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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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Patients with advanced chronic kidney disease (CKD), that is, with an estimated glomerular filtration rate (eGFR) of <30 ml/min/1.73 m^2 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%.[1] 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.[2] This excessively high death risk of advanced CKD is worse than that of most cancers,[3] in which the leading causes of death are cardiovascular and infectious.[1] 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,[4] increase in dialysis dose of hemodialysis[5] or peritoneal dialysis,[6] controlling hyperparathyroidism by calcimimetics,[7] or supplementation by vitamin D analogues.[8] Lowering blood pressure[9] or managing hyperlipidemia with statins have failed to improve outcomes, especially in dialysis patients.[10] 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.[11] These and other risk factor survival paradoxes, including the adiponectin paradox[12] and uric acid paradox,[13] 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.[14] Reverse epidemiology has also been observed in persons with heart failure,[15] chronic obstructive lung disease, liver cirrhosis, and metastatic cancer, as well as in the geriatric population.[16] 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."[17] 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.[18] 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.[11,17] 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.

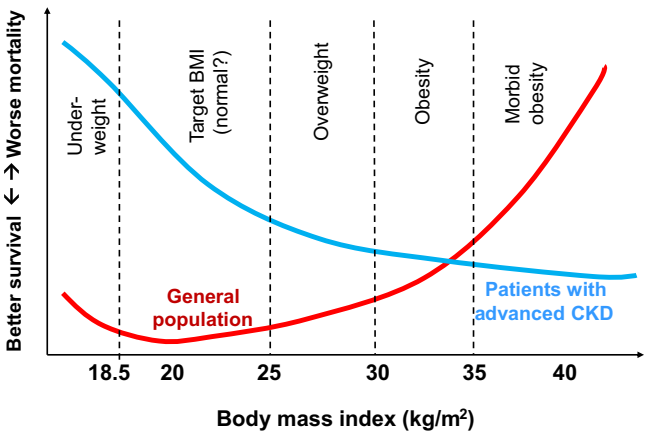

Figure 1. Reverse association of body mass index (BMI) and survival in patients with advanced chronic kidney disease (CKD) as compared to the general population.

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^2, especially in the context of metabolic syndrome and insulin resistance, is associated with higher risk of *de novo* CKD.[19] In a national cohort of more than 3 million US veterans without previously known renal insufficiency (eGFR $>$60 ml/min/1.73 m^2), higher BMI $>$ 30 kg/m^2 was associated with loss of kidney function across different ages.[20] The lowest risk for loss of kidney function was noted in patients with BMI levels between 25 and 30 kg/m^2, whereas a consistent U-shaped association between BMI and rapid loss of kidney function was noted for BMI levels $<$25 kg/m^2 and $>$30 kg/m^2, 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.[20] The investigators concluded that obesity, defined by a BMI of $>$30 kg/m^2, was associated with a rapid loss of kidney function in patients with eGFR $>$ 60 ml/min/1.73 m^2.[20] 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.[21,22] 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.[23]

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