

# The Obesity Paradox in Kidney Disease: How to Reconcile It With Obesity Management



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Obesity, a risk factor for *de novo* chronic kidney disease (CKD), confers survival advantages in advanced CKD. This so-called obesity paradox is the archetype of the reverse epidemiology of cardiovascular risks, in addition to the lipid, blood pressure, adiponectin, homocysteine, and uric acid paradoxes. These paradoxical phenomena are in sharp contradistinction to the known epidemiology of cardiovascular risks in the general population. In addition to advanced CKD, the obesity paradox has also been observed in heart failure, chronic obstructive lung disease, liver cirrhosis, and metastatic cancer, as well as in elderly individuals. These are populations in whom protein–energy wasting and inflammation are strong predictors of early death. Both larger muscle mass and higher body fat provide longevity in these patients, whereas thinner body habitus and weight loss are associated with higher mortality. Muscle mass appears to be superior to body fat in conferring an even greater survival. The obesity paradox may be the result of a time discrepancy between competing risk factors, that is, overnutrition as the long-term killer versus undernutrition as the short-term killer. Hemodynamic stability of obesity, lipoprotein defense against circulating endotoxins, protective cytokine profiles, toxin sequestration of fat mass, and antioxidation of muscle may play important roles. Despite claims that the obesity paradox is a statistical fallacy and a result of residual confounding, the consistency of data and other causality clues suggest a high biologic plausibility. Examining the causes and consequences of the obesity paradox may help uncover important pathophysiologic mechanisms leading to improved outcomes in patients with CKD.

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KEYWORDS: biologic plausibility; body mass index; fat mass; muscle mass; obesity paradox; protein–energy wasting; reverse epidemiology

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Patients with advanced chronic kidney disease (CKD), that is, with an estimated glomerular filtration rate (eGFR) of <30 ml/min/1.73 m<sup>2</sup> body surface area, including those with end-stage renal disease (ESRD) who receive maintenance dialysis therapy, have a substantially high annual mortality of 10% to 20%.<sup>1</sup> Indeed the mortality is even higher in the first several months of transitioning to dialysis therapy, and the annualized death rate may approach 30% to 40% or higher.<sup>2</sup> This excessively high death risk of advanced CKD is worse than that of most cancers,<sup>3</sup> in

which the leading causes of death are cardiovascular and infectious.<sup>1</sup> Hospitalizations, too, are exceptionally high in these patients, and their health-related quality of life is low. The etiology of such exceptionally poor clinical outcomes have remained obscure.

For decades, management efforts and strategies have focused on targeting the well-known and conventional risks factors of poor clinical outcomes in the general population such as hyperlipidemia, hypertension and obesity. However, these strategies, which were based on the extrapolation of findings from the general population, have not resulted in major improvements in survival. Furthermore, targeting CKD-specific factors including anemia, iron deficiency, hyperphosphatemia, hyperparathyroidism, vitamin D deficiency, hypercalcemia, and dialysis dose have also not led to improved clinical outcomes. Randomized clinical trials have failed to show any survival benefit with the normalization of

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hemoglobin level,<sup>4</sup> increase in dialysis dose of hemodialysis<sup>5</sup> or peritoneal dialysis,<sup>6</sup> controlling hyperparathyroidism by calcimimetics,<sup>7</sup> or supplementation by vitamin D analogues.<sup>8</sup> Lowering blood pressure<sup>9</sup> or managing hyperlipidemia with statins have failed to improve outcomes, especially in dialysis patients.<sup>10</sup> Although not all of these trials have examined survival as a primary endpoint, there is no meaningful survival differential in their primary and secondary analyses.

### The Obesity Paradox in the Context of Reverse Epidemiology

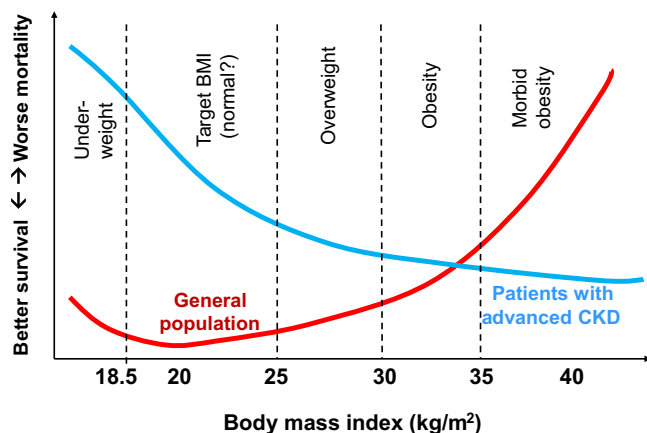
Over the past 1 to 2 decades, a large number of observational studies with very large sample sizes (usually more than 10,000 patients) have consistently indicated seemingly counterintuitive associations between the traditional risk factors for cardiovascular disease, in particular obesity as well as hypertension and hyperlipidemia, and paradoxically better survival.<sup>11</sup> These and other risk factor survival paradoxes, including the adiponectin paradox<sup>12</sup> and uric acid paradox,<sup>13</sup> have been collectively referred to as the “reverse epidemiology” phenomenon, or altered risk factor patterns, to highlight the associations that are in sharp contradistinction to conventional patterns.<sup>14</sup> Reverse epidemiology has also been observed in persons with heart failure,<sup>15</sup> chronic obstructive lung disease, liver cirrhosis, and metastatic cancer, as well as in the geriatric population.<sup>16</sup> Data on the reverse epidemiology of obesity have been remarkably consistent in showing that a lower body mass index (BMI) or weight loss over time are associated with poor outcomes, whereas higher BMI or gaining solid weight have been protective and associated with better survival (Figure 1). This phenomenon has been referred to

