The Obesity Paradox and the Role of Inflammation

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The prevalence of the metabolic syndrome and obesity has increased worldwide. Obesity represents a risk factor for both the development of CKD and the development of ESRD. Accordingly, because of the devastating effects of obesity, increasing numbers of patients are affected by CKD. Consequently, weight loss is recommended for early stages of CKD and the general population. However, in advanced CKD and subsequently, ESRD, the so-called obesity paradox has become widely apparent, and it has raised concern. Accumulating evidence has suggested that obesity confers a survival benefit in patients that require dialysis and patients with other chronic diseases. Many studies in American, Asian, and European populations have shown that a high body mass index (BMI) was associated with a survival advantage; indeed, a recent study reported that this association was observed across all age and dialysis vintage groups.

Several studies have attempted to explain this paradox by exploring the obesity paradox as a result of differential lengths of follow-up in dialysis compared with the general population and therefore, if it may reflect occult illness. de Mutsert et al. found that the association between BMI and mortality was similar among patients that required hemodialysis and individuals in the general population when age and time of follow-up were made strictly comparable. In one study, which included >300,000 study participants that received follow-ups that ranged up to 35 years, a high BMI was associated with increased risks of ESRD and mortality. That observation suggested that, over the very long term, a high BMI may be a risk factor for mortality and ESRD. In contrast, when short-term mortality is associated with being underweight, it is most likely attributable to an underlying illness. In this context, low body weight may indicate disease processes that may lead to mortality. This phenomenon is also referred to as reverse causation. Apart from these methodologic explanations, obesity was found to be a stronger risk factor for mortality among younger patients on dialysis than older patients on dialysis. Given the fact that the majority of patients that require dialysis are older, the effects of obesity may be weaker than in populations that do not require dialysis.

In this issue of the Journal of the American Society of Nephrology (JASN), results of a large cohort study have shown a novel important aspect of obesity—the effect modification by inflammation. Stenvinkel et al. found that the paradoxical association between BMI and mortality in patients that required hemodialysis was modified by inflammation. Stenvinkel et al. studied 5904 patients with incident hemodialysis from 15 European countries that were enrolled in the study in 2007–2009. Patients were divided into quintiles by BMI and stratified by the presence or absence of inflammation. Inflammation was defined as a serum level of C-reactive protein ≥10 mg/L and/or albumin ≤35 g/L. The study showed that, during a median follow-up of ≥3 years, in the higher BMI quintiles, obesity did not provide a protective effect in the absence of inflammation among patients on dialysis. In contrast, a higher BMI was associated with a survival advantage in patients that exhibited inflammation.

The study adds an important piece to the puzzle of the obesity paradox, because it suggests a major role of inflammation as an effect modifier. This finding deserves consideration in the clinical setting.

The results obtained in this study are supported by previous, similar findings obtained for cholesterol. In 2004, Liu et al. studied 823 patients on dialysis with the aim of determining
the relationship between cholesterol levels and all-cause as well as cardiovascular disease mortality after accounting for variations in inflammation and malnutrition. Liu et al.\(^9\) showed that higher levels of cholesterol were associated with increased risk for all-cause and cardiovascular disease mortality in the absence of malnutrition and/or inflammation. Conversely, higher levels of cholesterol were associated with decreased mortality in the presence of malnutrition and/or inflammation. Finally, a four-dimensional analysis showed that the effects of parathyroid hormone on mortality were modified by wasting and that inflammation, assessed by serum albumin levels, was an essential component.\(^10\) In that study, in total, 1,255 patients with diabetes that required dialysis were stratified according to the presence or absence of wasting. When wasting was absent, a higher parathyroid hormone was associated with higher risks of death and cardiovascular events; however, the association disappeared in the presence of wasting. Taken together, the previous findings and these findings have suggested an important role of inflammation for both risk assessment and clinical management of patients that require dialysis.

The article by Stenvinkel et al.\(^8\) that is in this issue of JASN brings weight management of obese patients on dialysis into context. What can be learned?

Obese patients in the general population are recommended to lose weight. However, this recommendation becomes uncertain for patients on dialysis because of the frequent observation of the obesity paradox. The article proposed that obese patients should be classified according to inflammation levels. This approach offers a means to identify patients that are most likely to derive potential benefit from intentional weight loss (i.e., obese patients without inflammation). In contrast, caution is required in prescribing weight loss for obese patients with inflammation. These patients may have an underlying disease process, and weight loss may not be warranted. In this context, inflammation is regarded an important feature of the wasting syndrome, which commonly occurs in patients on dialysis.\(^11\)

Up to three quarters of patients on dialysis are affected by wasting.\(^12\) Wasting is a severe syndrome, characterized by poor food intake, low muscle mass, inflammation, and development of comorbid conditions.\(^13\) It also has been referred to as a malnutrition-inflammation-atherosclerosis syndrome or malnutrition-inflammation complex syndrome. In general, patients that experience wasting have an excess risk of cardiovascular disease and death.\(^13\) In this setting, obese patients can experience wasting, despite a high body weight; it may be recognizable by signs of inflammation or weight loss, and underweight patients deserve particular consideration.

