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Influence of Body Mass Index on the Association of Weight Changes with Mortality in Hemodialysis Patients

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Summary

Background and Objectives A high body mass index (BMI) is associated with lower mortality in patients undergoing hemodialysis. Short-term weight gains and losses are also related to lower and higher mortality risk, respectively. The implications of weight gain or loss may, however, differ between obese individuals and their nonobese counterparts.

Design, Setting, Participants, & Measurements The Current Management of Secondary Hyperparathyroidism: A Multicenter Observational Study (COSMOS) is an observational study including 6797 European hemodialysis patients recruited between February 2005 and July 2007, with prospective data collection every 6 months for 3 years. Time-dependent Cox proportional hazard regressions assessed the effect of BMI and weight changes on mortality. Analyses were performed after patient stratification according to their starting BMI.

Results Among 6296 patients with complete data, 1643 died. At study entry, 42% of patients had a normal weight (BMI, 20–25 kg/m²), 11% were underweight, 31% were overweight, and 16% were obese (BMI ≥30 kg/m²). Weight loss or gain (<1% or >1% of body weight) was strongly associated with higher rates of mortality or survival, respectively. After stratification by BMI categories, this was true in nonobese categories and especially in underweight patients. In obese patients, however, the association between weight loss and mortality was attenuated (hazard ratio, 1.28 [95% confidence interval (CI), 0.74 to 2.14]), and no survival benefit of gaining weight was seen (hazard ratio, 0.98 [95% CI, 0.59 to 1.62]).

Conclusions Assuming that these weight changes were unintentional, our study brings attention to rapid weight variations as a clinical sign of health monitoring in hemodialysis patients. In addition, a patient's BMI modifies the strength of the association between weight changes with mortality.

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Introduction

Protein-energy wasting (PEW) is a common phenomenon in patients undergoing dialysis and a risk factor for poor clinical outcomes, including worse quality of life, increased hospitalizations, and mortality (1). The paradoxical association between traditional cardiovascular risk factors and better outcomes in dialysis patients probably reflects the powerful effect-modifying impact of PEW in this population (2,3). Such is the case of the “obesity paradox,” whereby a high body mass index (BMI) has been associated with longer survival in many (4–15) but not all (16–18) studies of dialysis patients. Although there are various hypotheses for this paradoxical disconnect, the most likely explanation is that dialysis patients are at such high risk of PEW that excess weight provides a measure of protection (15,19). Likewise, body weight losses have been associated with increased mortality, whereas weight gains have been associated with longer survival

(14,15,20). These associations are even stronger when weight changes are accompanied by concomitant changes in muscle mass (21).

Altogether, such data have created some uncertainty regarding how to handle obese dialysis patients (22,23), and, for some, these data suggest that nephrologists need to not only preserve body weight in dialysis patients but also promote weight gains, targeting both skeletal muscle and fat mass (24). It is plausible that obese patients undergoing hemodialysis (HD) may benefit differently (even oppositely) from these weight changes compared with normal-weight or overweight patients. This is important because obesity is associated with relevant metabolic complications (25,26) and is used by many transplant programs to determine the eligibility of dialysis patients for renal transplantation (27). It is fairly well established that BMI is a less accurate measure of adiposity than are other metrics of obesity, such as

Due to the number of contributing authors, the affiliations are provided in the Supplemental Material.

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waist circumference and waist-to-hip ratio, both in the general population and in dialysis patients (28). However, BMI still remains the most easily applicable measure of body build, and it is routinely assessed in most clinics. BMI nevertheless provides valuable information on the global nutritional status, including both muscle mass and fat mass (28). This study tested the hypothesis that the effect of body weight changes on patient survival is influenced by the patient's starting BMI, here taken as a global metric of nutritional status.

