

Kidney disease and obesity paradox

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Obesity has been considered as one of important risk factors for cardiovascular (CV) disease and mortality in the general population. As its harmful aspect has been too much emphasized, many physicians ignore other facets of overweight/obesity nowadays. A number of epidemiologic studies from large samples of chronic kidney disease (CKD) and end-stage renal disease (ESRD) have reported that worse survival was observed with a lower body mass index (BMI), and higher values of BMI reflecting overweight or obesity seemed to be associated with better survival. This phenomenon has been referred to *obesity paradox* [1]. It is universal phenomenon beyond regional and racial difference. In Korean patients with ESRD, BMI level was inversely associated with mortality and the association were very similar with Caucasians and African-Americans [2]. A recent nationwide cohort study in Korea also showed that subjects with a BMI of 25.0–29.9 kg/m² had a lower risk of mortality compared with the reference (BMI, 23–24.9 kg/m²) in the elderly and patients with chronic diseases (diabetes mellitus, hypertension, and CKD) [3]. Of note, *obesity paradox* was not restricted to patients with CKD/ESRD but has been also observed in the elderly and in patients with other chronic diseases such as congestive heart failure and malignancy.

Obesity paradox may not necessarily mean that the

principles of vascular pathology are different between a specific disease population and the general population. More dominant factors may overwhelm the traditional relation between obesity and worse outcomes as seen in the general population. Among several hypotheses, two points of view are worth bearing in mind [1]. The first is protein-energy wasting (PEW), which is a condition for simultaneous loss of systemic body protein and fat mass (energy reservoir) [4]. PEW may debilitate physiologic functions of the various organs and may affect clinical outcome in addition to a specific disease itself. In situation of deficiency or excessive consumption in energy, obesity may potentially attenuate the magnitude of PEW, resulting in favorable outcomes in patients. The second is time discrepancies among competing risks. Effects of obesity leading to cardio-metabolic derangement occur over a long period and have been reported from studies in long-living populations. However, favorable effects of obesity on PEW may, in the short term, outweigh harmful effects on CV disease in the long term. Please note that mean or median follow-up durations were less than 5 years in most studies reporting *obesity paradox* from patients with ESRD (Tables 1 and 2 in reference 1).

In acute disease, an association between obesity and outcome may also be explored in the view of PEW. In this issue of *Kidney Research and Clinical Practice*, Kim et al [5] evaluated intensive care unit (ICU) mortality by BMI in a total of 212 patients who had undergone continuous renal replacement therapy (CRRT) for various cause of acute kidney injury (AKI). They found that the highest tertile of BMI (25.5–37.1 kg/m²) was significantly associated with a decreased risk of 30-day ICU mortality compared to the lowest tertile of BMI (13.5–21.8 kg/m²) (hazard ratio, 0.57; 95% confidence interval, 0.37–0.87). The model was adjusted for other confounding factors

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including sex, age-adjusted Charlson comorbidity index, septic AKI, sepsis-related organ failure assessment score, white blood cell count, serum albumin level, and CRRT prescription. The associations with 60- and 90-day ICU mortality were similar. The result comes into line with previous studies reporting an association between BMI and mortality in ICU patients [6]. Obviously, critically ill patients with AKI on CRRT are in the extreme edge of PEW due to hypercatabolism, uremia, and nutritional loss via dialysis modality. Overweight or obesity seems to have a beneficial effect in this situation, and this observation may offer insights into possible explanations for *obesity paradox* in chronic disease.

It should be considered that BMI, as an index of obesity, has limitations. BMI has a limited ability to differentiate adiposity from muscle mass. A higher BMI may reflect a higher muscle mass as well as a higher fat mass in part. A favorable outcome observed in patients with a higher BMI might be due to adequate muscle mass. Many studies have consistently shown a relationship between low muscle mass (sarcopenia) and an increased risk of mortality [7]. Furthermore, the changes in body composition include an increase in body fat and a decline in skeletal muscle, although BMI may remain relatively unchanged. Sarcopenic obesity, an emerging concept, has become increasingly important but it is not clear whether *obesity paradox* is still present in this situation. Next, BMI cannot discriminate central (or visceral) obesity from generalized obesity. Central obesity is more closely related to cardiometabolic derangements. In CKD, central obesity was associated with increased inflammatory profiles, suggesting that circulating inflammatory cytokines and free fatty acid released by visceral fat may play a role in chronic low-grade inflammation. A higher BMI may be protective whereas a higher waist circumference (WC) may be predictive of mortality. The incidence rates of overall and CV death were highest in patients with relatively lower BMI scores and larger WCs, and the outcomes were best in patients with higher BMI scores and smaller WCs [8].

The *obesity paradox* in CKD/ESRD patients may have indeed serious clinical and public health implication. The study from Kim et al [5] has extend the issue of *obesity paradox* to AKI. Lots of evidences indicate that in observational studies, *obesity paradox* is not merely a biased result although our understanding of pathophysiological process underlying this phenomenon has been still insufficient. Etiology, biological mechanism,

and consequence of muscle and fat loss should be further investigated. Randomized trial based on biological knowledge and intervention would finally prove causal inference. At this point in time, adequate nutritional support is the best thing that we can do. To improve outcome in patients with kidney disease, it is worthy to struggle against PEW.

Conflicts of interest

The author has no conflicts of interest to declare.

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