Associations of body fat and its changes over time with quality of life and prospective mortality in hemodialysis patients[1–3]

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ABSTRACT

Background: In maintenance hemodialysis (MHD) patients, a larger body size is associated with better survival but a worse self-reported quality of life (QoL). It is not clear whether muscle mass or body fat confers the survival advantage.

Objective: We hypothesized that both a low baseline body fat percentage and a loss of fat over time were independently associated with higher mortality but with a better QoL score.

Design: In 535 adult MHD patients, body fat was measured directly with the use of near infrared interactance and QoL was measured with a Short Form 36 questionnaire. The patients were followed for ≤30 mo.

Results: Across four 12% increments of body fat at baseline, the reported QoL scores were progressively lower ($P < 0.01$). After a multivariate adjustment for demographics and surrogates of muscle mass and inflammation (ie, midarm muscle circumference, serum creatinine, and proinflammatory cytokines), 46 patients with body fat of <12% had a death hazard ratio (HR) 4 times that of 199 patients with body fat content between 24% and 36% (HR: 4.01; 95% CI: 1.61, 9.99; $P = 0.003$). In 411 MHD patients whose body fat was remeasured after 6 mo, a fat loss (≤−1%) was associated with a death risk 2 times that of patients who gained fat (≥1%) after a multivariate adjustment (HR: 2.06; 95% CI: 1.05, 4.05; $P = 0.04$).

Conclusions: A low baseline body fat percentage and fat loss over time are independently associated with higher mortality in MHD patients even after adjustment for demographics and surrogates of muscle mass and inflammation, whereas a tendency toward a worse QoL is reported by MHD patients with a higher body fat percentage. Obesity management in dialysis patients may need reconsideration.   *Am J Clin Nutr* 2006;83:202–10.

KEY WORDS   Obesity paradox, reverse epidemiology, near infrared, body fat, muscle mass, health-related quality of life, Short Form 36, mortality

INTRODUCTION

Currently, >20% of 300 000 persons with end-stage renal disease who undergo maintenance dialysis treatment die every year in the United States (1). Both epidemiologic studies and clinical trials have not confirmed the conventional associations between traditional cardiovascular disease risk factors and clinical outcomes that are observed in the general population. Indeed, the direction of the associations between traditional risk factors and cardiovascular outcomes appear to be changed and often reversed in maintenance hemodialysis (MHD) patients, a phenomenon that has been referred to as "reverse epidemiology" (2).

Many epidemiologic studies have consistently shown that overweight and obesity, ie, a body mass index (BMI; in kg/m^2) > 25, is associated with better survival in MHD patients, whereas a normal or low BMI confers higher all-cause and cardiovascular disease death risks (3–7). A database analysis of 70 028 MHD patients concluded that muscle mass, and not body fat, confers the survival advantage of the obesity paradox (8). In contrast, a larger database study of 418 055 patients showed that large body size and higher fat mass per se are associated with better survival in these patients (3). However, those studies did not measure body fat percentage or muscle mass in MHD patients directly but studied indirect surrogates. Moreover, some studies have

indicated that patients with a larger body size tend to have a worse self-reported, health-related quality of life (9, 10).

Body fat is known to be associated with increased proinflammatory cytokines both in the general population (11, 12) and in dialysis patients (13). Therefore, a protective effect of body fat on survival appears counterintuitive, especially because a higher body fat proportion, at least by virtue of its inflammatory modulation, is associated with known risk factors of cardiovascular diseases such as diabetes mellitus and hypertension (11, 12, 14). Hence, the simplified notion that the "obesity paradox" in dialysis or heart failure patients (15) is due to a higher muscle mass, as opposed to a possible survival advantage of body fat, tends to gain more acceptance among clinicians and scientists. These paradoxical findings have led to confusion with regard to obesity management in dialysis patients.

To ascertain whether body fat has an independent and paradoxical association with both health-related quality of life and survival in MHD patients, we examined the hypotheses that an incrementally higher baseline body fat percentage, after control for demographics and surrogates of muscle mass and inflammation, is associated with improved survival but worse quality of life in these patients. We also hypothesized that a decrease in body fat percentage over time is independently associated with a higher death rate, whereas a gain in fat over time confers survival advantages in MHD patients.

SUBJECTS AND METHODS

Patients

Subjects participating in the Nutritional and Inflammatory Evaluation in Dialysis (NIED) Study originated from a pool of ≈1400 MHD outpatients in 8 DaVita, Inc, dialysis facilities in the South Bay Los Angeles area [see NIED Study website at www.NIEDstudy.org and selected previous publications (16–18) for more details]. Inclusion criteria were outpatients who had been undergoing MHD for ≥8 wk, who were aged ≥18 y, and who had signed a written consent form. Patients with an anticipated life expectancy of <6 mo (eg, due to a metastaic malignancy or terminal HIV disease) were excluded. More than two-thirds of the qualified subjects who were invited to participate in the study agreed to be enrolled. The study was approved by the Institutional Review Board of Los Angeles Biomedical Research Institute at Harbor-UCLA.

