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Hidden Obesity in Dialysis Patients: Clinical Implications

Matthew K. Abramowitz^{1,2}, Deep Sharma¹, and Vaughn W. Folkert¹

¹Division of Nephrology, Department of Medicine, Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, New York

²Department of Epidemiology & Population Health, Albert Einstein College of Medicine, Bronx, New York

Abstract

While body-mass index (BMI) is used to diagnose obesity in the general population, its application in the end-stage renal disease (ESRD) population is fraught with difficulty. A major limitation is its inability to distinguish muscle mass from fat mass, thereby leading to misclassification of individuals with poor muscle mass but excess adipose tissue as non-obese (i.e. BMI <30 kg/m²). As muscle wasting is common among ESRD patients, this is an important problem. A substantial proportion of ESRD patients have levels of BMI in the normal range, yet excess adiposity based on other measures. The importance of this “hidden” obesity remains to be determined, but it must be recognized in order for obesity interventions to be appropriately targeted and tested in the ESRD population.

The prevalence of obesity has been steadily increasing in the end-stage renal disease (ESRD) population (1). Although a similar trend in the general population is clearly recognized as detrimental, this conclusion has not been easily extended to ESRD patients. Several epidemiologic studies have found no association, or a protective association, of body-mass index (BMI) levels in the obese range with mortality (2–5). As a result, some have questioned whether potential benefits of obesity outweigh its known risks in patients receiving dialysis. A large body of literature has examined this question, yet no consensus has been reached. For a clinician, it can be especially difficult to apply the existing data to the care of an individual patient.

One of the great difficulties is that our methodology for diagnosing obesity, the BMI, is an insensitive measure in people with significant muscle wasting, a problem quite common among dialysis patients. As a result, obesity may be unrecognized, or hidden, in many patients. Thus hidden obesity and muscle wasting are intertwined. There are tools for independently assessing fat mass and muscle mass, ranging from anthropometric measures that require minimal training to implement (e.g. triceps skinfold thickness and mid-arm muscle circumference) to bioimpedance spectroscopy to methods that are typically used only for research purposes (e.g. dual-energy x-ray absorptiometry, air displacement

Corresponding author: Matthew K. Abramowitz, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Ullmann 615, Bronx, NY 10461, (718) 430-8566, (718) 430-8963 (fax), matthew.abramowitz@einstein.yu.edu.

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plethysmography). But BMI is easily available to the clinician, and, as a survey of nephrologists outside the United States (mostly in Europe) found, is the most common tool used to diagnose obesity (6).

To appreciate the importance of hidden obesity, we must first address what is known more generally about obesity in ESRD patients. It is important to appreciate the contrast between these patients and the general population, so we begin here. In the general population, BMI is the major tool used to identify obesity in clinical practice. It is a simple measure that quickly identifies people who could benefit from lifestyle (7), and perhaps pharmacologic (8), intervention. However, BMI is a crude measure, in that its weight term does not distinguish muscle mass from fat mass. Therefore, even in the general population it has limitations for defining obesity. The greatest difficulty with its use in young, relatively healthy people is incorrectly labeling individuals with substantial muscle mass as overweight or obese. Nevertheless, overweight and obesity – defined using BMI – are clearly a risk factor for increased all-cause mortality, and specifically cardiovascular mortality, in the general population (9).

This is not the case for ESRD patients, in whom higher BMI is associated with a lower risk of death (2–4). Why do obese dialysis patients seem to have better outcomes? One possible explanation is that patients with higher levels of BMI not only have more fat mass than patients with lower BMI, but also more muscle mass, and it is differences in muscle mass that drive the protective association with mortality (2). In this scenario, greater muscle mass is a marker for healthier, more active and more robust patients; also, skeletal muscle may itself provide metabolic benefits that have yet to be characterized. Conversely, while patients with significant muscle wasting may be overweight, they also may have a normal BMI together with excess adiposity; their obesity is “hidden” by the reduction in BMI caused by loss of muscle mass. For example, a recent longitudinal analysis of 8,227 incident hemodialysis patients found that while fat mass progressively increased after initiation of dialysis, BMI only reflected about 60% of this change due to a concomitant loss of lean mass (10). While this may explain some of the paradoxical relationship of BMI with mortality, there are likely other factors involved.

Studies with more detailed measures of body composition have found increased mortality associated not only with low lean mass but with low fat mass as well (11–13). This suggests that excess adiposity does contribute to the protective association of a high BMI, and that it is not just due to differences in muscle mass. How can this be explained? Greater adiposity could be a marker for patients with better preserved nutritional intake. Perhaps adipose tissue stores are beneficial in patients receiving dialysis, possibly as an extra energy reserve during periods of illness. This may be especially true in the setting of inflammation, which itself is associated with cachexia and an increased risk of death. Inflammation appears to modify the association of BMI with mortality in ESRD patients, such that higher BMI only appears protective in those with serologic evidence of inflammation (14). Alternatively, the population of obese ESRD patients could be relatively enriched with ‘healthier’ obese. If obese patients with CKD, compared with non-obese patients, are relatively more likely to die than to reach ESRD, then the subgroup of obese survivors beginning dialysis would be

enriched with the healthiest members of that group. However, a recent analysis of a large Veterans Affairs cohort does not support this hypothesis (15).