as the “obesity paradox.”<sup>17</sup> Studies by different investigators have shown rather consistent and uniform findings on the obesity paradox in advanced CKD, especially in dialysis patients. Many recent studies have also confirmed the presence of the obesity paradox in contemporary cohorts across different ethnicities and races as well as geographic regions of the world.<sup>18</sup> Indeed these epidemiologic associations have been robust to many different types of statistical analyses, including marginal structural models, tempering concerns about substantial residual confounding and other biases.<sup>11,17</sup> A deeper understanding of the phenomenon of the obesity paradox in CKD patients is important, considering that the poor outcomes in this population may improve if any gain in solid weight is associated with greater survival. In this review, we summarize data on the obesity paradox and relate them to clinical practice and public health.

### Is Obesity Good or Bad for CKD?

Data are relatively consistent in showing that obesity is associated with higher risk of incident CKD. Large cohort studies suggest that obesity, that is, BMI > 30 kg/m<sup>2</sup>, especially in the context of metabolic syndrome and insulin resistance, is associated with higher risk of *de novo* CKD.<sup>19</sup> In a national cohort of more than 3 million US veterans without previously known renal insufficiency (eGFR >60 ml/min/1.73 m<sup>2</sup>), higher BMI > 30 kg/m<sup>2</sup> was associated with loss of kidney function across different ages.<sup>20</sup> The lowest risk for loss of kidney function was noted in patients with BMI levels between 25 and 30 kg/m<sup>2</sup>, whereas a consistent U-shaped association between BMI and rapid loss of kidney function was noted for BMI levels <25 kg/m<sup>2</sup> and >30 kg/m<sup>2</sup>, which was more prominent with advanced age, except in the patients who were younger than 40 years, in whom BMI was not predictive of renal function impairment.<sup>20</sup> The investigators concluded that obesity, defined by a BMI of >30 kg/m<sup>2</sup>, was associated with a rapid loss of kidney function in patients with eGFR > 60 ml/min/1.73 m<sup>2</sup>.<sup>20</sup> Emerging data suggest that weight loss interventions may prevent *de novo* CKD or may slow or reverse early CKD progression, although some bariatric surgical interventions may result in an initial drop in eGFR, which may be due to improvement in glomerular hyperfiltration and hence favorable sequelae.<sup>21,22</sup> Although the pathogenesis of CKD in obesity remains obscure, studies indicate that excess body fat can result in kidney disease by means of different mechanisms including secondary focal segmental glomerulosclerosis.<sup>23</sup>

Meta-analyses suggest that once CKD develops, overweight and obese ranges of BMI are paradoxically

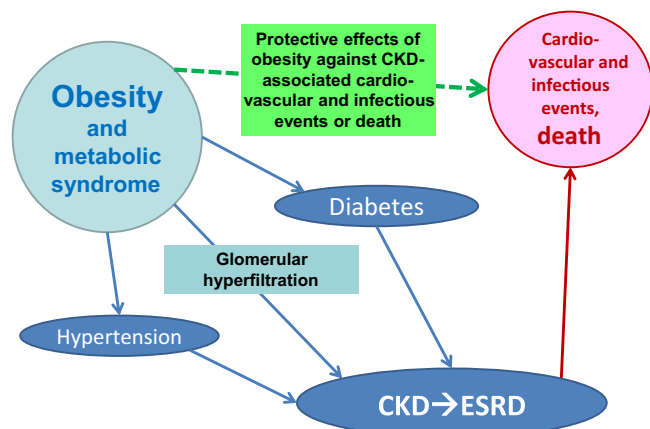


**Figure 1.** Reverse association of body mass index (BMI) and survival in patients with advanced chronic kidney disease (CKD) as compared to the general population.

associated with greater survival in advanced pre-dialysis (eGFR < 30 ml/min/1.73 m<sup>2</sup>) and dialysis-dependent CKD patients,<sup>24</sup> whereas a pooled analysis showed that higher pretransplantation BMI was associated with higher mortality in kidney transplantation recipients.<sup>25</sup> In dialysis patients, the obesity paradox data are quite consistent, especially in maintenance hemodialysis patients, as has been reviewed elsewhere.<sup>11,26</sup> Hence, it is important to acknowledge the role of obesity as an important risk factor for *de novo* CKD. However, once CKD has occurred, there appears to be a consistent association between obesity and better outcomes including lower mortality in those with advanced CKD, particularly among patients receiving hemodialysis therapy, suggesting that the reverse epidemiology of obesity is robust (Figure 2).

