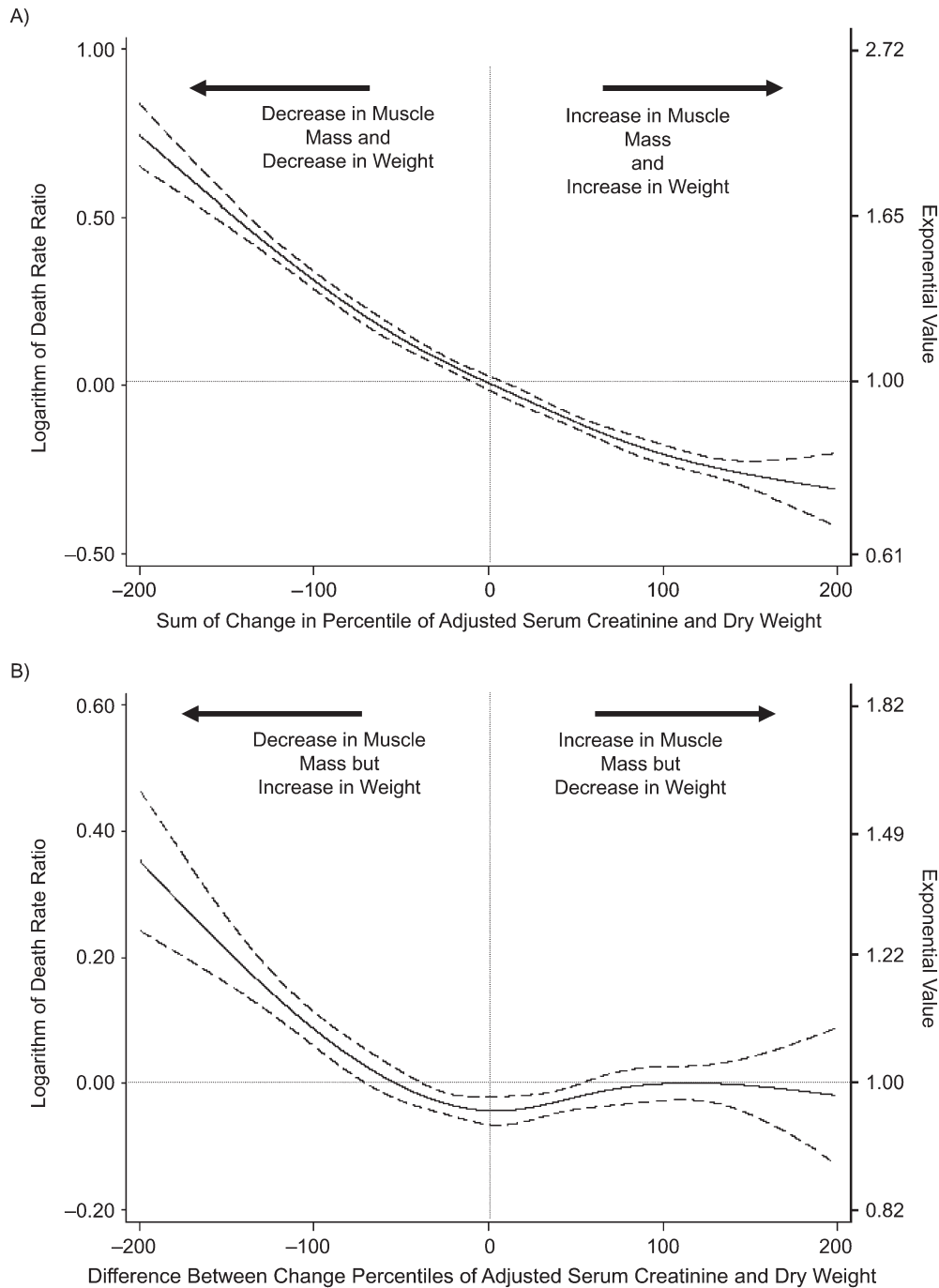


Figure 5. Association of mortality with changes in dry weight (measured using body mass index (weight (kg)/height (m)²) and serum creatinine over the first 6 months of the cohort in 50,831 hemodialysis patients. Each patient first received a percentile score between -100 and 100 according to the percentile rank of the change in dry weight or serum creatinine. The sum of scores resulted in a number between -200 and 200 (A), as did the difference (B). The y-axes show the rate ratios of all-cause mortality over 5 years based on the spline model, adjusted for case mix and malnutrition-inflammation-complex syndrome. Models were adjusted for age, sex, diabetes mellitus, dialysis vintage, primary insurance, marital status, dialysis dose, residual renal function, serum albumin, transferrin, ferritin, phosphorus, calcium, bicarbonate, peripheral white blood cell count, lymphocyte percentage, hemoglobin, and daily protein intake. Dashed lines are 95% pointwise confidence bands.