During a 30-mo period of the NIED Study (from 1 April 2002 to 31 September 2004), 551 patients from 8 dialysis clinics gave written informed consent. Subsequently, blood samples were obtained from all of these subjects at baseline. Because 16 patients were not present in the dialysis facilities at the time of the body composition evaluation, 535 patients were included in the current study. The medical chart of each MHD patient was thoroughly reviewed by collaborating nephrologists (KK-Z, NK, RSS, and DYW), and data pertaining to underlying kidney disease, cardiovascular disease history, and other comorbid conditions were extracted. A modified version of the Charlson comorbidity index, ie, without the age and kidney disease components, was used to assess the severity of comorbidity (19). All patients were followed until 1 January 2005. The information pertaining to the history of cardiovascular disease (ie, ischemic heart disease, congestive heart failure, peripheral vascular disease, and cerebrovascular disease) was also obtained via self-administered questionnaires and supplemented the information obtained via chart review.

Short Form 36 quality of life scoring system

The Short Form 36 (SF36) is a short form of the health-related quality of life scoring system with only 36 items and that includes 8 independent scales. It is a well-documented, self-administered questionnaire and has been widely used and validated in MHD patients (10, 20). The 8 scales of SF36 are summarized into 2 dimensions: physical health and mental health. We have used a more user-friendly format of SF36 that does not modify the content of the original questions or their answers (10). All but 23 patients who underwent tests of body composition (ie, 512 of 535 MHD patients) were also able to complete the SF36 questionnaire.

Anthropometric evaluation

Body weight assessment and anthropometric measurements were performed while patients were undergoing hemodialysis treatment or within 5–20 min after termination of the treatment. Biceps skinfold and triceps skinfold (TSF) thicknesses were measured with a conventional skinfold caliper with standard techniques, as described elsewhere (21, 22). The midarm circumference (MAC) was measured with a plastic tape. The midarm muscle circumference (MAMC), a measure of muscle mass, was calculated with the following equation (10): $MAMC = MAC − (3.1416 \times TSF)$. Height was obtained from the patient's chart. BMI was calculated with the average of the patient's postdialysis weight measures (in kg) divided by their height^2 (in m). The TSF-estimated body fat fraction was also calculated by using the following equation by Durnin and Womersley (23): body fat fraction $= 4.95/\{c − [m \times \log (TSF)] − 4.5\}$, where c and m are constant numbers based on sex and age groups, respectively.

Near infrared interactance

To measure the percentage body fat and estimate lean body mass, near infrared (NIR) interactance (24, 25) technology was used at the same time as the foregoing anthropometric measurements. NIR interactance is a noninvasive, simple, and rapid method of assessing the percentage body fat via light emission by using NIR spectroscopy, as first described by the US Department of Agriculture (26). NIR interactance is based on the principles of light absorption and reflection (27). When electromagnetic radiation strikes a material, the energy is reflected, adsorbed, or transmitted depending on the scattering and absorption properties of the sample. Energy scattered and reflected back out of the sample contains information about the chemical composition of the sample (27). The use of NIR light interactance to determine body composition was first investigated by Conway et al (28), who showed that NIR spectral data from the biceps of the dominant arm alone resulted in correlation coefficients equal to hydrostatic densitometry (ie, underwater weighing) values. The biceps site appears to be the most representative of total body fat, because the combination of skin and subcutaneous fat thickness at the biceps allows for optimal penetration and interactance of a low level of infrared radiation (27, 28) (see **Appendix A**).

In the present study, we used a commercial NIR interactance sensor with a CV of 0.5% for total body fat measurement (portable Futrex 6100, Gaithersburg, MD; www.futrex.com). After entering the required data (date of birth, sex, weight, and height)

from each patient, NIR measurements were performed by placing a Futrex sensor on the non-vascular accessed upper arm for several seconds. NIR measurements of body fat were shown to correlate significantly with other nutritional measures in MHD patients (24, 25). In a substudy of the NIED Study, NIR interactance was found to be a reliable test of body composition when compared with dual energy X-ray absoptiometry (DXA) (29).

Laboratory evaluation

Blood samples were obtained from the subjects and coincided chronologically with the quarterly blood tests from the DaVita facilities. The single-pool K_t/V was used to represent the weekly dialysis dose. All routine laboratory measurements were performed by DaVita Laboratories (Deland, FL) with automated methods. Serum C-reactive protein (CRP) and cytokine concentrations, including interleukin 6 (IL-6) and tumor necrosis factor α (TNF-α), were measured as indexes of the degree of inflammation. High-sensitivity CRP concentrations were measured by a turbidometric immunoassay in which a serum sample is mixed with latex beads coated with antihuman CRP antibodies that form an insoluble aggregate (WPCI, Osaka, Japan; normal range: <3.0 mg/L) (30, 31). IL-6 and TNF-α immunoassay kits based on a solid phase sandwich enzyme-linked immunosorbent assay with recombinant human IL-6 and TNF-α were used to measure serum proinflammatory cytokine concentrations (R&D Systems, Minneapolis, MN; normal ranges for IL-6 and TNF-α were <9.9 and <4.7 pg/mL, respectively) (32–34). CRP and cytokine concentrations were measured at the General Clinical Research Center Core Laboratory of the Los Angeles BioMedical Research Institute at Harbor-UCLA. Serum prealbumin concentrations were measured with automated methods at the Harbor-UCLA Clinical Laboratory.