### What Components of Body Mass Are Increased in Weight Gain?

Having a larger body size means having either greater solid weight or water weight. It is relatively well known that higher fluid retention is associated with poorer outcomes, particularly in dialysis patients.<sup>27</sup> A 2-year cohort of 34,107 hemodialysis patients who had an average weight gain of at least 0.5 kg above their postdialysis dry weight by the time of their subsequent hemodialysis treatment showed that higher weight gain increments were associated with higher risk of all-cause and cardiovascular mortality, so that the hazard ratios of cardiovascular death for weight gains of <1.0 kg and >4.0 kg (compared with 1.5–2.0 kg as the reference) were 0.67 (95% confidence interval: 0.58–0.76) and 1.25 (1.12–1.39), respectively.<sup>27</sup> The mechanisms by which fluid retention influences cardiovascular death in hemodialysis patients may be similar to that of the heart failure population and warrants further research.<sup>27</sup>



**Figure 2.** Obesity is a risk factor for chronic kidney disease (CKD), yet it protects against CKD-associated death. ESRD, end-stage renal disease.

Because the bone and viscera typically cannot expand, having a larger solid weight or weight gain is due to having or gaining more skeletal muscle mass or larger fat mass. A gain in fat mass is often the dominating development after a hypercatabolic event or acute illness has resolved or upon higher protein and calorie intake.<sup>28</sup> Indeed, the Minnesota study in volunteer soldiers who agreed to starve for days showed that, after losing weight with proportional losses of fat and muscle, regaining the same weight back to baseline was associated with disproportionately higher fat versus muscle regain.<sup>29</sup> Dullo *et al.* showed that in so-called yo-yo dieting, losing and gaining back the same amount of weight is invariably associated with more fat and less muscle mass accumulation, and is often associated with an even higher risk of insulin resistance, metabolic syndrome, and diabetes mellitus.<sup>30</sup> Gaining muscle is much more difficult and requires resistance exercise along with anabolic support such as high protein intake with high biologic value and sometimes anabolic steroids in chronic disease populations and those of older age.

### If Fat Is Good, Muscle Is Better

Several studies have shown that any gain in body weight is associated with better survival in CKD, whereas both fat mass and fat-free lean body mass, the latter of which is essentially representative of muscle mass, also confer survival advantage. There remains considerable challenge in differentiating fat and muscle mass routinely in the clinical setting. Fat mass can be assessed using dual energy x-ray absorptiometry (DEXA)<sup>31,32</sup> or near-infrared interactance.<sup>33</sup> Lean body mass can be estimated using imaging studies, anthropometry such as mid-arm muscle circumference,<sup>34,35</sup> or equations based on serum creatinine.<sup>36</sup> Serum creatinine has been shown to correlate closely with muscle mass, especially in dialysis patients,<sup>37</sup> and equations have been created that use serum creatinine and certain demographic data to estimate lean body mass, as published by Noori *et al.*<sup>36</sup>

In a study in 535 adult hemodialysis patients whose body fat was directly measured with near-infrared interactance, low baseline body fat percentage and fat loss over time were independently associated with higher mortality even after adjustment for demographics and surrogates of muscle mass and inflammation, whereas a tendency toward a worse quality of life was seen with a higher body fat percentage.<sup>38</sup> In a cohort of 742 hemodialysis patients comprising 391 males and 351 females who were separately divided into 4 quartiles of near-infrared interactance—measured lean body mass and fat mass, the highest versus lowest quartiles of fat mass and lean body mass were strongly