Of the predictors of death in dialysis patients, markers of poor nutritional status were the strongest and most consistent (24). Nutritional reserve may confer survival benefits to

these patients, consistent with inverse associations of BMI with mortality (25). We observed that both lower BMI, a partial surrogate of fat mass, and lower Kt/V-adjusted creatinine

level, a surrogate for lower muscle mass, were associated with increased mortality. Declines in dry weight (as measured by BMI) and creatinine also predicted increased mortality. Results of our composite ranking score analyses suggested that higher muscle mass was a more important determinant of a lower mortality rate than was BMI, especially because BMI did not accurately capture the association of body composition with health outcomes (18).

We used composite ranking score analyses to examine 2 collinear body composition measures. These measures can also be used for analyses of other collinear factors as often done in nutritional epidemiology, where the intake of certain favorable nutrients may be associated with simultaneous ingestion of deleterious nutrients, such as protein-rich diet that also includes a high phosphorus content. A recent example is dietary restriction to control serum phosphorus, which is routinely recommended for persons with CKD. This practice is associated with a reduction in protein intake and can lead to protein-energy wasting and increased mortality (23, 26). We examined whether a decline in serum phosphorus with a concomitant decline in protein intake was associated with increased mortality in a cohort of 30,075 hemodialysis patients followed for 3 years (23). Higher baseline phosphorus levels and lower protein intake were associated with higher mortality rates, whereas patients whose serum phosphorus decreased but whose protein intake increased had a lower mortality rate than did persons whose serum phosphorus and protein intake both rose over time (23). This suggests that the risk from controlling serum phosphorus by restricting dietary protein intake may outweigh the benefit of controlled phosphorus (23).

A limitation of our study is the lack of direct lean muscle mass and body fat measurements. BMI is not an optimal surrogate of fat mass compared with more reliable measurements of visceral or intra-abdominal fat (which correlate with poor outcomes in renal failure) (27, 28). We also did not have direct measurements of muscle mass, such as mid-arm muscle circumference (which is associated with survival in hemodialysis patients) (29, 30), and thus had to rely on serum creatinine concentration as a surrogate for muscle mass. Serum creatinine appears to be a reasonable measure in patients without substantial urinary creatinine excretion (19). In hemodialysis patients, however, residual urine usually declines over time; thus, with a stable dialysis dose, a rise in creatinine due to further loss in renal function should in theory be associated with worse outcomes. We observed the opposite, which suggests there may be an even larger role for muscle mass than our analysis indicated.

Strengths of our study include its use of uniform laboratory measurements, large sample size, time-averaged posthemodialysis dry weight and laboratory data, with most values representing means of up to 3 monthly measurements, and 5-year follow-up. Nonetheless, our study was based on prevalent dialysis patients, making it vulnerable to survivor bias, even though we adjusted for dialysis vintage. We preferred prevalent patients for this particular study because many incident dialysis patients could still have some residual renal function that rendered a part of serum creatinine variations a filtration marker rather than a muscle-mass surrogate.

Another limitation is the possibility that the results observed in the subcohorts were due in part or wholly to selection effects. Initial selection based on maintaining hemodialysis and having necessary data recorded resulted in selection of about three quarters of the national cohort for analysis. Of these, fewer than half survived the first 2 quarters and had follow-up information complete enough to be included in the change-score analyses. To some extent, any bias produced by these selection stages would have been controlled by covariate adjustment, but we have no way of evaluating the residual bias. We note, however, that for this residual bias to be of a given size, selection would have to have considerably larger associations with change and with mortality that were conditional on the adjustment for covariates. Liu et al. (10) recently found that a cholesterol paradox, a similar reverse epidemiology scenario, was more prominent in dialysis patients with chronic inflammation, who composed two thirds of their study population. Although explicit measurements of inflammatory markers were not available in our cohort, adjustment for available surrogates of the malnutrition-inflammation-complex syndrome produced similar associations. Additional studies with serial measurements of proinflammatory cytokines are needed to examine these interactions.