Statistical methods

A conventional Student's t test or analysis of variance with Bonferroni adjustment for multiple comparisons was used to detect significant differences between continuous variables in 2 or more groups, respectively. The chi-square method was used for nonparametric variables such as sex, race, ethnicity, and diabetes. Multivariate linear regression models were constructed to estimate partial correlations. Indicators for body fat groups were created for analyses of covariance to examine the association between body fat categories and health-related quality of life scores after adjustment for confounders. To calculate the relative risks of death, we obtained hazard ratios (HRs) to represent relative risks of death with the use of Cox proportional hazard models after control for confounders. Plots of log [−log (survival rate)] against log (survival time) were performed to establish the validity of the proportionality assumption. Three incremental levels of multivariate adjustment were conducted: *1)* demographic-adjusted models included age (continuous), sex (female or male), race (black or others), ethnicity (Hispanic or others), length of time on dialysis (<12 mo or longer), diabetes mellitus (yes or no), Charlson comorbidity index (continuous), and 3-mo averaged, single-pool K_t/V (continuous); *2)* muscle mass-adjusted models included all of the covariates under *1* plus MAMC (continuous) and serum creatinine concentration (continuous); *3)* muscle mass- and inflammation- adjusted models included all of the covariates under *1* and *2* plus serum CRP, IL-6, and TNF-α concentrations (continuous). When examining the

association between the changes of body fat over time and mortality, the demographics-adjusted model also included the baseline body fat and BMI values (continuous) to control for the body fat and size at baseline. Descriptive and multivariate statistics were carried out with the statistical software STATA 7.0 (Stata Corporation, College Station, TX).

RESULTS

All analyses were based on direct (NIR) measurements of body fat, but they were also repeated for TSF-estimated body fat. Anthropometric measures, including body fat percentage, were significantly greater in the women than in the men, with the exception of MAMC, which was greater in the men than in the women. In the 280 men examined in the study, the mean (±SD) NIR-measured body fat percentage was 19.7 ± 8.0%, whereas that in the 255 women was 34.2 ± 7.5% ($P < 0.001$). In contrast, MAMC showed the opposite distribution in the men and women (25.7 ± 5.3 and 24.4 ± 4.8 cm, respectively; $P = 0.005$).

To examine the effect of body fat percentage on quality of life and survival, the NIR-measured body fat percentage was divided into 4 categories in increments of 12% (ie, <12%, 12–23.9%, 24–35.9%, and ≥36%, as shown in **Table 1**). These increments were chosen because body fat percentage cutoffs of 24% and 36% had been used in other studies (35) and because the selected lowest and highest body fat percentage groups included an adequate and somewhat balanced number of subjects for most analyses. Consistent with the sex-specific distribution of body fat mentioned above, the lowest body fat percentage group (<12%) included less and the highest body fat percentage group (≥36%) included more women than men. Black MHD patients comprised over one-half the subjects in the lowest body fat group but less than one-third of the highest body fat percentage group. Advancing age was associated with a progressively higher body fat percentage. The prevalence of both diabetes mellitus and a prior history of cardiovascular disease showed an incremental rise across the increasing body fat percentage groups, as did the Charlson comorbidity index. Of the 2 possible surrogates of muscle mass in MHD patients, the MAMC was not significantly different in the 4 body fat percentage groups, but the serum creatinine concentration was incrementally lower across the higher body fat percentage groups; this decreasing trend remained essentially the same within each sex category (data not shown). Serum CRP concentrations were significantly higher in the lowest body fat percentage group than in the other 3 groups. Serum TNF-α concentrations tended to be higher in the lowest body fat percentage group ($P = 0.06$), but serum IL-6 concentrations did not differ significantly across the 4 body fat percentage groups. Finally, as shown in Table 1, the quality of life scores tended to worsen across increasing body fat percentage groups.

Multivariate models were constructed to additionally examine the associations between outcome measures and surrogates of body composition and inflammation after control for various confounders. As shown in **Table 2**, body fat percentage and surrogates of muscle mass (MAMC and serum creatinine concentrations) showed opposite associations with quality of life scores: an increase in body fat percentage was associated with a worse physical health score, whereas a higher serum creatinine concentration was associated with better physical and mental health scores. When the associations between the same body-composition surrogates and the 30-mo prospective mortality

TABLE 1
Relevant demographic, clinical, and laboratory values according to 4 selected total body fat groups in 535 maintenance hemodialysis patients[1]