associated with lower mortality in women, whereas the highest versus lowest quartiles of fat mass and percentage fat but not of lean body mass were associated with greater survival in men.<sup>39</sup> Cubic spline survival analyses showed greater survival with higher fat mass percentage and higher “fat mass minus lean body mass percentiles” in both sexes, whereas a higher lean body mass was protective in women. This study suggested that the survival advantage of fat mass was superior to that of lean body mass.<sup>39</sup> There are, however, other studies suggesting that both higher lean body mass and BMI are related to greater survival in hemodialysis patients. In a large cohort of 117,683 hemodialysis patients, higher estimated lean body mass, defined by creatinine based equations developed by Noori *et al.*,<sup>36</sup> was linearly associated with lower mortality.<sup>40</sup> Compared with the reference group (48.4 to <50.5 kg), patients with the lowest estimated lean body mass (<41.3 kg) had a 1.4-fold higher risk of mortality. A similar linear association was seen among patients with BMI < 35 kg/m<sup>2</sup> and in non-Hispanic Caucasian and African American subgroups. However, higher estimated lean body mass was not associated with improved survival in Hispanic patients or those with BMI > 35 kg/m<sup>2</sup>.<sup>40</sup> To better examine the role of different types of fat, a landmark study was conducted by Italian colleagues led by Zoccali *et al.* in a prospective cohort of 537 dialysis patients, in whom waist circumference was used as surrogate of intra-abdominal or visceral (truncal) fat.<sup>41</sup> In this study, each 10-cm increase in waist circumference was associated with 10% and 37% higher all-cause and cardiovascular death.<sup>41</sup>

To determine whether dry weight gain accompanied by an increase in muscle mass is associated with a survival benefit in a nationally representative 5-year cohort of 121,762 maintenance hemodialysis patients, 3-month averaged serum creatinine levels and their changes over time were used as muscle mass and as muscle mass change, respectively.<sup>42</sup> Dry weight loss or gain over time exhibited a graded association with higher rates of mortality or survival, respectively, as did changes in serum creatinine level over time. Among a subcohort of 50,831 patients who survived the first 6 months, those who lost weight but had an increased serum creatinine level had a greater survival rate than those who gained weight but had a decreased creatinine level.<sup>42</sup> These data suggest that there is a superiority of lean body mass to fat mass, in that larger body size with more muscle mass was associated with better survival, whereas a discordant muscle gain with weight loss over time conferred greater survival benefit as compared with weight gain while losing muscle.<sup>42</sup> Additional analyses of the same cohort using more sophisticated analytic techniques confirmed the

superiority of muscle mass while overall weight gain or loss maintained parallel associations with survival and mortality, respectively.<sup>43</sup> A decline in muscle mass appeared to be a stronger predictor of mortality than weight loss. These studies suggest that a considerable proportion of the obesity paradox in dialysis patients might be explained by the survival benefits of greater muscle mass.<sup>43</sup> In a large epidemiologic study by Beddhu *et al.*,<sup>44</sup> 24-hour urinary creatinine excretion was used as a measure of muscle mass in 70,028 patients who initiated hemodialysis in the US over 5 years (January 1995 to December 1999), and the outcomes of hemodialysis patients with high BMI and normal or high muscle mass (inferred low body fat) and high BMI and low muscle mass (inferred high body fat) were compared. The investigators found that patients with high BMI (>25 kg/m<sup>2</sup>) had 15% lower hazard of death, but that patients who had more muscle mass had even greater survival, whereas patients with high BMI but lower muscle mass had a 14% to 19% higher all-cause and cardiovascular mortality.<sup>44</sup> According to the authors' interpretation of their data, the protective effect conferred by high BMI is limited to higher muscle mass, as patients with higher BMI with inferred high body fat exhibited increased and not decreased mortality.<sup>44</sup> Hence, given the commonality of the muscle mass superiority despite mixed data about fat, controlled trials of muscle-enhancing interventions in patients receiving dialysis are warranted.

It is important to note that obesity paradox associations are not only observed in hemodialysis patients but have also been seen in peritoneal dialysis patients.<sup>45</sup> In a cohort of 10,896 peritoneal dialysis patients, the association of baseline serum creatinine level as a surrogate of muscle mass and its change during the first 3 months thereafter with all-cause mortality was examined.<sup>46</sup> Compared with patients with serum creatinine levels of 8.0 to <10 mg/dl, patients with serum creatinine levels of <4.0 mg/dl and 4.0 to <6 mg/dl had 36% and 19% higher risks of death, respectively, whereas patients with serum creatinine levels of 10.0 to <12 mg/dl, 12.0 to <14 mg/dl, and >14.0 mg/dl had 12%, 29%, and 36% lower risks of death, respectively. Decreases in serum creatinine level exceeding 1.0 mg/dl during the 3 months predicted an additional increased risk of death. The investigators concluded that muscle mass reflected in serum creatinine levels were associated with survival in peritoneal dialysis patients.<sup>46</sup>

### Is the Obesity Paradox a Statistical Fallacy?

It has been argued that the inverse association between BMI and mortality observed under the obesity paradox in dialysis patients may be a consequence of residual



confounding. Thus, marginal structural model analysis, a technique that accounts for time-varying confounders, may be more appropriate to investigate this association.<sup>47–50</sup> In a recent study of the associations between BMI and all-cause mortality among 123,624 adult hemodialysis patients comprising 45% women and 32% African Americans, BMI showed a linear incremental inverse association with mortality across all models.<sup>18</sup> Compared with the reference (BMI 25 to <27.5 kg/m<sup>2</sup>), a BMI of <18 kg/m<sup>2</sup> was associated with a 3.2-fold higher death risk (hazard rate [HR] = 3.17, 95% confidence interval [CI] = 3.05–3.29).<sup>18</sup> Furthermore, mortality risk was incrementally lower with increasing BMI levels, with the greatest survival advantage observed with a BMI of 40 to <45 kg/m<sup>2</sup> (HR = 0.69, 95% CI = 0.64–0.75).<sup>18</sup> This study suggested that the linear inverse relationship between BMI and mortality is robust across models, including marginal statistical model analyses that more completely account for time-varying confounders and biases.<sup>18</sup>

