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Original Investigation

Effect of Age and Dialysis Vintage on Obesity Paradox in Long-term Hemodialysis Patients

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Background: In contrast to the general population, higher body mass index (BMI) is associated with greater survival in patients receiving hemodialysis (HD; "obesity paradox"). We hypothesized that this paradoxical association between BMI and death may be modified by age and dialysis vintage.

Study Design: Retrospective observational study using a large HD patient cohort.

Setting & Participants: 123,383 maintenance HD patients treated in DaVita dialysis clinics between July 1, 2001, and June 30, 2006, with follow-up through September 30, 2009.

Predictors: Age, dialysis vintage, and time-averaged BMI. Time-averaged BMI was divided into 6 subgroups; <18.5, 18.5-<23.0, 23.0-<25.0, 25.0-<30.0, 30.0-<35.0, and ≥35.0 kg/m^2. BMI category of 23-<25 kg/m^2 was used as the reference category.

Outcomes: All-cause, cardiovascular, and infection-related mortality.

Results: Mean BMI of study participants was 27 ± 7 kg/m^2. Time-averaged BMI was <18.5 and ≥35 kg/m^2 in 5% and 11% of patients, respectively. With progressively higher time-averaged BMI, there was progressively lower all-cause, cardiovascular, and infection-related mortality in patients younger than 65 years. In those 65 years or older, even though overweight/obese patients had lower mortality compared with underweight/normal-weight patients, sequential increases in time-averaged BMI > 25 kg/m^2 added no additional benefit. Based on dialysis vintage, incident HD patients had greater all-cause and cardiovascular survival benefit with a higher time-averaged BMI compared with the longer term HD patients.

Limitations: Causality cannot be determined, and residual confounding cannot be excluded given the observational study design.

Conclusions: Higher BMI is associated with lower death risk across all age and dialysis vintage groups. This benefit is more pronounced in incident HD patients and those younger than 65 years. Given the robustness of the survival advantage of higher BMI, examining interventions to maintain or even increase dry weight in HD patients irrespective of age and vintage are warranted.

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INDEX WORDS: Obesity-mortality paradox; hemodialysis; BMI; mortality risk; ESRD.

A higher body mass index (BMI) is associated with higher all-cause and cardiovascular mortality in the general population. In contrast, several epidemiologic studies in dialysis patients have demonstrated a paradoxically inverse association between obesity and mortality.[1-9] A similar reverse epidemiology of obesity in other populations with chronic disease states, including the geriatric population[10-12] and patients with heart failure, has been described.[13,14] However, differences in mortality between different age groups of dialysis patients based on BMI have not been well studied. Previous studies that have evaluated this question were limited by their relatively smaller sample size and have yielded mixed results.[15-17] A more recent study that exclusively investigated this question concluded that younger patients have a U-shaped association between mortality and BMI, whereas there was no demonstrable association between body size and mortality in older patients (aged ≥ 65 years).[18]

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Similarly, the effect of dialysis vintage on the association between BMI and mortality is unknown. Because one of the explanations for the obesity paradox in dialysis patients is the short-term survival benefit conferred by obesity, it would be expected that in patients with a longer dialysis vintage, the lower death risk with larger body size will be attenuated, if not completely reversed. The aforementioned questions have important clinical implications. The NKF-KDOQI (National Kidney Foundation–Kidney Disease Outcomes Quality Initiative) guidelines recommend BMI to be maintained above the 50th percentile for dialysis patients (BMI $>$ 23.6 and 24.0 kg/m^2 for men and women, respectively).[19] However, it currently is unclear whether the ideal BMI should vary by a patient's age and dialysis vintage. Therefore, we undertook this study to test the hypothesis that the obesity paradox exists across all age groups, but only in patients with shorter dialysis vintages.

METHODS

Data Source

This observational cohort study uses data from maintenance hemodialysis (HD) patients treated in DaVita facilities between July 1, 2001, and June 30, 2006, linked to that from the USRDS (US Renal Data System) with follow up through September 2009. Data from DaVita were used to determine patient's age, sex, diabetes, body weight, height, dialysis modality, and dialysis dose. The MEDEVID file from the USRDS contains data from CMS (Centers for Medicare & Medicaid Services) Medical Evidence Form 2728, which is completed for all new patients with end-stage renal disease in the United States and was used to determine the day of dialysis therapy initiation, race/ethnicity, marital status, primary insurance, and comorbid conditions (atherosclerotic heart disease, including ischemic heart disease, myocardial infarction, and cardiac arrest; other cardiac diseases, including pericarditis and cardiac arrhythmia; congestive heart failure; hypertension; cerebrovascular disease; peripheral vascular disease; chronic obstructive pulmonary disease; tobacco smoking; cancer; and HIV [human immunodeficiency virus]). The date and cause of death were obtained from the USRDS.

