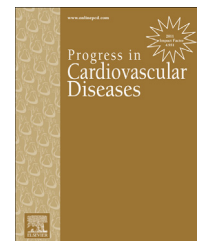


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## Obesity Paradox in End-Stage Kidney Disease Patients

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### ABSTRACT

In the general population, obesity is associated with increased cardiovascular risk and decreased survival. In patients with end-stage renal disease (ESRD), however, an “obesity paradox” or “reverse epidemiology” (to include lipid and hypertension paradoxes) has been consistently reported, i.e. a higher body mass index (BMI) is paradoxically associated with better survival. This survival advantage of large body size is relatively consistent for hemodialysis patients across racial and regional differences, although published results are mixed for peritoneal dialysis patients. Recent data indicate that both higher skeletal muscle mass and increased total body fat are protective, although there are mixed data on visceral (intra-abdominal) fat. The obesity paradox in ESRD is unlikely to be due to residual confounding alone and has biologic plausibility. Possible causes of the obesity paradox include protein-energy wasting and inflammation, time discrepancy among competitive risk factors (undernutrition versus overnutrition), hemodynamic stability, alteration of circulatory cytokines, sequestration of uremic toxin in adipose tissue, and endotoxin-lipoprotein interaction. The obesity paradox may have significant clinical implications in the management of ESRD patients especially if obese dialysis patients are forced to lose weight upon transplant wait-listing. Well-designed studies exploring the causes and consequences of the reverse epidemiology of cardiovascular risk factors, including the obesity paradox, among ESRD patients could provide more information on mechanisms. These could include controlled trials of nutritional and pharmacologic interventions to examine whether gain in lean body mass or even body fat can improve survival and quality of life in these patients.

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Patients with end-stage renal disease (ESRD) who receive maintenance dialysis therapy have a significantly higher mortality rate (about 20% per year in the United States and

10–15% in Europe), primarily due to cardiovascular disease (CVD).<sup>1,2</sup> Based on extrapolation of findings from the general population, treatment to reduce CVD morbidity and mortality

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### Abbreviations and Acronyms

BMI = body mass index

CKD = chronic kidney disease

CVD = cardiovascular diseases

ESRD = end-stage renal disease

HD = hemodialysis

PEW = protein energy wasting

PD = peritoneal dialysis

has focused on conventional risk factors, such as obesity, hypertension and hypercholesterolemia.

However, survival has not improved substantially in the past 3 decades. Additional efforts have targeted other possible correlates of the high mortality associated with

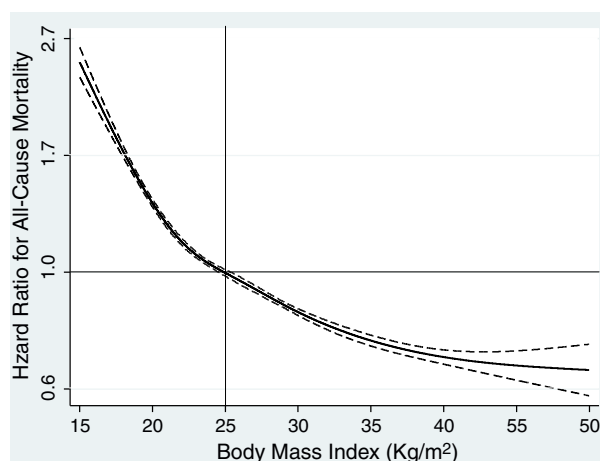
ESRD, such as anemia or dialysis dose. However, large clinical trials have failed to show any survival advantages of normalization of hemoglobin level<sup>3</sup> or increasing dialysis dose in hemodialysis (HD)<sup>4</sup> and peritoneal dialysis (PD).<sup>5</sup>

A number of epidemiologic studies with large samples of ESRD patients have indicated paradoxically inverse associations between classic risk factors for CVD and mortality.<sup>6</sup> In terms of obesity, worse survival has been observed with a lower body mass index (BMI), and findings have also indicated that higher values of BMI reflecting overweight or obesity seemed to be associated with better survival (Fig 1). This phenomenon has been referred to as the obesity paradox. This term may not necessarily mean that the principles of vascular pathophysiology are different in ESRD patients compared to the general population but may indicate that there are other superimposed and more dominant factors that overwhelm the traditional relation between obesity and outcomes as seen in the general population.