### Changes in Body Weight and Mortality

CKD patients, and in particular, incident dialysis patients, may experience rapid weight loss in the first several months of starting dialysis. However, there are limited data on trends in weight changes over time and their associations with mortality in CKD patients. In a large contemporary cohort of 58,106 patients who initiated hemodialysis over the 5-year period of January 2007 to December 2011 and survived the first year of dialysis therapy, trends in weight changes during the first year of treatment, as well as associations of postdialysis weight change with all-cause mortality were examined.<sup>51</sup> Patients' postdialysis weights rapidly decreased and reached a nadir at the 5th month of dialysis with an average decline of 2% from baseline, whereas obese patients, defined as those with a BMI > 30 kg/m<sup>2</sup>, did not reach a nadir and lost approximately 3.8% of their weight by the 12th month. Compared with the reference group (–2% to +2% change in weight), the mortality HRs (95% CI) of patients with –6% to –2% and greater than or equal to –6% weight loss during the first 5 months were 1.08 (1.02–1.14) and 1.14 (1.07–1.22), respectively.<sup>51</sup> Moreover, the mortality HRs (95% CI) with +2 to +6% and +>6% weight gain during the 5th to 12th months were 0.91 (0.85–0.97) and 0.92 (0.86–0.99), respectively.<sup>51</sup> The study concluded that in hemodialysis patients who survive the first year of hemodialysis, a decline in postdialysis weight is observed and reaches a nadir at the 5th month. In addition, an incrementally larger weight loss during the first month is associated with higher death risk, whereas weight gain is associated with greater survival

during the 5th to 12th month but not in the first 5 months of dialysis therapy.<sup>51</sup>

### Does Race Influence the Obesity Paradox?

An interesting issue is whether the obesity paradox is affected by race or ethnicity in CKD patients or differs across geographic regions. Glanton *et al.*<sup>52</sup> performed a historical cohort study in 151,027 incident dialysis patients and found that the obesity paradox was even stronger in African Americans. Johansen *et al.*<sup>53</sup> has also examined whether BMI is associated with better survival in Asian Americans, Caucasians, African Americans, and Hispanics. Rick *et al.*<sup>54</sup> evaluated whether higher BMI is more strongly associated with lower mortality among African Americans and Hispanics versus non-Hispanic Caucasians. In a cohort of 109,605 hemodialysis patients who comprised 39,090 African Americans, 17,417 Hispanics, and 53,098 non-Hispanic Caucasians, a higher BMI was linked with lower mortality across all racial/ethnic categories. Notably, a more potent association between higher BMI category and greater survival was observed among African American and Hispanic patients versus non-Hispanic Caucasians. Park *et al.*<sup>26</sup> also sought to determine whether the body size–mortality association among hemodialysis patients is uniform across different races, particularly East Asian versus Caucasian and African American patients. Among 20,818 South Korean hemodialysis patients who were matched to 20,000 US hemodialysis patients (10,000 Caucasian and 10,000 African American patients), the investigators found that BMI level was inversely and linearly associated with mortality even among East Asian hemodialysis patients. In addition, the strength of the association between BMI and mortality was similar across the 3 racial/ethnic groups, suggesting that the obesity paradox is a universal phenomenon, irrespective of race, in hemodialysis patients.

### Biologic Plausibility for the Obesity Paradox and Causality

The obesity paradox is not restricted to advanced CKD and has also been observed in other populations including the elderly individuals<sup>16,55</sup> and in those with chronic heart failure,<sup>15,56</sup> among others. It has been argued that the obesity paradox, along with other paradoxes such as the lipid paradox, are a hallmark of chronic disease states or conditions that are associated with wasting, sarcopenia, and full-blown cachexia.<sup>57,58</sup> Although we argue that weight loss is causally related to death in CKD and other similar conditions, others have questioned whether weight loss is truly in the causal pathway between CKD-associated protein–energy wasting and death, as shown in

**Figure 3.** According to the alternative hypothesis, weight loss and gain are epiphenomena in that they occur when a patient does poorly or favorably, respectively, whereas changes in weight or body composition are not causally related to survival (Figure 3, models 2 and 3). Hence, the inability of observational studies to prove causality is massively limited, no matter what kind of multivariate techniques are used.<sup>59</sup>

Despite the foregoing view about causal inference in epidemiological studies of the obesity paradox, there are some criteria required for making the leap from associations to causation, the most well-known of which were presented in the 1965 article of Sir Austin Bradford Hill, “The Environment and Disease: Association or Causation,”<sup>60</sup> in which several benchmarks—subsequently refined and expanded to 9 criteria—that “suggest” causality were listed (Table 1). The most important one is the “temporal relationship,” which indicates that the cause or “exposure,” say, weight loss to overt cachexia, should precede the effect or “outcome,” say, death. However, an inherent problem in studying the causes of death is the fact that death is inherently the final event preceding any risk factor or condition. Hence, temporality is universally present in this association and cannot discern causality.

