

Obesity: the verse and the reverse

Obesidade: o verso e o reverso

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Although the increasing prevalence of obesity and metabolic syndrome in the general population, its implications for individual and collective health, and the alarming added costs to the care of the affected population, nephrological community is surprised by the paradoxical association between overweight/obesity and lower mortality rates in dialysis patients, despite the high occurrence of diabetes, hypertension and cardiovascular disease in this population. Because in this scenario obesity may confer protection and not morbidity, these intriguing findings would indicate evidence of reverse epidemiology.

The use of the Body Mass Index (BMI) is standard to define and grade obesity in epidemiological studies, although there is some arbitrariness in the definition of dry weight in chronic uremia from which BMI is obtained. Although widely accepted as a valid indicator, BMI does not preserve specificity for adiposity or lean mass, and there is reasonable evidence that lean mass loss may best predict mortality risk.¹ To estimate the latter we can use additional resources such as serum creatinine, urinary creatinine excretion, anthropometric measurements or dual-energy X-ray absorptiometry (DEXA).

In addition, adiposity fills two compartments with distinct anatomical and metabolic activities. The subcutaneous fat is the largest one, with a predominance of white adipocytes that accumulate triglycerides, whereas the visceral adipose tissue is of smaller extension, distributing itself in the omentum, mesentery and around visceral organs, being quite implicated in the obesity-related abnormalities and outcomes. More than representing an energy

storage tissue, adiposity secretes adipokines and hormones with the potential to explain, for example, the prevalent micro-inflammatory condition in these patients, in addition to being associated with sympathetic hyperactivity.² Even more, it is recognizable that phenotypes seem to exist for obesity, since individuals with similar levels of accumulated adiposity may present different patterns of insulin resistance, non-alcoholic fatty liver disease, fetuin-A secretion, cardiovascular calcification, sedentary lifestyle, and morbidity.³

In spite of its conceptual limitations, obesity maintains multiple interactions with relevant players in the scenario of chronic kidney disease. In this volume of the BJN, Franco *et al.*⁴ analyze the relationship of baseline BMI with demographic and clinical characteristics in incident elderly patients in peritoneal dialysis, and BMI modifications over time with associated overall mortality. In short, the main findings are (1) it was observed 1% reduction in mortality for each unit increase of the BMI at baseline, and (2) the mortality is reduced by 12% for each 1 unit increase in BMI over time. In addition to an increased risk of death, malnourished patients were older, with lower literacy and greater functional impairment according to Karnofsky index. On the other hand, obese patients included a higher proportion of women, with longer follow-up and higher arterial pressures. The elegant use of the joint-model allows us to describe how longitudinal measurements (e.g. repeated BMI measurements) affect the survival outcome (e.g. mortality).

Among the hypotheses supported to explain the relative protection afforded

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by obesity are the largest nutritional reserve *per se*, since obesity can attenuate the full establishment of *protein-energy wasting* (PEW) and/or the prevalent inflammatory status in uremia.¹ Patients in a peritoneal dialysis program absorb daily 45% of the glucose content of the dialysis solution, which may explain the reduction in the difference between obese and malnourished outcomes. Another alternative to explain the paradox of obesity is the time discrepancies among competing risk factors, which reflect the recognition that survival expectancy (very limited in chronic kidney disease and heavily dependent on malnutrition and catabolic factors) interacts to pervert the usual relationships between traditional cardiovascular risk factors and hard outcomes. For the purpose of this discussion, the study by Franco *et al.*⁴ presents a group of obese patients with greater representation of women, more literacy and longer follow-up, characteristics that may already have positive prognostic implications, especially in a population of low survival in which the very later consequences of obesity are more difficult to visualize than those of the PEW.

In addition, obesity has been associated with greater hemodynamic stability in the short term, and less occurrence of hypotensive episodes, and possibly causing e.g. smaller myocardial stunning. In addition, in obesity overlapping with chronic uremia, there are altered cytokine profiles, as well as uremic toxins sequestered by adipose tissue and by higher levels of lipoproteins typically seen in obesity. It is also possible that specific relations between obesity and outcomes could be modified by particular processes that resulted in the uremic population as we know, specially the fact that the majority of CKD patients do not live enough to reach the final stages of their disease, a phenomena called *survival bias*.

Although not explored, there is a practical interest in accessing how individuals with similar BMI would

evolve if the course of their longitudinal measurements differed. Obese patients with progressive gain or weight loss would have the same prognosis? And the malnourished, do they do differently? As the current study is observational, trials will be required to test some intervention measures.

The study by Franco *et al.*⁴ launches new concerns about our initiatives to reduce weight of obese patients, as well as stimulates us to explore the interface between obesity, its anabolic and catabolic aspects, and related outcomes. Inflammation may be an interesting feature to interact with the protective effect of obesity.^{5,6} In addition, we can expect new intervention studies involving factors recognized in observational studies that may translate into better clinical outcomes in ESRD patients in the future.

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