Where What Is Not Stated or Required May Be the Most Illuminating

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In this issue of *CJASN*, Khatri and colleagues report that increasing adherence to a Mediterranean diet is directly associated with a significantly lower risk of developing incident CKD (defined as eGFR<60 ml/min per 1.73 m^2) after a mean 6.9 years of follow-up in 900 ethnically diverse participants of the Northern Manhattan Study (NOMAS) (1).

Moreover, each additional 1-point increase representing Mediterranean diet adherence was associated with a 12% decreased odds ratio (OR) of being in the highest quartile of eGFR decline (≥2.5 ml/min per 1.73 m^2 per year, which is notably higher than the 1 ml/min per 1.73 m^2 per year expected with normal aging). The association between Mediterranean diet adherence and incident eGFR<60 ml/min per 1.73 m^2 was stronger in patients without diabetes than patients with diabetes. Furthermore, this association was statistically significant in those individuals who were not taking angiotensin-converting enzyme inhibitors or angiotensin receptor blocker medications (adjusted OR per 1-unit increase in MeDi score, 0.76; 95% confidence interval [95% CI], 0.63 to 0.90; $P=0.002$) but was nonsignificant in the 18% who were taking these medications at baseline (adjusted OR, 1.06; 95% CI, 0.80 to 1.39; $P=0.69$).

Perhaps what is not mentioned is more revealing and informative than what is provided in the article by Khatri *et al.* (and others). For example, very few details are given in this article as to what constitutes a Mediterranean diet, which prevents readers eager to adopt this diet immediately from easily doing so. The sparse information on how to follow a Mediterranean diet is likely based on an assumption that the main concepts are already familiar to the expected audience.

Such an assumption is certainly reasonable in light of the recent and frequent reports of the benefits of the Mediterranean diet in the mainstream media. In 1999, the Lyon Diet Heart Study reported that patients who survived their first myocardial infarction (MI) who were randomized to the Mediterranean diet had a ≥47% risk reduction for cardiovascular and mortality end points compared with the group assigned to a "prudent Western-style diet" (2). In 2013, another randomized controlled study of 7447 Spanish participants (Prevención con Dieta Mediterránea [PREDIMED]) at high risk for cardiovascular disease (CVD) found that those assigned to one of two Mediterranean diets had an approximately 30% reduced risk of a composite end point of MI, stroke, or cardiovascular death compared with a control diet (3). It is important to note that the Lyon Diet Heart Study was a secondary prevention trial in patients who had already experienced a MI event, whereas the Spanish PREDIMED study focused on primary prevention in people who were at high risk for CVD (49% with type 2 diabetes, 83% with hypertension, and >90% with overweight or obesity by body mass index). The population studied in NOMAS was healthier than these other two cohorts (*e.g.*, 19% with diabetes, 69% with hypertension, and all without prior history of stroke), but a beneficial association between Mediterranean diet and lower risk of incident cardiovascular disease was also observed (4).

Although the consistency of an association of the Mediterranean diet with both macrovascular (heart and brain) and microvascular (kidney) health is expected, the effect modification by diabetes status and renin-angiotensin-aldosterone system medication use observed in the study by Khatri *et al.* (1) is interesting. Perhaps that is why in their conclusion, the investigators advocate for a randomized controlled clinical trial of the Mediterranean diet to confirm or refute their findings of how this dietary pattern may affect kidney function change over time. A proposal for interventional trials is the typical, expected next step after a potential beneficial effect has been reported in an observational study. However, in further considering the sizeable resources and long follow-up time needed to perform a high-quality randomized trial to study diet and kidney function, doubts begin to arise. First, based on the large body of work in nutritional epidemiology, a hope of identifying a key nutrient or food as driving most of the health benefit in this dietary pattern seems unlikely to be realized. Second, because two randomized trials as well as a meta-analysis of approximately 1.5 million people (5) have already reported decreased risk in primary and secondary prevention of CVD, would a null result in kidney function decline lead to a recommendation against a Mediterranean diet? No, and furthermore, the probability of this dietary pattern having a detrimental effect on renal function when the evidence is on the side of benefits to macrovascular disease presumably through lowering of lipids and inflammatory markers (6,7) seems highly unlikely.