Materials and Methods

Study Population

The Current Management of Secondary Hyperparathyroidism: A Multicenter Observational Study (COSMOS) is a multicenter, prospective, open cohort study with 3 years of follow-up that included patients undergoing maintenance HD from 227 facilities in 20 European countries. The original aim of the cohort was to survey mineral and bone disturbances and related clinical practice patterns. Patients and facilities were randomly selected among a complete list of hospital and satellite dialysis centers from the 20 participating countries. The number of patients recruited in each country was proportional to its dialysis population, and each center was expected to recruit 20 patients. COSMOS initially recruited 4500 patients and monitored them with data collections every 6 months for up to 3 years. Patients who died or left the study for other reasons (renal transplantation, change to a non-COSMOS facility, or switch to peritoneal dialysis) during that period were replaced by 2297 new patients, totaling 6797. Recruitment took place between February 2005 and July 2007, and follow-up ended in July 2010. Study design and random recruitment characteristics have been described in detail elsewhere (29–31). The institutional review boards of the participating centers approved the study, and patients provided informed consent for study participation.

Demographic, Clinical, and Laboratory Data

Data on age, sex, height, post-HD dry weight, smoking (never, former, or current smoker), diabetes mellitus, primary kidney disease, cardiovascular disease, country, type of facility (public or private), and HD-related variables (vintage, modality, and hours per week) were collected when the patients entered the study. Data on dry weight, HD modality, and hours per week were collected every 6 months during the 3-year observation period. According to protocol design, dry weight was defined as the body weight measured immediately after the hemodialysis session. Laboratory values of hemoglobin, parathyroid hormone, calcium, and phosphate were measured monthly by standardized methods and collected from routine clinical practice. In conjunction with the clinical data, the 6-month average of laboratory measurements was calculated at every patient visit.

Survival Analyses

Patients were followed for survival for up to 3 years since recruitment. Patients were censored if they underwent renal transplantation ($n=648$), were lost to follow-up (*i.e.*, moved to a non-COSMOS facility) ($n=242$), switched to

peritoneal dialysis ($n=24$), or ended the study, whichever happened first. During this follow-up, 1643 patients died and causes of death were collected from medical records.

Statistical Analyses

Categorical variables are presented as percentages and continuous variables as mean \pm SD or median (interquartile range), where appropriate. BMI was calculated as dry weight in kilograms divided by the square of height in meters. BMI was analyzed as a continuous variable and after stratification by BMI categories. According to the World Health Organization guidelines, obesity was defined as a BMI ≥ 30 kg/m² and overweight as a BMI of 25–29 kg/m² (32). We defined normal weight as a BMI of 20–24 kg/m², which is within the normal range according to the World Health Organization, and underweight as a BMI < 20 kg/m². Normal weight was used as the reference category. Dry weight changes during a 6-month period were calculated according to the difference between consecutive dry weight values, expressed as a percentage. Weight change was defined as follows: weight loss (decreases $< 1\%$), weight gain (increases $> 1\%$), and stable dry weight (dry weight changes of $< \pm 1\%$ from initial body weight). Stable dry weight was considered the reference category.

Time-dependent Cox proportional hazards regressions were used to assess the effect of BMI and of dry weight changes on all-cause mortality, using 6-month study visits. Outcomes were also assessed in different strata separately. For each analysis, we applied two different models of multivariate adjustment: (1) Multivariate model 1 adjusted for age, sex, smoking, country, type of center (public or private), and primary kidney disease, and (2) multivariate model 2 included the previous covariates plus diabetes, dialysis vintage, and parathyroid hormone. All covariates were considered time-dependent except for sex, smoking, diabetes mellitus, country, type of HD center, and primary kidney disease. Data preceding death were ignored to avoid reverse causality. To evaluate the interaction between BMI and dry weight change on mortality, the product term BMI \times dry weight change was introduced in the models described previously. Survival data are expressed as hazard ratio (HR) and 95% confidence intervals (CIs).

