Risk Factor Paradox in CKD and ESRD: Does a Healthy Lifestyle Matter?

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Compared with the general population, cardiovascular (CV) events and mortality are higher in the ESRD population. However, the role of conventional CV risk factors in increased risk of CV events and mortality in the ESRD population has been controversial. In particular, obesity, hypertension, and dyslipidemia are not associated with increased mortality in the hemodialysis population (1). This risk factor paradox raises troubling questions. If obesity is good and hypertension and dyslipidemia are not bad, should we even bother with a healthy lifestyle in dialysis patients? Are these risk factors different in the nondialysis CKD population?

In this issue of *CJASN*, Ricardo *et al.* (2) have evaluated the association of lifestyle factors with mortality in nondialysis CKD in the National Health and Nutrition Examination Survey (NHANES) III cohort. Ricardo *et al.* (2) defined healthy lifestyle by diet, body mass index (BMI), physical activity, and smoking. They found that, similar to the general population studies, adherence to a healthy lifestyle was associated with lower all-cause mortality. When individual components of the lifestyle scores were examined, the greatest reduction in mortality was related to nonsmoking. Physical activity was also independently associated with lower risk of death. In studying the association of body size with mortality, a higher risk of mortality was observed in those individuals with lower BMI (18.5 to <22 kg/m^2) compared with those individuals with healthy BMI (22 to <25 kg/m^2). However, compared with the healthy BMI group, those individuals who were overweight (BMI of 25 to <30 kg/m^2) or obese (BMI>30 kg/m^2) did not have increased mortality. No significant association was also observed with diet and all-cause mortality in the fully adjusted model.

This study has several major strengths. Ricardo *et al.* (2) examined a question of considerable clinical relevance. Furthermore, the complex survey design of NHANES is such that the sample is representative of the noninstitutionalized US civilian population, and the correct use of sampling units and survey weights allows the results to be extrapolated to the noninstitutionalized US civilian population. Furthermore, the data collection in NHANES follows stringent standards. However, because this study is an observational study, caution is warranted in interpreting the findings, and strong causal inferences should not be drawn.

Nonetheless, this study has important implications. One of the least controversial issues in lifestyle modification is smoking cessation. Smoking has been associated with increased mortality in the general population and CKD population as well as the dialysis population (3). Furthermore, in a Swedish survey, high daily dose, longer duration, and high cumulative dose of smoking were associated with increased odds of kidney disease (4). In NHANES II data, smoking at baseline was independently associated with higher subsequent risk of reaching ESRD (5). Therefore, smoking cessation should be a priority for decreasing risk of kidney disease progression as well as mortality in those individuals with CKD.

Physical inactivity has been associated with increased mortality in CKD (6) and ESRD (7,8) populations. Frailty, a measure of physical functioning, has been associated with increased mortality (9). It remains to be tested whether physical activity interventions could improve frailty and decrease mortality in CKD. Although the current national recommendations in the general population are for 150 minutes per week of moderate activity or 75 minutes per week of vigorous activity (10), LOOK-Action for Health in Diabetes (AHEAD), a large randomized controlled trial conducted by the National Institutes of Health, was stopped 2 years early, because the intensive lifestyle intervention program of weight loss achieved by decreased caloric intake (1200–1500 kcal per day) and increased moderate/vigorous activities (175 minutes per week) did not reduce the primary cardiac composite end point (11). Similar interventional trials examining hard end points have not been conducted in the CKD or ESRD population. However, increased physical activity might improve physical functioning and quality of life. Hence, increased physical activity should be encouraged in the CKD population.

Ricardo *et al.* (2) found that a higher healthy eating index was associated with lower mortality, but this finding was nonsignificant when fully adjusted. However, caution is warranted in interpreting fully adjusted models. First, no epidemiologic study will be able to fully adjust for the measured and unmeasured confounders. Second, fully adjusted models might adjust for covariates without considering the causal pathway. If healthy eating decreases mortality by decreasing the risk for diabetes, hypertension, and dyslipidemia, then adjusting for

these factors should attenuate/eliminate the association of healthy eating with mortality. In that situation, it is erroneous to conclude that healthy eating does not matter.