The nephrology world is understandably cautious about relying solely on noninterventional data because

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multiple observational studies initially established an association between anemia and adverse outcomes in patients with CKD/ESRD, leading to initial guidelines for targeting hemoglobin in the normal range. Subsequently, multiple clinical trials with erythropoiesis-stimulating agent (ESA) therapy reported worse outcomes at higher hemoglobin levels in patients with kidney disease, although whether this stems from direct effects of ESA therapy or achieving a high hemoglobin target continues to be debated. An important distinction, however, is that although ESA therapy has recognized adverse effects and risks, there is theoretically no risk to following a healthy diet pattern. Perhaps this assumption is overly optimistic and unfounded?

Because this is the 21st century, I turned to the Google search engine to search for the top "hits" related to any potential adverse effects of the Mediterranean diet. Key words used for the searches included "adverse," "events," "Mediterranean," "diet," "disadvantages," and "detrimental." Only a few relevant websites were found. The first website, the ubiquitous Wikipedia (http://en.wikipedia.org/wiki/Mediterranean_diet), revealed a reasonably comprehensive summary and cited several articles reporting a beneficial association with health outcomes and none with adverse outcomes. An IndiaParenting.com article entitled "Disadvantages of Mediterranean Diet" (8) cited the following concerns: risky for the hypersensitive system, not cost-effective, many other alternative diet plans exist, and few benefits compared with disadvantages. In the last section, the writer makes the excellent point that this diet alone will not confer health and that smoking cessation and physical activity are also important, but otherwise does a poor job of supporting the claim of few benefits. In an article posted on AgeWatch.com, Baber (9) mentions that their review "found no adverse effects mentioned in the research" with the possible exception that the diet may not be well suited for those with irritable bowel syndrome. There were also a number of websites containing complaints constituting that a Mediterranean diet is vague and difficult to follow.

Those who bemoan the lack of clarity about how to follow a Mediterranean diet need only to refer to the published article (or even the Wikipedia entry above) for illumination. For example, referring to the information published in the PREDIMED trial (3), the Mediterranean diet is characterized by high intake of fruits and vegetables (≥5 servings per day), fish and seafood (≥3 servings per day), legumes (beans, peas, and lentils) (≥3 servings per week), nuts (≥3 servings per week), and olive oil (≥4 tbsp per day), with optional moderate alcohol intake with meals (presumably 1–2 servings per day) as well as eating "white meat" (lean animal protein). The recommendations of low-fat dairy intake as well as whole grains do vary between descriptions of Mediterranean diets, but the focus on what foods to avoid may be the real key. These foods include soda, commercial baked goods, and red and processed meats, which essentially amounts to limiting ingestion of highly processed or refined sugars and grains as well as meats (and animal-based cooking oils such as lard) high in saturated fats (characteristics of a Western-style diet). Notably, other observational epidemiology studies have reported that Western-style diets are associated with more rapid eGFR decline and microalbuminuria (10), whereas healthy diet patterns characterized by higher intake of fruits, vegetables, and whole grains are associated with lower risk of rapid eGFR decline (10) or presence of microalbuminuria (11).

In continuing the theme of what is missing may be the most important, the PREDIMED trial demonstrated a health benefit of the Mediterranean diet in people at high risk for CVD without directed efforts to increase physical activity or improve overweight/obesity status. By contrast, a multidisciplinary approach to type 2 diabetes management including diet, exercise, smoking cessation, as well as medications appears to be effective in reducing vascular complications by approximately 50% compared with the standard of care (12).

In summary, perhaps there is already sufficient research to assert that a Mediterranean-style dietary pattern as defined above is only one component of an overall healthy lifestyle, which also needs to incorporate regular physical activity for the maintenance of healthy weight and muscle mass throughout our lifetimes, especially at more advanced ages. Although this is a seemingly simple goal, achieving this is challenging. We need to begin by embracing the reality that there is no magic pill or miracle food, only vigilance and discipline with diet and regular exercise and the rare indulgence in cake for very special occasions.

Disclosures

J.L. is an employee of Genzyme Corporation.

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