A chi-squared test was used to evaluate differences in causes of death across BMI categories. Restricted cubic spline graphs were used to graphically evaluate systematic relationships between body weight changes and mortality, depicting the body weight changes occurring during the first 6 months of inclusion in the study. Statistical significance was set at the level of $P < 0.05$. All statistical analyses were performed using Stata software, version 12.1 (Stata Corp., College Station, TX).

Results

The COSMOS cohort recruited 6797 patients undergoing HD. Follow-up data for 485 patients (7.1%) were not available, and no information on BMI was available for 16 patients. The present analysis was therefore performed on the remaining 6296 patients. Most of them (94.5%) had undergone HD for at least 3 months. The median time of permanence in the study was 24 (interquartile range, 12–36)

months. Table 1 presents the most relevant baseline patient characteristics at the start of COSMOS and according to BMI categories. At study entry, 690 (11%) of patients were underweight (BMI < 20 kg/m²), 1955 (31%) were overweight (BMI, 25–29 kg/m²), 987 (15.7%) were obese (BMI ≥30 kg/m²), and 2664 (42.3%) had a normal weight (BMI, 20–24 kg/m²).

BMI and Mortality

During follow-up, 1643 patients died. Table 2 shows the results of Cox proportional hazards models with BMI as a time-varying predictor of all-cause mortality. Using BMI as a continuous variable, we observed an 8% longer survival in fully adjusted models (HR, 0.92 [95% CI, 0.91 to 0.94] per kg/m²). At a second step, patients were stratified by their BMI categories. Whereas underweight patients had an increased mortality risk, overweight and obese patients showed the opposite trend in both crude and adjusted models (Table 2). Table 3 shows the causes of

death in these patients. Cardiovascular conditions were more often the cause of death across increasing BMI categories, and noncardiovascular causes of death were proportionally higher in underweight patients.

Dry Weight Changes and Mortality

Figure 1 illustrates the association between percentage body weight change (as a continuous variable) and mortality during the first 6 months in the study: Patients undergoing a dry weight loss are associated with an increased mortality risk. Survival was longer for patients undergoing a 6-month dry weight gain. These results were confirmed in time-dependent Cox analyses using the stratification of body weight changes of <1% or >1% of body weight, and the associations remained similar across different strata (Figure 2).

We hypothesized that the association between body weight changes and mortality would depend on the patient's starting BMI. In models including both BMI

Table 1. Baseline patients' characteristics according to body mass index categories

| Characteristic | All Patients (n=6296) | Body Mass Index | | | |
|--------------------------------------|--------------------------|----------------------------------|---------------------------------------|---------------------------------------|----------------------------------|
| | | <20 kg/m ² (n=690) | 20–24.9 kg/m ² (n=2664) | 25–29.9 kg/m ² (n=1955) | ≥30 kg/m ² (n=987) |
| Age (yr) | 64±14 | 61±18 | 64±15 | 65±13 | 63±12 |
| Men (%) | 61 | 47 | 64 | 65 | 53 |
| Body mass index (kg/m ²) | 25.3±4.9 | 18.4±1.3 | 22.6±1.4 | 27.1±1.4 | 33.8±3.8 |
| Diabetes mellitus (%) | 31 | 15 | 24 | 35 | 53 |
| Cardiovascular disease (%) | 72 | 67 | 71 | 74 | 74 |
| Smokers (%) | | | | | |
| Current | 17 | 24 | 18 | 15 | 11 |
| Former | 19 | 11 | 20 | 20 | 20 |
| Never | 64 | 65 | 62 | 65 | 69 |
| Primary kidney disease (%) | | | | | |
| Diabetes mellitus | 21 | 9 | 17 | 24 | 36 |
| Hypertension | 20 | 21 | 19 | 23 | 17 |
| GN | 17 | 24 | 20 | 14 | 12 |
| Obstructive/interstitial | 12 | 12 | 12 | 11 | 11 |
| Polycystic kidney disease | 8 | 8 | 9 | 8 | 7 |
| Tumors | 2 | 2 | 2 | 1 | 2 |
| Unknown | 12 | 13 | 12 | 12 | 9 |
| Other | 8 | 11 | 9 | 7 | 6 |
| Vintage (mo) | 20 (8–51) | 26 (8–67) | 22 (8–57) | 19 (8–47) | 16 (7–40) |
| Hemodialysis modality (%) | | | | | |
| Conventional low-flux | 54 | 59 | 54 | 54 | 51 |
| Conventional high-flux | 37 | 33 | 37 | 37 | 39 |
| Other | 9 | 7 | 9 | 9 | 10 |
| Hemodialysis hours per week (%) | | | | | |
| <12 | 21 | 28 | 22 | 20 | 15 |
| 12 | 55 | 56 | 57 | 55 | 51 |
| >12 | 24 | 16 | 21 | 25 | 34 |
| Parathyroid hormone (pg/ml) | 211 (108–376) | 188 (99–363) | 201 (102–362) | 214 (111–383) | 242 (132–422) |
| Calcium (mg/dl) | 9.1±0.7 | 9.1±0.7 | 9.1±0.8 | 9.1±0.7 | 9±0.7 |
| Phosphate (mg/dl) | 5.4±1.4 | 5.2±1.4 | 5.2±1.4 | 5.5±1.4 | 5.6±1.5 |
| Hemoglobin (g/dl) | 11.2±2.1 | 11.2±1.9 | 11.2±2.1 | 11.3±2.0 | 11.3±2.0 |