	Percentage of NIR-measured total body fat				
	<12% (n = 46)	12–23.9% (n = 182)	24–35.9% (n = 199)	≥36% (n = 108)	P^2
Demographics					
Women (%)	7	9	35	80	< 0.001
Hispanics (%)	38	55	58	48	0.13
Blacks (%)	53	26	24	31	0.005
<12 mo on dialysis (%)	24	26	27	26	0.9
Age (y)	41 ± 15^3	51 ± 16	55 ± 14	58 ± 14	< 0.001
Morbidity					
Diabetes mellitus (%)	20	46	53	65	< 0.001
History of cardiovascular disease (%)	32	51	61	58	0.02
Charlson comorbidity index	1.1 ± 1.2	1.8 ± 1.6	2.0 ± 1.7	2.1 ± 1.6	0.005
Mortality (% in 30 mo)	24	18	17	26	0.23
Anthropometric measures					
NIR-measured total body fat (%)	8.1 ± 2.4	18.3 ± 2.2	30.4 ± 3.5	41.3 ± 3.2	< 0.001
TSF-estimated total body fat (%)	18.0 ± 5.3	25.6 ± 5.8	33.1 ± 5.8	40.1 ± 5.5	< 0.001
Triceps skinfold thickness (mm)	7 ± 3	10 ± 5	15 ± 5	24 ± 9	< 0.001
Biceps skinfold thickness (mm)	4 ± 4	6 ± 4	9 ± 6	15 ± 8	< 0.001
Midarm muscle circumference (cm)	24.9 ± 3.7	24.5 ± 4.5	24.5 ± 5.0	25.8 ± 5.7	0.06
BMI (kg/m^2)	20.8 ± 2.4	23.2 ± 3.0	26.2 ± 4.6	33.3 ± 6.2	< 0.001
Laboratory values					
K_t/V (single pool)	1.6 ± 0.3	1.6 ± 0.3	1.7 ± 0.3	1.6 ± 0.3	0.01
Serum creatinine (mg/dL)	12.9 ± 3.4	11.0 ± 3.3	10.0 ± 3.1	9.9 ± 2.9	< 0.001
CRP (mg/L)	7.0 ± 8.6	4.6 ± 5.6	5.6 ± 6.3	6.6 ± 6.6	0.03
IL-6 (pg/ml)	11.9 ± 10.7	11.0 ± 12.1	11.1 ± 16.7	14.7 ± 37.0	0.5
TNF-α (pg/ml)	10.4 ± 20.3	6.0 ± 5.5	6.9 ± 7.1	6.8 ± 7.7	0.06
Albumin (g/dL)	3.92 ± 0.51	3.96 ± 0.38	3.88 ± 0.36	3.82 ± 0.29	0.01
Prealbumin (mg/dL)	29 ± 10	30 ± 10	29 ± 9	28 ± 8	0.4
Blood hemoglobin (g/dL)	12.0 ± 1.1	12.1 ± 0.9	12.1 ± 0.8	12.1 ± 0.8	0.6
Quality of life					
SF36 physical health score	63 ± 30	48 ± 25	47 ± 27	42 ± 23	< 0.001
SF36 mental health score	66 ± 18	56 ± 21	58 ± 28	52 ± 22	0.007

[1] NIR, near infrared interactance; TSF, triceps skinfold thickness; CRP, C-reactive protein; IL-6, interleukin 6; TNF-α, tumor necrosis factor α; SF36, short form with 36 items.
[2] ANOVA.
[3] $\bar{x} \pm$ SD (all such values).

were examined with Cox proportional hazard regression models and the same covariates, an increase in both body fat percentage and serum creatinine concentrations were associated with better survival (Table 2).

To examine the independent associations between the body fat increments and 30-mo prospective mortality in 535 MHD patients, Cox proportional hazard regression models were constructed with the use of the 24-35.9% body fat percentage group

TABLE 2
Multivariate-adjusted correlation coefficients between the 2 main scores of the health-related quality of life and selected measures of body composition and inflammation in 535 maintenance hemodialysis patients[1]

	Multivariate-adjusted correlation coefficients		
	Physical health score [0–100]	Mental health score [0–100]	30-mo Mortality hazard ratios (95% CIs)
NIR body fat (% total body)	−0.14	−0.08	0.97 (0.94, 0.99)
P	0.003	0.06	0.04
Midarm muscle circumference (cm)	0.09	0.06	0.99 (0.95, 1.02)
P	0.05	0.18	0.5
Serum creatinine (mg/dL)	0.15	0.11	0.91 (0.83, 0.99)
P	0.001	0.02	0.03
Serum C-reactive protein (mg/L)	−0.05	−0.04	1.01 (0.98, 1.03)
P	0.4	0.4	0.6

[1] Body-composition covariates included body fat, midarm muscle circumference, and serum creatinine; inflammation covariate included serum C-reactive protein. Multivariate-adjusted hazard ratios of death have also been shown for each unit increase of the same measures. Other covariates in the multivariate regression models included age, sex, race (black or other), ethnicity (Hispanic or other), diabetes mellitus, length of time on dialysis (<12 mo or ≥12 mo), Charlson comorbidity index, and K_t/V (single pool). NIR, near infrared interactance.