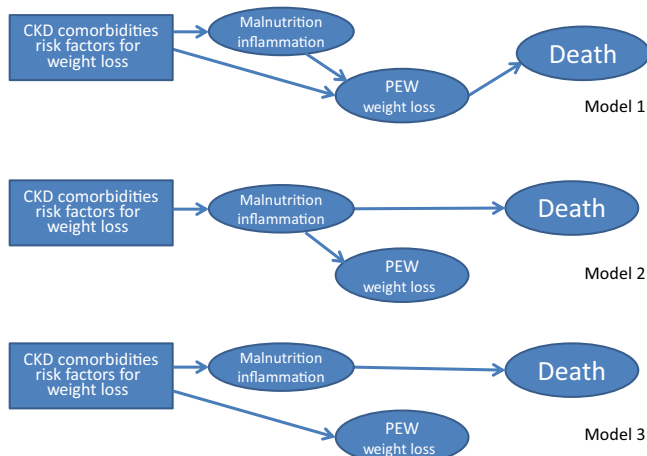
It is important to note that even though Hill’s criteria can be used to carefully shift interpretations from associations toward that of causation, epidemiology can never prove causality. Table 1 lists pros and cons pertaining to each of Hill’s 9 considerations. Given the observational nature of most of these benchmarks in the obesity paradox, the current state of knowledge does not sufficiently confirm that a higher body mass or even weight loss or gain are the main drivers of the longevity in advanced CKD. Nevertheless, the obesity

paradox is not restricted to CKD but also exists in chronic heart failure, chronic obstructive pulmonary disease, cancer, AIDS, rheumatoid arthritis, and in elderly individuals. These populations apparently have slowly progressive to full-blown wasting and significantly greater short-term mortality than the general population.<sup>57</sup> Hence, the consistency of the associative data, the remarkable strength of the obesity paradox, the early occurrence of death following progressive weight loss in CKD, and emerging evidence from basic science and animal models suggest that the causality element may be present and may soon be identified. Nevertheless, it is important to note that Hill’s criteria have been applied primarily in cases in which clinical trials are not ethically or logistically feasible, such as smoking and lung cancer,<sup>61</sup> whereas this is not quite the case with the obesity question in CKD, where the plausibility of Hill’s criteria should not dissuade from conducting randomized controlled trials related to weight management or other nutritional interventions.<sup>62</sup>

### Putative Pathophysiology of the Obesity Paradox

Several hypotheses have been advanced to explain a biologically plausible model for the obesity paradox in CKD (Figure 4). The leading hypothesis pertains to protein–energy wasting (PEW), which is frequently observed in patients with advanced CKD.<sup>63,64</sup> The pathophysiology of PEW in CKD is related to the induction of inflammatory processes,<sup>65–67</sup> such as activation of inflammatory cytokines including interleukin-6 and/or tumor necrosis factor- $\alpha$ , that suppress appetite and promote muscle breakdown and subsequent hypoalbuminemia.<sup>68</sup> Loss of muscle and fat mass and inflammation may subsequently lead to heightened risk of cardiovascular disease and death via pathways related to vascular endothelial damage.<sup>69–71</sup> Animal models also suggest that malnutrition may precipitate inflammation.<sup>72</sup> As such, the malnutrition–inflammation–cachexia syndrome is thought to contribute to the obesity and other paradoxes in CKD and other chronic disease states.<sup>73</sup>

Obesity may potentially attenuate the magnitude of PEW and thereby provide protection against the downstream sequelae of inflammation such as cardiovascular disease. For example, patients with greater adipose tissue mass may be at lower risk of developing PEW in the context of malnutrition due to greater energy and/or protein reserves. In contrast, patients with poor nutrition may be more vulnerable to the ill effects of inflammation.<sup>64,74</sup> Lowrie *et al.*<sup>75</sup> proposed that in the setting of inflammation, protein stores may be harnessed to restore injured tissues and mitigate



**Figure 3.** Three hypothetical “causal” models of the weight loss and death associations in chronic kidney disease (CKD) and the role of protein–energy wasting (PEW).