Categorical data are shown as percentage; continuous data are shown as mean ± SD, except for parathyroid hormone and vintage, which are shown as median and interquartile range (25th and 75th percentiles).

Table 2. Time-dependent associations (every 6 months) between body mass index and all-cause mortality in 6296 hemodialysis patients

| Variable | Hazard Ratio (95% Confidence Interval) | | |
|--|--|----------------------|----------------------|
| | Crude | Model 1 ^a | Model 2 ^b |
| In all patients | | | |
| BMI (per kg/m ²) | 0.93 (0.92 to 0.94) | 0.92 (0.91 to 0.93) | 0.92 (0.90 to 0.93) |
| After stratification by BMI categories | | | |
| BMI <20 kg/m ² | 1.92 (1.69 to 2.19) | 2.12 (1.86 to 2.41) | 2.13 (1.81 to 2.53) |
| BMI 20–24 kg/m ² | 1 | 1 | 1 |
| BMI 25–29 kg/m ² | 0.72 (0.63 to 0.82) | 0.67 (0.59 to 0.76) | 0.65 (0.55 to 0.77) |
| BMI ≥30 kg/m ² | 0.64 (0.54 to 0.76) | 0.62 (0.57 to 0.75) | 0.58 (0.45 to 0.73) |

Represented are crude and adjusted hazard ratios and 95% confidence intervals for all-cause mortality using time-dependent Cox regression analyses every 6 months and during 3 years of follow-up. Analyses contemplated repeated BMI assessments at each study visit or BMI categories at each study visit. BMI, body mass index.

^aModel 1 includes multivariate adjustment for age, sex, smoking, country, type of center (public or private), and primary kidney disease.

^bModel 2 includes multivariate adjustment of the variables included in model 1 plus diabetes, dialysis vintage, and parathyroid hormone.

Table 3. Causes of death during 3 years of follow-up in 6296 hemodialysis patients according to baseline body mass index categories

| Body Mass Index | Cardiovascular, <i>n</i> (%) | Noncardiovascular, <i>n</i> (%) | Unknown, <i>n</i> (%) | Chi-Squared <i>P</i> Value |
|-------------------------|------------------------------|---------------------------------|-----------------------|----------------------------|
| <20 kg/m ² | 79 (34) | 118 (52) | 33 (14) | 0.01 |
| 20–24 kg/m ² | 312 (43) | 329 (46) | 78 (11) | |
| 25–29 kg/m ² | 220 (47) | 190 (41) | 56 (12) | |
| ≥30 kg/m ² | 113 (50) | 89 (39) | 26 (11) | |