A limitation of all observational studies on this topic is the inability to definitively determine whether weight and muscle mass loss contribute directly to patient death or instead simply reflect poorer health status of patients (31). Although this residual confounding by health status cannot be ruled out, it can be addressed at least in part by adjustment for covariates. Assuming that this confounding and survival selection were adequately controlled by our adjustments, our ranking analyses suggest that muscle mass may be more important than fat for explaining the obesity paradox among dialysis patients. Even if the observed associations are only due to confounding, they suggest that indicators of muscle mass can provide better identification of high-risk patients than can BMI alone.

ACKNOWLEDGMENTS

Author affiliations: Harold Simmons Center for Chronic Disease Research and Epidemiology, Torrance, California (Kamyar Kalantar-Zadeh, Elani Streja, Miklos Z. Molnar, Lilia R. Lukowsky); Division of Nephrology and Hypertension, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, University of California, Los Angeles, Torrance, California (Kamyar Kalantar-Zadeh, Miklos Z. Molnar); David Geffen School of Medicine at UCLA, University of California, Los Angeles, Los Angeles, California (Kamyar Kalantar-Zadeh); Department of Epidemiology, School of Public Health, University of California, Los Angeles, Los Angeles, California (Kamyar Kalantar-Zadeh, Elani Streja, Lilia R. Lukowsky, Sander Greenland); DaVita Inc., El Segundo, California (Mahesh Krishnan); and Salem Veterans Administration Medical Center, Salem, Virginia (Csaba P. Kovessy).

The study was supported by Dr. Kalantar-Zadeh's research grants from the National Institute of Diabetes, Digestive and Kidney Disease (R01 DK078106 and K24 DK091419), a grant from the American Heart Association (0655776Y), a grant from DaVita Clinical Research, and a philanthropic grant from Harold Simmons, as well as an additional DaVita Clinical Research grant for the Division of Nephrology and Hypertension at Harbor-UCLA Medical Center.

These data were presented in part at the American Society of Nephrology 42nd Annual Meeting and Scientific Exposition, October 27–31, 2009, San Diego, California.

Conflict of Interest: Dr. Krishnan is an employee of DaVita, Inc. Dr. Kalantar-Zadeh is the medical director of the DaVita Harbor-UCLA/Medical Foundation, Inc., Chronic Dialysis Center in Long Beach, California. The other authors have no conflicts to declare.