**Table 1.** Hill’s considerations<sup>60</sup> for the inference of causality in the obesity paradox

Benchmark	Definition/comments	Application to the obesity paradox
1. Temporality <sup>a</sup>	The cause (exposure) must precede the effect (outcome).	PRO: Dialysis patients who gain more edema-free (dry) weight live longer. Wasting and weight loss precedes death and is associated with higher death risk. CON: Death is inherently the final event. Death may also occur during weight gain (e.g., upon nutritional support).
2. Strength of association	Stronger association may make causality more likely.	PRO: Most studies indicate strong and consistent associations between higher BMI and greater survival, especially in dialysis patients. CON: The reported strengths of the associations are not consistent. CKD stage and renal insufficiency severity confound the association.
3. Biological gradient (dose–response)	Greater exposure increases the incidence or magnitude of the effect.	PRO: Greater weight loss may be associated with higher likelihood of death, whereas incrementally higher BMI is associated with better survival. CON: The wasting severity is inconsistent and in some studies even has a weak association with death risk especially in less severe stages of CKD.
4. Consistency	The association can be replicated in studies in different settings using different methods.	PRO: The obesity paradox is observed in both hemodialysis and peritoneal dialysis as well as in more advanced stages of NDD-CKD. CON: Some types of weight loss such as intentional weight loss may not be associated with higher death risk.
5. Biologic plausibility	The association is consistent with known biological or pathological processes.	PRO: Higher fat and muscle mass may provide better cardiovascular profiles, whereas weight loss may lead to thromboembolic events, arrhythmia, sudden cardiac death, immune system disorders, and higher rates of cardiovascular and infectious disease events and death. CON: There is essentially no clear pathophysiologic pathway to explain the protective effects of higher muscle and fat mass.
6. Experimentation	The putative effect can be altered (prevented or mitigated) by an experimental regimen.	PRO: In some animal models of CKD, starvation and weight loss can lead to death. Improving wasting in human dialysis patients appears to improve survival. CON: The current CKD animal models are scarce and not convincing. There are very few trials of nutritional support interventions in human CKD subjects, and survival is rarely examined.
7. Specificity	A single cause produces the effect without other pathways.	PRO: Preceding wasting and weight loss can fully explain death events. CON: Weight loss is only 1 of the correlates of protein–energy wasting and may be an epiphenomenon. It is not clear how to explain survival advantage of obesity or weight gain.
8. Biologic coherence	The association is consistent with the natural history of the disease or laboratory findings.	PRO: A lower risk of death should result from preventing weight loss or by nutritional support in CKD patients. CON: Death events in CKD are mainly cardiovascular or infectious and have little to do with wasting and weight loss.

(Continued)

**Table 1.** (Continued)

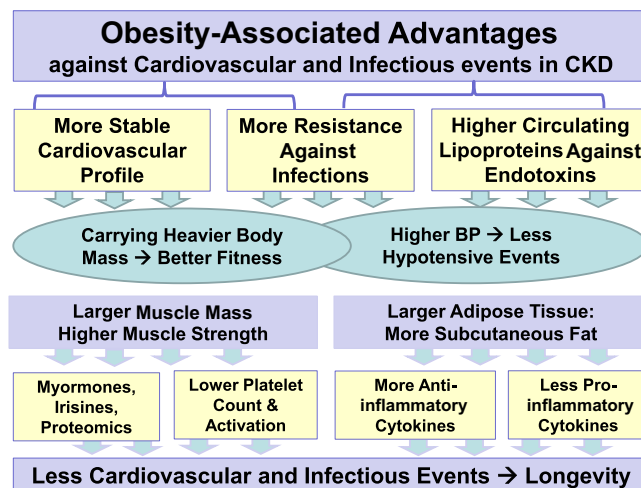
Benchmark	Definition/comments	Application to the obesity paradox
9. Analogy	The effect of similar factors may be considered in other populations or under different settings.	PRO: Wasting, fat, and muscle mass loss precede death in other chronic disease states such as heart failure, COPD, and metastatic cancer. CON: There is little biologically plausible analogy in death due to other conditions, such as cardiovascular (atherosclerosis) or cancer death.

Each causality benchmark is examined for the cachexia-death association. BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; NDD, non-dialysis dependent.

<sup>a</sup>Temporality is the only requisite condition of causality.

inflammatory conditions. This may in part explain the lower mortality observed among dialysis patients with a high BMI or creatinine concentration but with low nutritional reserves.