and body weight change, a significant interaction for the product term BMI × dry weight change was observed (*P* for interaction = 0.007). Figure 3 shows survival associated with body weight changes after stratification by starting BMI. Weight losses were significantly associated with increased mortality risk across all BMI categories except for in obese individuals, who showed non-statistically significant but still increased hazards (fully adjusted HR, 1.28 [95% CI, 0.74 to 2.14]). Weight gains were significantly associated with lower mortality risk across all BMI categories except for in obese individuals, who showed no association or trend (fully adjusted HR, 0.98 [95% CI, 0.59 to 1.62]). The strongest effect of body weight changes on outcome was observed in underweight patients, and a trend toward weaker associations was observed with increasing BMI categories. No relevant differences in causes of death were observed among these groups (data not shown). Figure 4 illustrates the association between percentage body weight change (as a continuous variable) and mortality during the first 6 months in the study in each BMI category. The association is maximized in underweight patients and gradually flattens as BMI category increases. The results of Figure 3 and 4 are not exclusive; in Figure 3 we analyze all available patient visits during follow-up. In Figure 4 we analyze only

body weight changes occurring during the first 6 months of inclusion in the study.

Discussion

In the COSMOS cohort, which is representative of the European HD population, we report that dry weight loss or gain during a 6-month period was associated with higher rates of mortality or survival, respectively. We expanded this knowledge by demonstrating that starting BMI modifies the survival associated with these body weight changes. Body weight changes during a 6-month period may have important outcome associations, especially in underweight patients, and to a lesser extent in normal-weight and overweight patients. Obese individuals gaining body weight showed no association with mortality, and the mortality risk associated with body weight loss was attenuated.

In 2006, Kramer *et al.* (33) reported a progressive increase in the incidence and prevalence of obesity in dialysis patients, outpacing that of the general United States population; most dialysis patients in the United States were overweight (28%) or obese (25%), and only 29.4% had a normal weight. This is in keeping with other large contemporary dialysis cohort studies in the United States (12,13,21), in which the rate of obesity ranged between

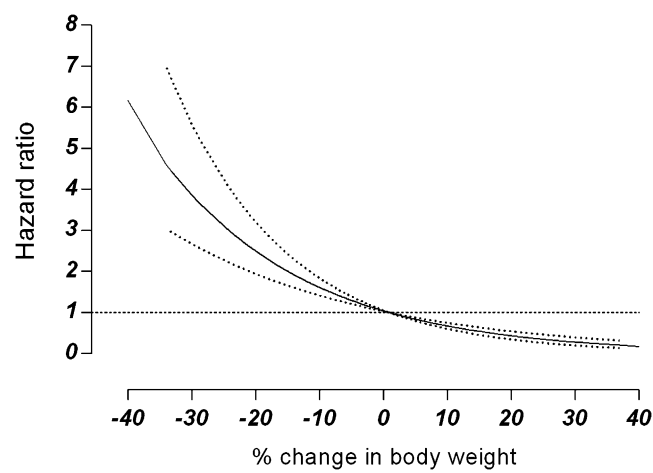


Figure 1. | Restricted spline curve showing the fully adjusted hazard ratios and 95% confidence intervals (dashed lines) for mortality associated with body weight changes (in percentage) in 6296 hemodialysis patients and during the first 6 months of inclusion in the study. The model is plotted as restricted cubic splines with five knots. Adjusted hazard ratios are those achieved after controlling for age, sex, smoking, country, type of center (public or private), primary kidney disease, diabetes, dialysis vintage, and parathyroid hormone.