A better understanding of the phenomenon of the obesity paradox in ESRD patients may help improve the poor outcomes in this population. In addition to earlier observations, recent studies have indicated the presence of the obesity paradox in contemporary cohorts across different races and geographic regions. In this article, the inverse association of BMI and mortality in ESRD patients and several hypotheses to it are reviewed. The distinct effects of dialysis modalities (HD versus PD) on nutritional parameters, and studies conducted exclusively in PD patients were summarized separately.

## Body size and mortality in HD patients

HD patients appear to have a lower BMI than age- and sex-matched control subjects from the general population.<sup>7</sup> In a matched analysis comparing the lipid profiles of 285 HD patients with those of 285 non-ESRD patients matched in a one-to-one fashion on age, sex, race, and diabetes, BMI was found to be significantly lower in the HD patients than in the control subjects ( $26.2 \pm 6.0$  compared with  $31.5 \pm 7.8$  kg/m<sup>2</sup>,  $P < 0.001$ ).<sup>8</sup> A lower BMI was consistently found to be a strong predictor of increased mortality. Unlike the general population, however, a higher BMI (overweight or obesity) was generally not associated with an increase in mortality risk.<sup>9–19</sup> In spite of recent advances in HD techniques and drug therapies, this phenomenon remains present in virtually all large contemporary cohorts.<sup>20–29</sup> Most studies have shown that the inverse association between BMI and mortality in HD



**Fig 1 – Association of baseline BMI with mortality in 121,762 US HD patients over 5 years (July 2001–June 2006). The y-axis shows the hazard ratio for all-cause mortality over 5 years based on the spline model (log scale), adjusted for age, sex, DM, dialysis vintage, primary insurance, marital status, dialysis dose, residual renal function, hemoglobin, serum albumin, transferrin, ferritin, calcium, phosphorus, bicarbonate, peripheral white blood cell count, lymphocyte percentage, and daily protein intake. Dashed lines are 95% point-wise confidence bands.**

patients is independent of demographics, co-morbidities and other nutritional markers, although because of methodological differences, only limited comparisons can be made. Important epidemiologic studies are summarized in Table 1. These clinical studies all take into account the clinical characteristics of the patients.

The first report came from the Diaphane collaborative study in France, which reported a paradoxical observation of a lack of increase in mortality with high BMI in HD patients.<sup>9</sup> This study included a cohort of 1,453 younger, mostly non-diabetic French HD patients followed between 1972 and 1978 in 33 French dialysis units. Leavey et al.<sup>10</sup> confirmed the lack of association between higher BMI values and increased mortality risk in a national sample of 3,607 HD patients in the United States Renal Data System (USRDS). The mean BMI was  $24.4 \pm 5.3$  kg/m<sup>2</sup> in this study. Low BMI was independently and significantly predictive of increased mortality. With the use of time-varying effect models, it was observed that the greatest predictive value of BMI occurred early during the follow-up period but its independent predictive ability for mortality risk persisted even 5 years later. No significant interactions were identified between BMI and other demographic, co-morbid conditions or laboratory variables. Fleischmann et al.<sup>11</sup> reported higher survival rates for overweight and obese HD patients ( $BMI \geq 27.5$  kg/m<sup>2</sup>) than for patients with a normal BMI of 20.0 to  $<27.5$  kg/m<sup>2</sup>. This suggested for the first time that obesity might be protective in this population. The result also showed that for every unit increase in BMI, the relative risk of mortality was reduced by 10%.

Thereafter, the obesity paradox was replicated in various large, nationally representative or international cohorts. Kopple et al.<sup>12</sup> evaluated 12,965 HD patients and found that

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