Height is another consideration. In the general population, taller people are less likely to die, but taller dialysis patients have an increased risk of mortality, even adjusted for weight (16, 17). As height is the denominator in BMI, some of the paradoxical association of BMI with mortality in the ESRD population could be explained by differences in height as opposed to weight.

Clearly, there are a number of possible explanations, and the relative importance of each remains unclear. The underlying question, however, is whether there is a causal relationship between body composition and mortality in ESRD patients, and if so, if it is correctly characterized.

Careful analyses of very large cohorts (>1 million adults) have demonstrated the importance of residual confounding in studies of body composition (18, 19). Exclusion of smokers and people with a history of cancer – factors that cause muscle wasting and weight loss and contribute to excess mortality – magnified the mortality risk associated with higher BMI. The relative hazard of higher BMI also declines with age (20). In other words, the effects of chronic illness and other catabolic factors mask the risk associated with obesity, and simple adjustment in statistical models does not necessarily fix this problem.

The possibility should not be discounted that such residual confounding affects all studies linking body composition with outcomes in the ESRD literature. In fact, the confounding effect could be more severe in that the population under study is one in which all participants have years of chronic illness exposure and a majority have a significant burden of comorbidity. The sickest are likely to have the greatest weight loss.

It is implausible to address these concerns in studies of ESRD patients by excluding the sources of confounding, as was done in the general population. Protein-energy wasting, which is characterized by muscle wasting and weight loss and is a powerful risk factor for death, is highly prevalent among ESRD patients (21). Longitudinal data would help, examining changes in body composition as CKD progresses and as patients transition to dialysis. This would clarify whether the seemingly protective effect of high BMI and greater fat mass in dialysis patients is due to changes in body composition that occurred prior to ESRD.

Data on changes in body composition do exist for patients who have reached ESRD. Weight loss and fat loss associate with increased mortality (11, 22), which raises concerns about the safety of weight loss interventions in this population. However, these studies could not differentiate intentional and unintentional weight loss, and the association may not be present among obese ESRD patients (23). Furthermore, others have reported successful and apparently safe weight loss in obese ESRD patients, albeit in small, select populations (24, 25).

Is weight loss safe for obese dialysis patients? As a starting point, we take the position that generally speaking it is, if performed in a structured setting with close nutritional

observation. The harmful effects of obesity have been documented extensively, and weight loss produces numerous benefits in the general population, most notably positive effects on metabolism. Paradoxically, weight loss could be beneficial even if there is also a true benefit to obesity. For example, let us assume that obesity is protective in patients with ESRD and that the findings of the aforementioned observational studies reflect a causal relationship. If this protection is due to extra energy reserves, these reserves would be less important if patients experienced fewer bouts of illness and hospitalization. Since weight loss and its attendant metabolic benefits might lower inflammation, improve immune function, and lessen the frequency and severity of illness, it may outweigh the risks of lower energy reserves.

We suggest reframing the question: Are there obese dialysis patients for whom intentional weight loss is unsafe? Perhaps patients with chronic infections, or those at risk for recurrent infections (e.g. patients with tunneled catheters), and others with high levels of inflammatory markers, are such exceptions (14). There are also patients for whom weight loss is unlikely to affect prognosis, such as those with very poor life expectancy. For the remainder of obese ESRD patients, however, structured weight loss might be beneficial. This is most likely to be the case for patients with the most prolonged life expectancy (e.g. those listed for transplantation) as many of the risks associated with obesity take years to manifest. However, there are also potential quality-of-life and mobility benefits that could apply to a larger proportion of the ESRD population (26, 27). This question can only be answered by randomized trials that test the hypothesis that weight loss is safe and improves clinical outcomes in obese ESRD patients. Ideally a comprehensive weight loss intervention would be tested, which would include both dietary modification and increased physical activity and exercise. Pharmacologic agents could also be tested. Approaches to identify patients who might benefit from structured weight loss have been reviewed in detail (28, 29).

If weight loss indeed benefits obese dialysis patients, as defined by BMI, then the problem of misclassification of obesity becomes important. An accurate definition of obesity is needed for ESRD patients, one that can be easily translated to clinical practice. Its measurement should not be unduly cumbersome, yet provide an accurate assessment of body composition. To be useful, this definition should be tied to clinical outcomes so that its use in guiding clinical interventions is relatively straightforward. BMI is clearly insufficient; although easy to obtain, it misclassifies people with excess adiposity but low muscle mass as non-obese. If muscle wasting is severe, even people with substantially increased fat mass are very unlikely to have a BMI in the obese range. For example, only 2.3% of individuals who were both sarcopenic and obese (based on percent body fat) in a nationally representative survey had a BMI ≥ 30 kg/m² (30).