The initial study cohort consisted of 164,789 patients. Patients were assigned to the dialysis modality they were being treated with at the time of entry into the cohort. The following patients were excluded: patients treated with peritoneal dialysis (PD); those with missing data for dialysis modality; and those who died, underwent kidney transplantation, or were not followed up or recovered their kidney function by day 90 from dialysis therapy initiation (n = 26,433). From the entire HD cohort, patients younger than 18 years also were excluded (n = 286). Furthermore, patients with missing data for BMI (n = 9,040), age (n = 9), and dialysis vintage (n = 5,638) were excluded. Thus, the final cohort consisted of 123,383 HD patients. Table S1 (provided as online supplementary material) summarizes the differences in characteristics of HD patients older than 18 years who were included and excluded (those missing data for BMI, age, and dialysis vintage).

Post-HD dry weight for each patient during each calendar quarter was the average of up to 39 measured weight values at the end of each thrice-weekly HD treatment, measured in dialysis facilities using a standardized digital scale (Seca Digital Scale; Seca North America). These data were used to calculate the average BMI (in kg/m^2) in each calendar quarter. Time-averaged BMI for each individual patient was defined as the average BMI obtained from up to 33 calendar quarters. Dialysis vintage was defined as the time between the first day of dialysis treatment and the first day that the patient entered the study cohort. The first studied quarter for each patient was the first calendar quarter in which the patient's vintage was longer than 90 days. Dialysis dose was measured by single-pool Kt/V using urea kinetic modeling equations.

All blood samples were shipped to a single central DaVita laboratory in Deland, FL. Quarterly averages were calculated for each laboratory variable using all measurements made during that 3-month period. Subjects were divided a priori into 6 categories based on time-averaged BMI (<18.5, 18.5-<23.0, 23.0-<25.0, 25.0-<30.0, 30.0-<35.0, and ≥35.0 kg/m^2).

Statistical Methods

Complete data were available for sex and diabetes. Missing data were as follows: for comorbid conditions (other than HIV), 4%; HIV status, 49%; race, 1%; insurance status, 8%; marital status and parathyroid hormone level, 19% each; and serum albumin, total iron-binding capacity, ferritin, creatinine, calcium, phosphorus, alkaline phosphatase, hemoglobin, white blood cell count, lymphocyte percentage, and normalized protein catabolic rate values, 8%-11% of the cohort. Missing data were imputed using a multiple imputation method. Data for all-cause mortality were available until only 2007.

Data are summarized as mean ± standard deviation, median (interquartile range), and proportion as appropriate. Survival analyses using Cox proportional hazard regression was performed to determine the relationships between time-averaged BMI with all-cause, cardiovascular, and infection-related mortality in: (1) the entire cohort of HD patients, (2) the cohort of HD patients categorized by age (<18, 18-<45, 45-<65, 65-<70, 70-<75, and ≥75 years), and (3) the cohort of HD patients categorized by dialysis vintage (<6 months, 6 months to <2 years, 2-<5 years, and ≥5 years). Time-averaged BMI of 23-<25 kg/m^2 was used as the reference category because the NKF-KDOQI guidelines recommend that BMI of maintenance dialysis patients be maintained to at least 23.6 and 24.0 kg/m^2 for men and women, respectively.[19] For each regression analysis, 3 levels of adjustment were examined: (1) unadjusted model that included only mortality data and time-averaged BMI; (2) case-mix–adjusted model that included variables in the unadjusted model along with sex, race/ethnicity (whites, blacks, Hispanics, and others), dialysis dose, presence of diabetes, comorbid conditions, smoking status, primary insurance status (Medicare, Medicaid, private, and others), and marital status (divorced, married, single, and other); and (3) case-mix– and laboratory data–adjusted model that included serum total iron-binding capacity, ferritin, creatinine, calcium, phosphorus, alkaline phosphatase, parathyroid hormone, albumin, bicarbonate, white blood cell count, lymphocyte percentage, hemoglobin, dialysis dose, and normalized protein catabolic rate values as additional covariates. The analyses were carried out using STATA, version 11.2 (StataCorp LP). Sigma plot graphs were used as data analyses strategies to illustrate the relationship between BMI and mortality in different age and dialysis vintage groups. Another set of analyses was carried out to model the longitudinal BMI values and time to event jointly using a joint model approach. This analysis was carried out using STATA, version 12. The study was approved by the Institutional Review Board of Los Angeles Biomedical Research Institute at Harbor–University of California Los Angeles as exempt from informed consent.

RESULTS

Patient Characteristics

Baseline characteristics of the cohort, stratified by different levels of time-averaged BMI, are summarized in Table 1. Although most patients were incident HD