It is important to highlight that the time discrepancies observed among competing risk factors for death are a likely an explanatory factor for the obesity paradox in advanced CKD. In long-term studies of the general population residing in industrialized nations, overnutrition has been observed to be a predictor of cardiovascular disease and death. However, in developing countries, which comprise a large proportion of the global population, undernutrition is a powerful determinant of reduced life expectancy.<sup>76</sup> Similarly, survival advantages that exist in obese CKD patients may, in the short term, outweigh the harmful effects of obesity on cardiovascular disease in the long term. Indeed even in non-CKD patients, obesity may confer certain short-term benefits even though it is associated with poorer outcomes long term.<sup>77</sup> Given that dialysis patients have an extremely poor short-term survival, with a large proportion of deaths occurring within the first 5 years of initiating dialysis,<sup>78,79</sup> the long-term



**Figure 4.** Putative mechanisms of the survival advantages of obesity in chronic kidney disease (CKD). BP, blood pressure.

effects of obesity as a traditional cardiovascular and mortality risk factor may be overwhelmed by the short-term ill effects of malnutrition and inflammation. It is important to note that in peritoneal dialysis patients, the obesity paradox has been less consistent, which may be related to the said differences in the follow-up time. For instance, Snyder *et al.*<sup>80</sup> showed that in a 5-year (1995–2000) cohort of 418,021 US dialysis patients including 11% peritoneal dialysis patients, the likelihood of peritoneal dialysis modality assignment at dialysis initiation was 23% to 27% lower in overweight (BMI 25 to <30 kg/m<sup>2</sup>) and obese (BMI > 30 kg/m<sup>2</sup>) patients, respectively, whereas overweight and obese peritoneal dialysis patients still exhibited better survival in the first several years than those with lower BMI. However, in an 11-year (April 1991 to March 2002) cohort of 9679 Australian peritoneal dialysis patients, McDonald *et al.*<sup>81</sup> reported that obesity was associated with 36% higher mortality and 17% higher dialysis technique failure except among patients of New Zealand Maori/Pacific Islander origin, for whom there was no significant relationship between BMI and death during peritoneal dialysis treatment.

Obesity may also be associated with better short-term hemodynamic stability. Many CKD patients on dialysis experience heart failure and/or fluid overload. Despite having similar pulmonary capillary wedge pressure and cardiac indices, overweight and obese patients with heart failure tend to have higher systolic blood pressure values,<sup>56</sup> and thus may have better resilience against large volumes and faster rates of ultrafiltration during dialysis and lower likelihood of transient hypotension. This may attenuate sympathetic and renin–angiotensin–aldosterone activity<sup>82</sup> which are linked with poor outcomes in heart failure and CKD patients.<sup>83</sup> This bears particular relevance, as hypotension and subsequent myocardial stunning during the hemodialysis procedure may contribute to the extremely high cardiovascular mortality of ESRD patients.<sup>84–86</sup>

Cytokine alterations may also contribute to better outcomes in obese patients. Adipose tissue produces tumor necrosis factor- $\alpha$  receptors, which are elevated in CKD patients and may lead to cardiac insult via proapoptotic and negative inotropic effects.<sup>71,87</sup> Conversely, increased tumor necrosis factor- $\alpha$  receptors may also play a cardioprotective role by neutralizing the adverse effect of tumor necrosis factor- $\alpha$ .<sup>88</sup> In the context of adipose accumulation, uremic toxins may also be more effectively sequestered in these tissues. In addition, loss of weight and adipose tissue were found to be associated with increased release of circulating lipophilic hexachlorobenzene and other chlorinated hydrocarbons.<sup>89</sup> This may in part explain why loss of body fat is associated with higher

risk of death in ESRD patients.<sup>38</sup> On average, obese patients have higher lipid and lipoprotein concentrations; given that lipopolysaccharide levels are elevated in fluid overload,<sup>90,91</sup> a higher concentration of lipoproteins (which bind to lipopolysaccharides) may mitigate the adverse sequelae of circulating endotoxins.<sup>91</sup> Finally, platelet activation may be associated with high mortality risk in dialysis patients with PEW; it has been suggested that relative thrombocytosis in the context of an unfavorable malnutrition–inflammation–cachexia syndrome profile may lead to greater thromboembolism, cardiovascular disease, and death.<sup>92</sup>

### Concluding Remarks

The seemingly counterintuitive obesity paradox is commonly observed in chronic disease states and conditions associated with wasting, such as advanced CKD. Studying similarities between CKD and other populations with a reverse epidemiology of cardiovascular risk may help to reveal common pathophysiologic mechanisms of the obesity paradox, leading to a major shift in clinical medicine and public health beyond conventional paradigms. Future studies that will advance our understanding of the existence, etiology, and components of the obesity paradox, as well as the role of PEW and the malnutrition–inflammation–cachexia syndrome in its development in advanced CKD, remain of paramount importance. Malnutrition and inflammation may be potentially modifiable, and as such may result in improved clinical outcomes. More research is needed to define all of the populations with versus without the obesity paradox, as this will drive future nutritional and therapeutic management decisions in patients at risk. These efforts may eventually lead to novel therapeutic approaches, including nutritional interventions that would improve the short-term and long-term survival of CKD and other vulnerable populations.

### DISCLOSURE

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