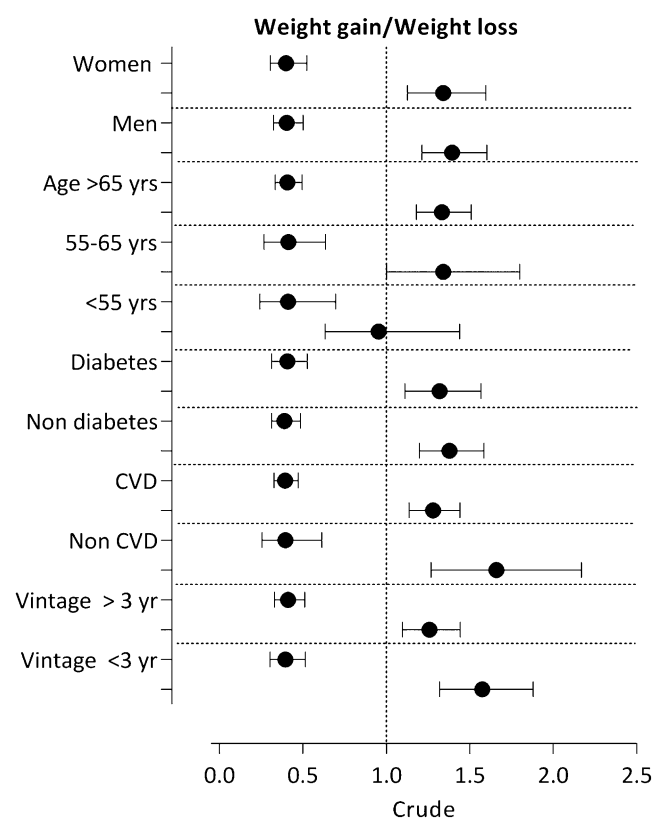


Figure 2. | Crude time-dependent associations between 6-month changes in dry weight and all-cause mortality in different patient strata and according to the loss or gain of body weight. Stable weight was used as the reference group. Represented are hazard ratios and 95% confidence intervals. Body weight gains and losses were defined as >1% of initial body weight. CVD, cardiovascular disease.

22% and 25% and class II obesity represented up to 11% of patients. Such high prevalence contrasts with our data from Europe, as 42% of the HD patients included in COSMOS fall within the normal weight range, and only 16% were obese (just 4% had class II obesity). Similar proportions have been reported in dialysis cohorts from The Netherlands (34) and Italy (35) and a multinational French, Italian, and Portuguese cohort (14). Altogether, this suggests a disparity in the burden of obesity between the United States and Europe.

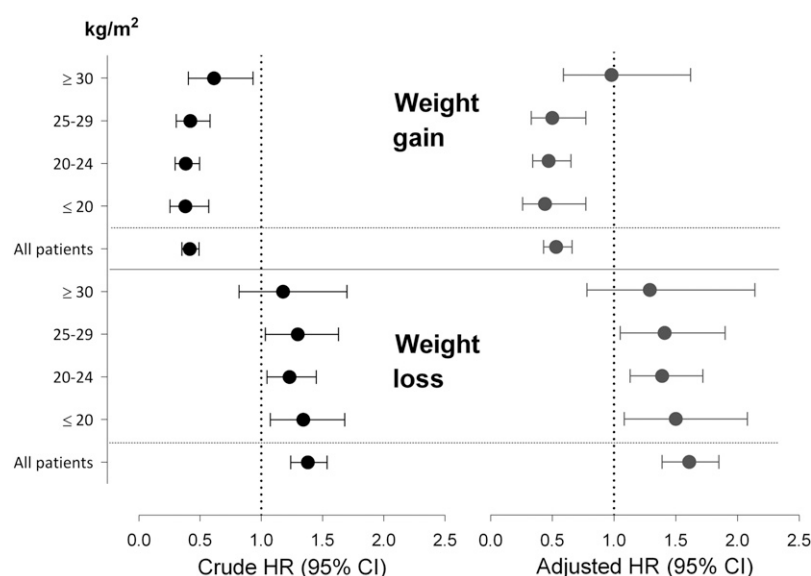


Figure 3. | Crude and fully adjusted time-dependent associations between dry body weight losses or gains during a 6-month period and mortality in 6296 hemodialysis patients and after stratification by body mass index categories. Stable weight was used as the reference group. Body weight gains and losses were defined as $>1\%$ of initial body weight. Adjusted hazard ratios (HRs) are those achieved after controlling for age, sex, smoking, country, type of center (public or private), primary kidney disease, diabetes, dialysis vintage, and parathyroid hormone.