REFERENCES

- Chertow GM, Hsu CY, Johansen KL. The enlarging body of evidence: obesity and chronic kidney disease. *J Am Soc Nephrol.* 2006;17(6):1501–1502.
- Lavie CJ, Milani RV, Ventura HO. Obesity and cardiovascular disease: risk factor, paradox, and impact of weight loss. *J Am Coll Cardiol.* 2009;53(21):1925–1932.
- Lavie CJ, Milani RV, Artham SM, et al. The obesity paradox, weight loss, and coronary disease. *Am J Med.* 2009;122(12):1106–1114.
- Salahudeen AK. Obesity and survival on dialysis. *Am J Kidney Dis.* 2003;41(5):925–932.
- Curtis JP, Selter JG, Wang Y, et al. The obesity paradox: body mass index and outcomes in patients with heart failure. *Arch Intern Med.* 2005;165(1):55–61.
- Oreopoulos A, Padwal R, McAlister FA, et al. Association between obesity and health-related quality of life in patients with coronary artery disease. *Int J Obes (Lond).* 2010;34(9):1434–1441.
- Landbo C, Prescott E, Lange P, et al. Prognostic value of nutritional status in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 1999;160(6):1856–1861.
- Oreopoulos A, Kalantar-Zadeh K, Sharma AM, et al. The obesity paradox in the elderly: potential mechanisms and clinical implications. *Clin Geriatr Med.* 2009;25(4):643–659.
- Molnar MZ, Lukowsky LR, Streja E, et al. Blood pressure and survival in long-term hemodialysis patients with and without polycystic kidney disease. *J Hypertens.* 2010;28(12):2475–2484.
- Liu Y, Coresh J, Eustace JA, et al. Association between cholesterol level and mortality in dialysis patients: role of inflammation and malnutrition. *JAMA.* 2004;291(4):451–459.
- Suliman ME, Qureshi AR, Bárány P, et al. Hyperhomocysteinemia, nutritional status, and cardiovascular disease in hemodialysis patients. *Kidney Int.* 2000;57(4):1727–1735.
- Kopple JD. The phenomenon of altered risk factor patterns or reverse epidemiology in persons with advanced chronic kidney failure. *Am J Clin Nutr.* 2005;81(6):1257–1266.
- United States Renal Data System. *USRDS 2010 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States.* Bethesda, MD: National Institutes of Health; 2010.
- Bross R, Chandramohan G, Kovesdy CP, et al. Comparing body composition tests for assessment of body fat in chronic kidney disease. *Am J Kidney Dis.* 2010;55(5):885–896.
- Beddhu S, Samore MH, Roberts MS, et al. Creatinine production, nutrition, and glomerular filtration rate estimation. *J Am Soc Nephrol.* 2003;14(4):1000–1005.
- Keshaviah PR, Nolph KD, Moore HL, et al. Lean body mass estimation by creatinine kinetics. *J Am Soc Nephrol.* 1994;4(7):1475–1485.
- Schutte JE, Longhurst JC, Gaffney FA, et al. Total plasma creatinine: an accurate measure of total striated muscle mass. *J Appl Physiol.* 1981;51(3):762–766.
- Michels KB, Greenland S, Rosner BA. Does body mass index adequately capture the relation of body composition and body size to health outcomes? *Am J Epidemiol.* 1998;147(2):167–172.
- Kalantar-Zadeh K, Streja E, Kovesdy CP, et al. The obesity paradox and mortality associated with surrogates of body size and muscle mass in patients receiving hemodialysis. *Mayo Clin Proc.* 2010;85(11):991–1001.
- Miller JE, Kovesdy CP, Nissenson AR, et al. Association of hemodialysis treatment time and dose with mortality and the role of race and sex. *Am J Kidney Dis.* 2010;55(1):100–112.
- Colman S, Bross R, Benner D, et al. The Nutritional and Inflammatory Evaluation in Dialysis Patients (NIED) Study: overview of the NIED Study and the role of dietitians. *J Ren Nutr.* 2005;15(2):231–243.
- Noori N, Kovesdy CP, Dukkupati R, et al. Survival predictability of lean and fat mass in men and women undergoing maintenance hemodialysis. *Am J Clin Nutr.* 2010;92(5):1060–1070.
- Shinaberger CS, Greenland S, Kopple JD, et al. Is controlling phosphorus by decreasing dietary protein intake beneficial or harmful in persons with chronic kidney disease? *Am J Clin Nutr.* 2008;88(6):1511–1518.
- Kovesdy CP, Kalantar-Zadeh K. Why is protein-energy wasting associated with mortality in chronic kidney disease? *Semin Nephrol.* 2009;29(1):3–14.
- Ades PA, Savage PD. The obesity paradox: perception vs knowledge. *Mayo Clin Proc.* 2010;85(2):112–114.
- Kovesdy CP, Shinaberger CS, Kalantar-Zadeh K. Epidemiology of dietary nutrient intake in ESRD. *Semin Dial.* 2010;23(4):353–358.
- Postorino M, Marino C, Tripepi G, et al. Abdominal obesity and all-cause and cardiovascular mortality in end-stage renal disease. CREDIT (Calabria Registry of Dialysis and Transplantation) Working Group. *J Am Coll Cardiol.* 2009;53(15):1265–1272.
- Elsayed EF, Tighiouart H, Weiner DE, et al. Waist-to-hip ratio and body mass index as risk factors for cardiovascular events in CKD. *Am J Kidney Dis.* 2008;52(1):49–57.
- Huang CX, Tighiouart H, Beddhu S, et al. Both low muscle mass and low fat are associated with higher all-cause mortality in hemodialysis patients. *Kidney Int.* 2010;77(7):624–629.
- Noori N, Kopple JD, Kovesdy CP, et al. Mid-arm muscle circumference and quality of life and survival in maintenance hemodialysis patients. *Clin J Am Soc Nephrol.* 2010;5(12):2258–2268.
- Flegal KM, Graubard BI, Williamson DF, et al. Reverse causation and illness-related weight loss in observational studies of body weight and mortality. *Am J Epidemiol.* 2011;173(1):1–9.