The article by Stenvinkel et al.\(^8\) also provides important advice for underweight patients. As the article points out, underweight patients on dialysis represent a high-risk population. Compared with obese patients without inflammation, underweight patients with inflammation exhibited an over five-fold higher mortality risk. This mortality risk may be interpreted partly as a result of reverse causation, in the sense that the majority of patients are likely to have an ongoing disease process (e.g., muscle wasting). Careful treatment of this high-risk group is important. It may include dialysis-related strategies, such as avoiding the use of central venous catheters, and regimens associated with improving inflammatory status, such as daily dialysis for short time periods, appropriate fluid management, or anti-inflammatory interventions.\(^11\) However, an optimal approach for treating the wasting syndrome remains to be found.

In summary, an important new piece has been added to the puzzle of the obesity paradox, which has extended our understanding of its complexity. The implications of obesity in patients on dialysis are heterogeneous and carry differential prognostic information in those who are versus are not inflamed. This novel information can be applied in clinical practice by stratifying patients for risk to ensure appropriate treatment in widespread clinical practices. In contrast, treatment for patients with inflammation, regardless of whether they are overweight or underweight, should focus on resolving the inflammation and treating the underlying causes. The findings of this paper, using observational data, suggest that weight loss may have potential advantages for obese patients on dialysis without evidence of inflammation.\(^8\) This finding should be confirmed in intervention studies before incorporation into clinical practice.

### DISCLOSURES

None.

### REFERENCES

Cancer in ESRD: Clear on the Epidemiology, Hazy on the Mechanisms

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Cancer has long been recognized as a major barrier to long-term survival for patients with treated ESRD, particularly those sustained by kidney transplantation. Cumulative incidence data for cancer among Australian and New Zealand recipients of a first kidney transplant clearly demonstrates the inexorable growth of this problem with time after transplantation (Figure 1).

Our understanding of the incidence of cancer among patients with ESRD was significantly advanced nearly a decade ago by a major linkage project, whereby the authors linked the Australia and New Zealand Dialysis and Transplant registry, containing data for all Australians receiving RRT, with The National Cancer Statistics Clearing House, which compiles data from all Australian population-based cancer registries. Through a series of reports, this group provided cumulative incidence rates of various types of cancer for patients with ESRD prior to RRT, during dialysis, and while transplanted.1,2 Most importantly, by comparing these to the expected rates of each type of cancer among the age-, sex-, and era-matched general population of Australia, standardized incidence ratios (SIRs) were calculated highlighting the differential effects of various states of ESRD on cancer incidence.1

This data illustrated trends consistent with epidemiologic, biologic, and mechanistic concepts: (1) an increased incidence of cancer diagnoses after transplantation, including common cancers such as colon and lung cancer, consistent with the effects of immunosuppression; (2) a profound increase in virus-associated cancer after transplantation, consistent with the effects of immunosuppressive drugs in hindering antiviral defenses; (3) unaltered rates of endocrine-related cancers after transplant, including breast, prostate, and ovarian cancer; (4) modest, though significant, increases in cancer among patients with ESRD prior to the initiation of RRT (SIR, 1.16; 95% confidence interval [95% CI], 1.08 to 1.25) and in dialysis-dependent patients (SIR, 1.35; 95% CI, 1.27 to 1.45) as compared with the general population, with substantially increased incidence of cancers related to renal failure such as myeloma, kidney, renal tract, and thyroid cancers, and some virus-related cancers including Kaposi sarcoma and lymphoma.1 This data, coupled with population-based reports from other countries,3,4 has been used to inform risk and guide practice in transplant recipient management.

In this edition of the Journal of the American Society of Nephrology, Yanik et al. confirm and significantly extend these findings through a much larger study conducted by linking the Scientific Registry of Transplant Recipients to various United States population-based cancer registries.5 In this study of over 200,000 kidney transplant recipients, the authors were powered to not only provide SIR estimates for various cancer types during periods of kidney transplant function and during time on dialysis, but also to track changes in SIRs between periods of transplant function and periods of dialysis among those who experienced graft failure, returned to dialysis, and were then retransplanted. Such sequential observations dramatically highlight the peaks in incidence of so-called virus- and immune-mediated cancers during transplantation, with corresponding falls in incidence following return to dialysis. Consistent with the Australian data,1,2 cancers linked to kidney failure, including kidney, urinary tract, and thyroid cancers, were increased maximally during times of dialysis and only modestly increased over the incidence in the general population during intervals of transplant function.

Several potentially important differences between the studies are noteworthy. The SIRs of cervical, liver, and colon cancers were significantly increased during dialysis and further increased after transplantation in the Australian study,1,2 though not in the United States study.5 Potential explanations include: (1) era...