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Does an Apple (or Many) Each Day, Keep Mortality Away?

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In this issue of the *Clinical Journal of the American Society of Nephrology*, Saglimbene *et al.* (1) highlight the importance of fruit and vegetable intake in 9757 patients undergoing dialysis across 11 European and South American countries by demonstrating that a higher number of fruits and vegetables consumed per week is associated with lower risk of all cause and noncardiovascular mortality. Assessment of intake was by self-report by asking two questions that are part of the GA^{2}LEN questionnaire—"How often did you eat fresh fruit during the previous year?" and "How often did you eat any vegetables (excluding potatoes) during the previous year?"—at a single point in time. Patients were followed for a median 2.7 years and the primary outcome of mortality was coded as "cardiovascular" and "noncardiovascular." The authors show that in comparison to two servings of fruits and vegetables per week, 17 servings per week are associated with a 20% lower hazard of all-cause mortality, the primary outcome (HR, 0.80; 95% CI, 0.71 to 0.91) and a 23% lower hazard of noncardiovascular mortality (HR, 0.77; 95% CI, 0.66 to 0.91), with no significant relationship with cardiovascular mortality, which is surprising, given the purported benefits of fruits and vegetables, but mirrors findings in a large cohort study in the general population (2).

The putative benefits of fruit and vegetable intake include benefits to BP, lipid control, and improvements in endothelial function and insulin sensitivity. Despite these benefits, typical intakes of fruits and

Dietary Guidelines for Americans 2015–2020, as well as various European guidelines, recommend four to five servings of fruits and vegetables daily (3). But, in a general population cohort of 135,335 adults from 18 countries, only 30% ate more than the recommended four servings a day (2). However, Saglimbene *et al.* show that this deficit is a far cry from that of patients on prevalent hemodialysis. In this study, only 4% of participants ate more than a median of four servings daily. As a result of this poor daily intake, overall fruit and vegetable consumption in patients on hemodialysis had to be expressed as servings per week in this analysis, to even be meaningful. The overall median combined fruit and vegetable intake was only a median of eight servings per week, with variability across countries surveyed.

Inadequate fruit and vegetable intake may be a lifelong habit in some individuals, but the findings from this study demonstrate that it is dramatically lower in those on hemodialysis compared with the general population. As the authors point out, patients undergoing hemodialysis are routinely advised to eat a diet

including 2 g potassium per day. Patient education materials often include food lists categorizing potassium-containing foods. Foods listed as “high potassium” or >200 mg per serving, the majority of which are fruits and vegetables, are labeled to avoid (4). There are also “low potassium vegetables and fruits” listed with the implicit “warning” that large portions (more than half a cup) of even the “low” potassium foods may contain excess potassium. Given the repeated advice patients on dialysis hear to avoid potassium-containing foods (as well as for years in predialysis CKD clinics), it is plausible that many patients just chose to avoid fruits and vegetables to limit potassium. The inadvertent consequence of this avoidance is that they fail to derive benefits from fruits and vegetables such as the antioxidants, fiber, and other benefits. Despite this recommendation, there is actually little data to support that eating fruits and vegetables increases serum potassium. A recent study in 140 patients undergoing dialysis showed no significant correlations between reported mean potassium intake and predialysis serum potassium level (4). Consistent with this, Saglimbene *et al.* (1) reports that predialysis potassium was not significantly different across tertiles of potassium intake. In our study of patients with CKD stage 4, we similarly did not see an increase in serum potassium levels after switching to a 70% plant-based diet (5). Although hyperkalemia is indisputably an important health risk in those with CKD, it may be that avoiding fruits and vegetables is not the best answer (4). Potassium intake and fruit/vegetable goals may need to be to individualized in those on dialysis, taking into account that multifactorial nature of hyperkalemia, with muscle breakdown, systemic pH, insulin-mediated tissue distribution, and dialysis adequacy all playing a role.

A recent set of semistructured interviews regarding diet in patients on dialysis shows that they believe that diets would improve their disease symptoms but that they are frustrated with confusing advice they receive with respect to their diets (6). A word search of the term “diet” through each of the Kidney Disease Improving Global Outcomes (KDIGO) Guideline Statements reveals a few references. The KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of CKD recommends “that individuals with CKD receive expert dietary advice and information in the context of an education program, tailored to severity of CKD and the need to intervene on salt, phosphate, potassium, and protein intake where indicated” (1B) as well as recommendations for level of protein intake (2C) and lowering salt intake (1C) (7), whereas the 2017 revised KDIGO CKD mineral bone disorder recommendations has a statement “to consider phosphate source (*e.g.*, animal, vegetable, additives) in making dietary recommendations” that is not graded (8). The 2013 Lipid Guidelines discuss dietary changes to reduce serum triglycerides, with the caveat that it is a weak recommendation, made on the basis of very low-quality evidence (9). In summary, patients on hemodialysis want dietary advice, but evidence regarding specific aspects of diets (including fruit and vegetable intake) as well as a “unified” approach to prescribe eating patterns across nutrients in CKD stage 5D is currently lacking and, when available, extrapolated from the general population. This makes it difficult for clinicians to tailor dietary recommendations to patients on hemodialysis.

How might the study by Saglimbene *et al.* (1) fit into the current literature for dietary management for patients undergoing dialysis? In observational studies, larger magnitudes of effect sizes, a dose–response gradient, and freedom from bias allow some upward rating of the quality of a study during a formal evidence review process (10). This study showed a 10% lower hazard of mortality with higher fruit and vegetable serving size from two to eight per week, and a 20% lower hazard ratio with 17 servings per week (compared with two per week), suggesting a dose–response gradient associated with the median number of servings of fruits and vegetables and all-cause mortality. This dose–response relationship increases our confidence on the effect of fruit and vegetable intake in this study population. In this study, selection bias was likely low, the primary outcome is a definitive clinical outcome (mortality), and exposure assessment (fruit and vegetable intake) is available in the majority of participants (83%). These are all strengths of the study. There are, however, limitations, the most important of which is that asking a question on food intake for the previous year at a single point in time leads to significant potential for recall bias. The design of the study also limited the authors’ ability to adjust for some prognostic variables that could be responsible for

residual confounding, such as dialysis bath potassium, residual kidney function, seasonal variability in fruit and vegetable intake, and whether vegetables were eaten cooked or raw. The manner of cooking vegetables may affect level of dietary fat and advanced glycation end products and thereby outcomes (11). These unaccounted-for details in fruit and vegetable intake could explain the lack of relationship with cardiovascular mortality. However, these limitations do not minimize the importance of the study by Saglimbene *et al.* (1), as the impressive 20% reduction in all-cause mortality with higher fruit and vegetable intake will hopefully spur future studies by this group and others. The hope is this excellent cohort study will form the basis of well designed, randomized, controlled trials to test the effect of fruits and vegetables in patients undergoing hemodialysis, so we, as their nephrologists, along with dieticians, can provide the details of dietary guidance they deserve.

Disclosures

None.

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Footnotes

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See related article, “Fruit and Vegetable Intake and Mortality in Adults undergoing Maintenance Hemodialysis,” on pages 250–260.

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