TABLE 3
Hazard ratios (HRs) of death according to body fat percentage categories in all 535 maintenance hemodialysis patients of the Nutritional and Inflammatory Evaluation of Dialysis patients cohort[1]

	30-mo Mortality HRs (95% CIs)		
	Adjusted for demographics, comorbidity, length of time on dialysis, and dialysis dose[2]	Additionally adjusted for surrogates of muscle mass (MAMC and serum creatinine)	Additionally adjusted for surrogates of inflammation (CRP, IL-6, and TNF-α)
Fat <12%	3.89 (1.59, 9.52)	3.84 (1.56, 9.45)	4.01 (1.61, 9.99)
P	0.003	0.003	0.003
Fat ≥12% and <24%	2.03 (1.06, 3.91)	1.94 (1.01, 3.72)	1.98 (1.03, 3.82)
P	0.03	0.04	0.04
Fat ≥24% and <36%	1.00 (reference)	1.00 (reference)	1.00 (reference)
Fat ≥36%	1.18 (0.70, 1.98)	1.03 (0.76, 2.24)	1.28 (0.74, 2.21)
P	0.5	0.3	0.4
Charlson comorbidity index	1.25 (1.09, 1.44)	1.26 (1.09, 1.45)	1.25 (1.09, 1.44)
P	0.001	0.001	0.003
MAMC (each 1-cm increase)	—	0.98 (0.94, 1.01)	0.98 (0.94, 1.02)
P		0.21	0.22
Serum creatinine (each 1-mg/dL increase)	—	0.91 (0.84, 0.94)	0.92 (0.84, 1.00)
P		0.04	0.05
Serum CRP (each 1-mg/L increase)	—	—	1.00 (0.98, 1.03)
P			0.8
Serum IL-6 (each 1-pg/mL increase)	—	—	1.00 (0.99, 1.01)
P			0.8
Serum TNF-α (each 1-pg/mL increase)	—	—	0.99 (0.98, 1.00)
P			0.9

[1] Three hierarchical levels of multivariate adjustments were examined. MAMC, midarm muscle circumference; CRP, C-reactive protein; IL-6, interleukin 6; TNF-α, tumor necrosis factor α.

[2] Covariates adjusted for included age, sex, race (black or other), ethnicity (Hispanic or other), diabetes mellitus, length of time on dialysis (<12 mo or ≥12 mo), Charlson comorbidity index, and K_t/V (single pool).

as the reference group. This group was selected as the reference group because it had both the largest population ($n = 199$) and the largest number of death cases ($n = 34$). The adjusted relative risks of death for each body fat percentage group was 3.89 for the lowest body fat percentage group (<12%) and 2.03 for the second lowest body fat percentage group (≥12% and <24%) when compared with the reference group (**Table 3**). After additional adjustment for the surrogates of muscle mass and inflammation, the death risk ratios remained essentially unchanged (HRs: 4.01 and 1.98, respectively). The proportion of the surviving patients in each of the 4 body fat categories after the same multivariate adjustment for demographics and dialysis dose (Kaplan-Meier $P < 0.001$) is illustrated in **Figure 1**. Cox models were also repeated for continuous values of body fat percentage. In the full model that included all surrogates of inflammation and muscle mass, a 1% increase in NIR body fat was associated with a 3% lower death risk (HR: 0.97; 95% CI: 0.94, 0.99; $P = 0.04$).

To ascertain whether sex was an effect modifier of the association between body fat percentage and survival, separate multivariate models for each sex were examined. The same trends, but with mitigated statistical significances, were observed (**Table 4**). All analyses were repeated after adjustment for serum albumin, prealbumin, and inflammatory marker concentrations; the resultant HR and trends were essentially the same, but with an additional reduction in statistical significance (data not shown). All analyses were also repeated for cardiovascular mortality. Although the same trends were observed, the estimated summary measures were not statistically significant (data not shown).

To examine the hypothesis that an increase in body fat over time improves survival whereas losing body fat leads to an increased death risk in MHD patients, the changes in body fat percentage were calculated for all 411 patients who remained in
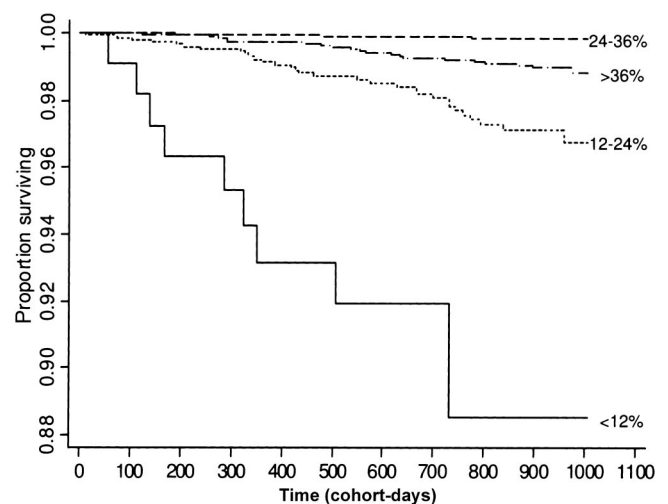

FIGURE 1. Multivariate-adjusted Kaplan-Meier proportion of surviving patients in each of the 4 body fat groups in 535 maintenance hemodialysis patients. Covariates adjusted for included age, sex, race (black or other), ethnicity (Hispanic or other), diabetes mellitus, legnth of time on dialysis (<12 mo or ≥12 mo), Charlson comorbidity index, and dialysis dose (K_t/V). Kaplan-Meier $P < 0.001$.