This becomes an important limitation of using BMI in people with advanced kidney disease. Among people with stage 4 CKD in the same nationally representative cohort, 18% were sarcopenic-obese, and approximately 40% of those who were obese based on excess adiposity did not have a BMI ≥ 30 kg/m² (30). The problem of misclassification of obesity by BMI is likely greater in ESRD patients given their high prevalence of protein-energy wasting. Several studies of hemodialysis patients have found misclassification rates of 30–85% using BMI (31–33). In the largest of these, which used bioimpedance spectroscopy to

determine fat mass, 393 of 620 prevalent patients were obese based on body fat percentage, yet 49% of them had a BMI <30 kg/m² (32).

If BMI is inadequate, what is available to replace it? There is a large body of literature on alternative measures to define body composition in ESRD patients, and this has been reviewed extensively elsewhere (34, 35). These include anthropometric measurements, bioimpedance analysis, dual-energy x-ray absorptiometry, and other techniques that are available only in research facilities. Methods of assessing abdominal obesity, such as waist circumference and waist-hip ratio, stand out for their relative ease and utility. Abdominal obesity is predictive of poor outcomes even in people with ESRD (36). This is consistent with the hypothesis that visceral adiposity carries a greater metabolic risk than excessive subcutaneous adipose tissue. That waist circumference associates with outcomes in people with CKD in the same direction as in the general population is due to two factors: (1) lesser confounding by differences in muscle mass compared with BMI, and (2) better representation of visceral adiposity, which is probably harmful in ESRD patients as it is in the general population.

Clinically, the most important obstacle to using any of these alternative measures is the application of cutoffs to guide clinical decision-making. Perhaps the best approach at this time is to view these methods as possible supplements to the use of BMI. It seems reasonable to conclude that nearly all ESRD patients with BMI ≥ 30 kg/m² are obese (31–33). For those who are obese, and especially morbidly obese, weight loss and other typical interventions should be considered based on overall prognosis. For patients with BMI <30 kg/m², waist circumference may be a useful next step to identify excess adiposity. Interventional studies could then examine weight loss and exercise interventions in patients who meet the criteria for abdominal obesity based on waist circumference but are not obese based on their BMI.

In addition to determining the most practical and cost-effective tool to identify ESRD patients with hidden obesity, the unique needs of this population must be determined. Whereas people with BMI ≥ 30 kg/m² are very unlikely to be sarcopenic, those with excess adiposity but BMI <30 kg/m² have a high probability of sarcopenia (30). Thus the appropriateness of targeted weight loss needs to be determined separately for these patients, as there are risks that must be considered. This applies as well to patients with BMI ≥ 30 kg/m² who have experienced loss of muscle mass, even if not severe enough to meet a diagnostic threshold.

For patients with hidden obesity, interventions specifically targeted to build muscle might be most appropriate, with reduction of fat mass a secondary target. In overweight and obese adults, lean mass comprises 25% of weight lost during caloric restriction (37, 38). For a typical obese person with substantial muscle mass, this is not a concern. For someone who is already sarcopenic, further loss of muscle mass is undesirable and could increase morbidity. The same concerns that have been raised in the obese elderly about isolated caloric restriction would extend to ESRD patients with hidden obesity. Due to the high prevalence of sarcopenia among obese elderly people, it has been suggested that dietary interventions always be accompanied by exercise programs (39–41). This combination results in similar

fat loss as caloric restriction alone with the benefit of relative preservation of muscle mass (38, 41–44). One might consider prescribing exercise without a dietary intervention in some patients, although this is less optimal for the management of obesity: while aerobic training interventions improve exercise capacity, they produce only modest fat loss, and resistance training improves muscle mass and strength but does not lead to weight loss (41). Clearly, any intervention in ESRD patients with hidden obesity needs close supervision, and exercise should always be included.

The appropriateness of pharmacologic interventions might also differ in this population. Take liraglutide as an example. Three randomized trials have demonstrated that treatment with liraglutide induces clinically meaningful weight loss in obese individuals (8, 45, 46). Each of these trials used BMI as a central inclusion criterion, as would be expected. If liraglutide were used in the ESRD population, would it be beneficial, safe, and appropriate for patients with normal BMI and excessive adiposity given the accompanying sarcopenia?

Many questions need to be answered to optimize the care of ESRD patients with hidden obesity. The use of BMI to assess body composition in ESRD patients is fraught with difficulty. This impacts clinical care, including the ability to appropriately direct weight-loss interventions and to test their efficacy. Therefore, we must move beyond BMI and test different methods of assessing body composition by examining their effect on outcomes and as a guide to direct clinical interventions. Only then will we clarify the importance of hidden obesity in dialysis patients.

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