Indeed, other epidemiologic studies suggest that a diet high in fruits and vegetables and low in salt and sugar might be beneficial in the CKD population. There might be physiologic benefits to a diet high in vegetable sources in more advanced CKD. A higher intake of fiber was associated with decreased inflammation and mortality in CKD (12). The production of uremic toxins, such as p-cresyl sulfate and indoxyl sulfate, is lower with vegetable sources of protein (13). Vegetable sources of protein also result in lower serum phosphorus (14), decreased serum fibroblast growth factor-23 levels (14), and lower endogenous production of acid. In the African American Study of Kidney Disease and Hypertension cohort, higher estimated net endogenous acid production was associated with lower serum bicarbonate (15) and greater loss of measured GFR (16). A Western dietary pattern (higher intake of processed and red meats, refined grains, sweets, and dessert) was associated with rapid estimated GFR (eGFR) decline, whereas Dietary Approaches to Stop Hypertension (DASH) dietary patterns (high in fruits and vegetables) had decreased risk of rapid eGFR decline (17). Consumption of more than or equal to two servings per day of artificially sweetened soda was also independently associated with eGFR decline (18).

Although the patterns of the associations of smoking, physical activity, and healthy eating with mortality and other outcomes are similar in the general, CKD, and dialysis populations, the most striking pattern is the consistent observation that higher BMI is associated with increased mortality in the general population but lower mortality in the dialysis population (19–28). Hence, it has been suggested that obesity is good in dialysis patients (21).

This finding raises obvious questions. What are the molecular mechanisms by which obesity increases mortality in the general population? Does uremia alter these mechanisms? In addition to energy homeostasis, the adipose tissue is metabolically active and secrets several cytokines referred to as adipokines, such as adiponectin, leptin, visfatin, TNF-α, TGF-β, IL-6, and monocyte chemo attractant protein-1, that mediate the metabolic effects of obesity, such as inflammation and insulin resistance (29). In the CKD population as well as the dialysis population, the metabolic effects of adiposity are similar to the effects seen in the general population. For instance, obesity is associated with metabolic syndrome (30) and increased cardiovascular events (31) in CKD patients, and obesity is associated with diabetes (32), inflammation (33), coronary calcification (34,35), and carotid atherosclerosis (36) in dialysis patients.

Thus, the survival advantage conferred by obesity in dialysis patients cannot be explained by modification of the metabolic effects. Then, what explains the BMI paradox?

A potential explanation is that adiposity has dual competing effects on survival: a protective nutritional effect and a deleterious metabolic effect. The balance between these effects is modified by the level of kidney function. In individuals who are obese with normal kidney function, the metabolic effects dominate the nutritional effects, leading to increased mortality compared with individuals who have normal BMI and normal kidney function. In individuals who are obese and have ESRD, the nutritional effects dominate the metabolic effects, leading to better survival (despite the greater prevalence of inflammation and insulin resistance) compared with ESRD patients with normal BMI. The protective nutritional effects and the deleterious metabolic effects cancel out each other in nondialysis CKD, leading to no survival differences in those individuals with CKD and obesity compared with those individuals with CKD and normal BMI. Indeed, a previous study found that, despite the greater prevalence of metabolic syndrome in obese CKD patients compared with nonobese CKD patients, there were no survival differences (30). In the study by Ricardo *et al.* (2), there was also no increased mortality with obesity in CKD.

Finally, should we encourage weight loss in CKD and dialysis patients? Body composition matters in dialysis patients (19). Although higher fat mass does confer a survival benefit compared with lower fat mass, the best survival is seen in individuals who have high muscle mass. In other words, although fat is good, muscle is better. Instead of focusing on weight loss, it might be beneficial to focus on losing fat and gaining muscle in CKD and dialysis patients. Indeed, this benefit is the effect of exercise.

In summary, in CKD and dialysis patients, despite the apparent risk factor paradox, a healthy lifestyle of not smoking, increased physical activity, and a diet high in fruits and vegetables and low in concentrated sweets is warranted. Interventions that increase muscle mass and decrease fat mass are likely to be beneficial in the CKD and dialysis populations. The work by Ricardo *et al.* (2) should stimulate interest in lifestyle interventions in CKD and dialysis patients.

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Disclosures

None.

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