TABLE 4
Hazard ratios (HRs) of death (2.5 y) according to body fat percentage categories in male and female maintenance hemodialysis patients[1]

	30-mo Mortality HRs (95% CIs)		
	Adjusted for demographics, comorbidity, length of time on dialysis, and dialysis dose[2]	Additionally adjusted for surrogates of muscle mass (MAMC and serum creatinine)	Additionally adjusted for surrogates of inflammation (CRP, IL-6, and TNF-α)
Men (n = 280)			
Fat <12%	2.90 (1.10, 7.69)	2.83 (1.03, 7.80)	2.95 (1.03, 8.41)
P	0.03	0.04	0.04
Fat ≥12% and <24%	1.42 (0.67, 3.07)	1.56 (0.70, 3.47)	1.53 (0.70, 3.45)
P	0.4	0.3	0.3
Fat ≥24%	1.00 (reference)	1.00 (reference)	1.00 (reference)
Women (n = 255)			
Fat <24%	2.74 (1.03, 7.31)	2.30 (0.81, 6.57)	2.44 (0.83, 7.19)
P	0.04	0.10	0.10
Fat ≥24% and <36%	0.98 (0.57, 1.71)	1.03 (0.57, 1.86)	1.05 (0.58, 1.90)
P	0.9	0.9	0.8
Fat ≥36%	1.00 (reference)	1.00 (reference)	1.00 (reference)

[1] Note that the upper and lower end groups of the body fat categories for men and women are not the same because of the different sex-specific body fat distribution pattern. MAMC, midarm muscle circumference; CRP, C-reactive protein; IL-6, interleukin 6; TNF-α, tumor necrosis factor α.

[2] Covariates adjusted for included age, race (black or other), ethnicity (Hispanic or other), diabetes mellitus, length of time on dialysis (<12 mo or ≥12 mo), Charlson comorbidity index, and K_t/V (single pool).

the cohort for ≥6 mo after the initial body composition evaluation and who underwent a second body fat measurement with the same NIR technology. The following 3 groups were constructed: 1) no change in body fat (ie, an increase or decrease in body fat <1%); 2) body fat loss (ie, a change in body fat ≤−1% over 6 mo); and 3) body fat gain (ie, a change in body fat ≥1% in 6 mo). The baseline values of several relevant measures in the 3 selected groups of body fat change are shown in **Table 5**. The death HRs in the 3 body fat change groups are shown in **Table 6**. Compared with the fat-gain group, the no-change and fat-loss groups had an

TABLE 5
Relevant demographic, clinical, and laboratory variables according to the 3 groups of changes in body fat during the first 6 mo of the cohort in 411 maintenance hemodialysis patients[1]

	Body fat loss ≤−1% (n = 113)	No change in body fat (−1% to 1%) (n = 175)	Body fat gain ≥1% (n = 123)	P[2]
Anthropometric measures				
Baseline NIR body fat (%)	28.0 ± 9.9[3]	27.0 ± 11.7	26.4 ± 0.8	0.5
Change in NIR body fat (%)	−3.4 ± 3.2	0.1 ± 0.5	2.7 ± 2.3	
MAMC (cm)	25.7 ± 5.4	25.2 ± 5.4	24.9 ± 5.3	0.6
Triceps skinfold thickness (mm)	17.2 ± 8.9	17.9 ± 10.5	16.8 ± 9.0	0.6
Biceps skinfold thickness (mm)	11.3 ± 7.4	10.6 ± 8.0	9.1 ± 7.4	0.08
BMI (kg/m^2)	26.3 ± 5.6	27.0 ± 6.9	26.0 ± 5.4	0.3
Demographic measures				
Age (y)	55.4 ± 15.5	52.3 ± 16.1	55.6 ± 13.3	0.11
Women (%)	52	46	49	0.6
Diabetes mellitus (%)	49	51	59	0.25
Charlson comorbidity index	1.9 ± 1.5	1.6 ± 1.5	2.2 ± 1.8	0.01
All-cause mortality (24 mo %)	21	13	12	0.09
Laboratory variables				
Serum albumin (g/dL)	3.87 ± 0.41	3.99 ± 0.34	3.89 ± 0.31	0.04
Serum prealbumin (mg/dL)	29 ± 8	30 ± 9	29 ± 9	0.8
Serum creatinine (mg/dL)	10.9 ± 3.5	10.6 ± 3.3	10.5 ± 3.1	0.5
Serum CRP (mg/L)	6.2 ± 6.8	5.4 ± 5.7	6.3 ± 7.3	0.4
Serum IL-6 (ng/L)	11.5 ± 11.9	10.8 ± 30.7	15.8 ± 34.5	0.3
Quality of life				
SF36 physical health score	55 ± 16	52 ± 16	56 ± 13	0.08
SF36 mental health score	58 ± 28	58 ± 24	55 ± 22	0.5

[1] NIR, near infrared interactance; CRP, C-reactive protein; IL-6, interleukin 6; SF36, short form with 36 items; MAMC, midarm muscle circumference.