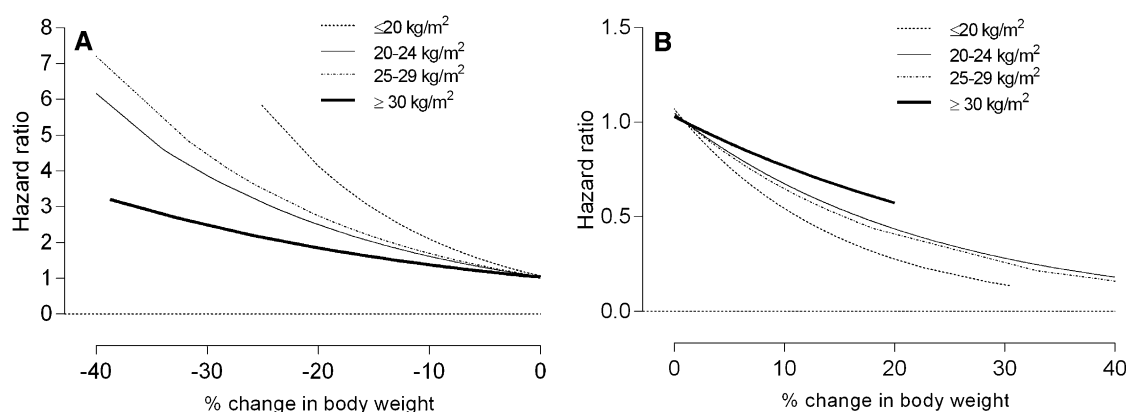


Figure 4. | Restricted spline curves showing the fully adjusted hazard ratios for mortality associated with body weight changes (in percentage) in 6296 hemodialysis patients and during the first 6 months of inclusion in the study. Analyses are performed in each body mass index strata separately and divided into two panels, according to body weight losses (A) or gains (B). The models are plotted as restricted cubic splines with five knots. Adjusted hazard ratios are those achieved after controlling for age, sex, smoking, country, type of center (public or private), primary kidney disease, diabetes, dialysis vintage, and parathyroid hormone.

Notwithstanding this difference, our results clearly confirm the presence of the obesity paradox, whereby underweight was associated with a higher 3-year mortality risk and overweight/obesity had a survival benefit. Several hypotheses have been proposed to explain the obesity paradox, including differences in duration of follow-up and age (18) or survivor bias (2). The most accepted explanation is that in the short term the catabolism induced by PEW surpasses the risk that obesity *per se* poses in the long-term. Obesity would confer, via increased adiposity and muscle stores, a nutritional reserve that allows a longer resistance to the short-term catabolic effects of PEW (10,12,36). Such explanation is indirectly supported by our observation that causes of death vary among the different

BMI categories: While underweight patients were more prone to die of noncardiovascular causes (including wasting and septicemia), obese patients more often died of cardiovascular events, emphasizing the metabolic risk associated with obesity (25). Recently, Flegal *et al.* (37) performed a meta-analysis of the association between BMI categories with all-cause mortality at a general population level. Results demonstrated that the increased mortality hazards of obese versus normal-weight individuals were restricted to obesity class II (BMI, 35–40 kg/m²) and class III (BMI >40 kg/m²), but not class I (BMI 30–35 kg/m²). Furthermore, overweight was associated with lower mortality rates compared with normal-weight individuals. Altogether, we may be facing a paradigm

shift on the importance of moderately high adiposity for survival.