[2] ANOVA.

[3] $\bar{x}$ ± SD (all such values).

TABLE 6
Hazard ratios (HRs) of 24-mo death according to the changes in body fat percentage categories over the first 6 mo of the cohort in 411 maintenance hemodialysis patients of the Nutritional and Inflammatory Evaluation of Dialysis patients Study[1]

	30-mo Mortality HRs (95% CIs)		
	Adjusted for demographics, comorbidity, length of time on dialysis, and dialysis dose[2]	Additionally adjusted for surrogates of muscle mass (MAMC and serum creatinine)	Additionally adjusted for surrogates of inflammation (CRP, IL-6, and TNF-α)
Body fat loss ($\leq-1\%$ in 6 mo)	1.98 (1.02, 3.85)	2.03 (1.04, 3.96)	2.06 (1.05, 4.05)
P	0.04	0.04	0.04
No change in body fat (-1% to 1%)	1.51 (0.77, 2.97)	1.49 (0.76, 2.92)	1.51 (0.77, 2.98)
P	0.23	0.25	0.23
Body fat gain ($\geq1\%$ in 6 mo)	1.00 (reference)	1.00 (reference)	1.00 (reference)

[1] All models also included the baseline near infrared interactance body fat percentage and BMI in order to control for the potential effect of initial body size on outcome. MAMC, midarm muscle circumference; CRP, C-reactive protein; IL-6, interleukin 6; TNF-α, tumor necrosis factor α.

[2] Covariates adjusted for included age, race (black or other), ethnicity (Hispanic or other), diabetes mellitus, length of time on dialysis (<12 mo or $\geq$12 mo), Charlson comorbidity index, and K_t/V (single pool).

incremental increase in the death risk; the fat-loss group had 2 times the risk of death even after extensive multivariate adjustment for demographic covariates, surrogates of muscle mass and inflammation, and nutritional status at baseline (HR = 2.06; P = 0.04). Similar results were obtained for TSF-estimated body fat percentage (data not shown).

DISCUSSION

In the present longitudinal and prospective study, we showed that a low, rather than a high, baseline body fat percentage was an independent risk factor of poor survival in 535 MHD patients, even after adjustment for the fact that patients with higher body fat percentage were sicker and had a higher prevalence of diabetes and prior history of cardiovascular disease than did patients with lower body fat percentage. Moreover, a loss in body fat over time was associated with a higher death risk than was a gain in body fat. These trends were preserved even after extensive multivariate adjustment for surrogates of muscle mass and inflammation. In contrast, the self-reported quality of life showed the opposite trend, especially in the male MHD patients in whom a lower body fat percentage was weakly but significantly associated with a better quality of life. Although these findings may partially explain the consistently observed obesity paradox or reverse epidemiology of body mass in MHD patients (7, 36), they question whether such associations are indeed causal and the mechanisms through which a high body fat percentage at baseline or a gain in body fat over time tend to confer survival advantages in MHD patients.

Adipose tissue is not only a main source of energy but also secretes various adipocytokines, including leptin, IL-6, TNF, and adiponectin (13, 37). Indeed, up to 20% of the total circulating IL-6 may originate from adipose tissue, mostly from visceral, rather than subcutaneous, fat cells (38–40). A recent cross-sectional study of 197 dialysis patients showed that visceral fat mass correlated significantly with circulating concentrations of IL-6, whereas no significant correlation was shown between subcutaneous fat mass and IL-6 (13). However, TNF receptors are also produced by adipose tissue (38), which may mitigate the deleterious effect of TNF-α (7). In most people, including in

most MHD patients, a high BMI likely reflects high body fat percentage rather than high muscle mass, and the fat is more likely to be nonvisceral; the higher the BMI, the lower the proportion of visceral fat in total body fat (41). In our study, the NIR measured subcutaneous fat on the upper arm. Hence, our findings pertaining to the possible protective effect of fat on survival and its lack of association with inflammation cannot be generalized to visceral fat mass. However, as shown in Table 1, a strong association between NIR-measured body fat percentage and BMI was noticed.

It is not clear how fat may play a protective role in MHD patients. Abundant energy stores may confer survival advantages during stress or starvation (42). In a vulnerable patient population, such as dialysis or heart failure patients who are also subject to intermittent catabolic events such as infectious complications, having extra fat may explain the cause of the so-called obesity paradox (15). Although BMI is most frequently used in nutritional assessment surveys as a surrogate of nutritional status, it does not precisely reflect body composition, nor does it differentiate between muscle and fat mass. A study of 70 028 incident MHD patients reported that a protective effect from a high BMI is only present in patients with a normal or high muscle mass (8). However, virtually all epidemiologic studies conducted in MHD patients (7), including the study by Beddhu et al (8), have consistently shown that obese MHD patients have a significantly better survival than do nonobese MHD patients. Moreover, the foregoing study (8) showed that in the MHD patients with less muscle mass, a higher BMI, which was probably due to fat, was still associated with better survival (43).

In our study, a paradoxically negative association was found between fat mass and the self-reported, health-related quality of life score. In another study conducted in a different cohort of MHD patients from northern California, we reported a similar association between BMI and SF36 scores (10). Han et al (44) used SF36 in >4000 healthy persons and found that large waist circumferences and high BMIs were more likely to be associated with an impaired quality of life and disability. Goller et al (45) found that in a group of chronic peritoneal dialysis patients, in whom a higher BMI is more frequently present than in MHD patients, overweight patients had lower SF36 scores and were

more impaired in physical functioning. If a low SF36 score, ie, an independent predictor of high prospective death, has a weak but negative correlation with BMI and body fat percentage, which are associated with survival advantages, this puzzling contradiction may indicate that a low body fat percentage is an even stronger predictor of poor outcome in MHD patients than is self-perceived body image and the resultant quality of life. Future studies are needed to additionally explore these paradoxes.

The strengths of our study included the following: *1)* a direct measurement of body fat percentage with the use of NIR as well as an additional estimate of body fat percentage based on TSF in over 500 hemodialysis patients; *2)* repeated measurements of body fat percentage after 6 mo in most subjects; *3)* a longitudinal follow-up of the patients for ≤2.5 y; and *4)* a comparison between 2 different outcome measures, ie, mortality and quality of life. The use of NIR interactance in place of DXA should be mentioned among the limitations of our study. NIR interactance reliability has been shown previously (46, 47), including in our own studies (24, 25, 29). Indeed, with the use of DXA as the reference standard, we recently showed that NIR-measured body fat percentages correspond closely to those measured with DXA (29). During the initial recruitment, it is possible that only those MHD patients who were generally healthier or more health-conscious agreed to participate. This is evident from the fact that the annual mortality rate in the studied dialysis units in the same period of time was lower than the national rate, and the death rate in the recruited MHD patients for the NIED Study was even lower (16). However, a selection bias with such a direction would generally lead to a bias toward the null, so that without this selection bias our positive results would have probably been even stronger and the associations more prominent.

In conclusion, our study is the first to show the independent effect of increased body fat percentage both at baseline and over time on improving survival in dialysis patients, even after control for surrogates of muscle mass and inflammation. These findings may have major clinical implications because the current practice of medicine has a heavy basis on the undifferentiated advice for obese persons to lose fat (48). Many dialysis patients are asked aggressively to lose weight as a requisite to be listed on and to remain in kidney transplant waiting lists, a practice that was recently questioned (3). Clinical trials to increase weight, muscle mass, and even body fat in cachectic dialysis patients may be indicated.

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APPENDIX A

Near infrared methodology to estimate body fat percentage

We used a commercially available NIR measuring device, Futrex 6100 (Futrex Inc, Gaithersburg, MD), which is a portable, 900 g, $12 \times 24 \times 5.5$ cm minicomputer with an NIR measurement estimating range between 2.5% and 50.0% (percentage body fat) (1). The minicomputer is connected, via a light cable, to a microphone-sized NIR-emitting sensor. Before placing the sensor window on the midupper arm, the sensor window is equipped with a light shield to ensure that no external light interferes with the estimation of percentage body fat. Only several seconds are required to enter a patient's data, which includes sex, weight, height, and age, into the NIR computer. Subsequently, an NIR measurement is performed while the sensor is placed on the arm for a few seconds. After the NIR sensor has measured the amount of optical interactance of the subcutaneous fat layers twice, the minicomputer calculates the total body fat on the basis of the following 6-term regression equation (1):

$$\text{Body fat (\%)} = K_0 + K_1 \times OD_1 + K_2 \times OD_2 + K_3$$
$$\times \text{Ht} + K_4 \times \text{Wt} + K_5 \times \text{age} + K_6 \times \text{sex} \quad (A1)$$

where Wt is weight, Ht is height, and K_0–K_6 are term coefficients. The OD (absorption) is the negative logarithm of the amount of infrared of the fat content underneath the skin, as measured with optical interactance. The NIR measurement of the fat content is based on the assumption that the concentration of any chemical constituent (including fat) is proportional to the optical absorption of that constituent, as it pertains to the near infrared spectrum (2, 3). The Futrex computer takes the difference between 2 ODs into account to eliminate the influence of pressure applied on the skin with the optical standard.

In our study, NIR measurement was done by placing the Futrex 6100 sensor on the nonaccess upper arm (arm that was not used for dialysis) of each dialysis patient for a few seconds after the individual data were logged into the computer. Patients were sitting in their dialysis chairs during the NIR measurement and no exercise was performed while being tested.

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