In agreement with two previous United States studies in prevalent patients (15,21), short-term dry weight losses were associated with higher mortality risk in this study, whereas weight gains were associated with better outcomes. By contrast, in a large population of incident dialysis patients from southern Europe (14), only severe weight losses ($>5.8\%$) were associated with outcome; mild losses and weight gains were not. Unintentional weight loss in prevalent patients may be interpreted mainly as progressive malnutrition, whereas weight loss in incident patients due to fluid removal secondary to extracellular volume accumulation in the predialysis period may interfere with the interpretation of body weight changes at the initiation of dialysis therapy (38,39).

A novel finding in our study is that the patient's starting BMI influences the effect of weight changes on mortality. Weight gains were associated with better outcomes in all BMI groups considered except in obese patients, in whom no benefit was observed. These results contradict the hypothesis that body weight gains in overweight/obese individuals, as categorized according to BMI, may represent a mortality risk factor by virtue of enhancing the metabolic alterations associated with obesity (cardiovascular disease, atherosclerosis, diabetes, or inflammation, among others) (25). A potential explanation lies in the fact that life expectancy of dialysis patients is short (5 years in the case of a 60-year-old dialysis patient), particularly so in patients with normal or low body mass, who are more easily affected by PEW than by excessive fatness.

BMI has several weaknesses as a metric of body fat in patients with CKD because it encompasses both lean and fat mass; therefore, the diagnosis of obesity by BMI in these patients is influenced by determinants of muscle mass (such as age, sex, ethnicity, and frailty) and fluid retention (28,40). Indeed, the relationships between waist circumference and BMI with the risk of death are opposing ones (35,41). Weight changes, however, indicate modifications in body composition. Thus, an interesting observation in our study is the increased mortality risk associated with weight losses in nonobese patients. Most likely, short-term weight loss is a measure of progressive deterioration in health status (losses of both fat and muscle), and it is uncertain whether it may represent a modifiable risk factor. The association between weight losses and mortality is not so apparent in obese patients, probably because of larger stores to stand against the wasting process. However, we must emphasize that although not statistically significant, hazards were increased, and any kind of unintentional weight loss should be carefully monitored. Expanding on previous reports (14,15), these results suggest that short-term body weight losses may give relevant clinical insight into a patient's risk profile and should represent a call for appropriate corrective measures. Nevertheless, although nutritional support may effectively increase body weight and improve other nutritional biomarkers in dialysis patients (19), clinical trials have not yet shown that targeting body weight improves the survival of HD patients. Given the bulk of evidence accumulated since the first description of the obesity paradox (2), the need for these clinical trials is well justified.

Our findings need to be interpreted with consideration of additional strengths and limitations. Strengths include its contemporary nature; the prospective and careful design of the cohort, including their random recruitment; the completeness of data; and the use of time-dependent models for examining repeated measurements every 6 months. Its large sample size and representativeness of the European HD population, together with the adjustment for potential confounders, are also strengths.

Limitations of the study include the observational nature, the ancillary nature of the analysis, and lack of information on race or additional surrogates of muscle and fat stores. In addition, we lack information on the intentionality of these body weight gains or losses. Given the short time frame studied (6-month periods) and the absence of consensus guidelines on this issue, we are assuming them to be unintentional. As in all observational cohort studies, residual confounding may have played a role. Finally, the predominantly prevalent nature of the HD patients included makes the study vulnerable to survivor bias despite adjustment for dialysis vintage.

In summary, patient BMI influences the benefits and detriments associated with short-term body weight changes. Changes of $>1\%$ during a 6-month period showed strong associations with the mortality and survival of underweight, normal-weight, and overweight HD patients. This finding contrasts with the nonsignificant or null mortality association observed in obese patients losing or gaining body weight, respectively. From a clinical point of view, and assuming these changes were unintentional, this study brings overall attention to rapid weight losses in HD patients, which are probably a clinical sign of progressive deterioration of health status or underlying protein-energy wasting. These results should not, however, be extrapolated to weight loss as a result of controlled or programmed body weight changes by lifestyle or surgical interventions.

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Disclosures

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