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Time to Think About Nutrient Needs in Chronic Disease

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There is renewed interest in health benefits of folic acid supplementation since the China Stroke Prevention Primary Prevention Trial (CSPPT) showed the potential benefits of folic acid in preventing stroke in Chinese adults with hypertension.¹ It has long been known that folic acid prevents neural tube defects, which are among the most severe and debilitating congenital birth defects worldwide. The CSPPT was terminated early when 800 µg of folic acid in combination with 10 mg of enalapril significantly reduced primary stroke incidence compared with the enalapril alone treatment arm. This finding was unexpected as other studies had failed to find a preventive effect of folic acid supplementation on cardiovascular events.² In this issue of *JAMA Internal Medicine*, Xu et al³ report findings from a prespecified CSPPT substudy that demonstrated that the folic acid–enalapril combination was more effective than enalapril alone in the secondary prevention of renal function decline among Chinese adults with hypertension across a spectrum of mild to moderate chronic kidney disease (CKD).

Folic acid is commonly administered to treat hyperhomocysteinemia, but the benefits of homocysteine lowering on the prevention or management of most chronic diseases associated with hyperhomocysteinemia remains unproven.² In the renal substudy of the CSPPT,³ Xu and colleagues report that 42% of participants with CKD exhibited hyperhomocysteinemia (serum homocysteine 15 µM) and 24% had diabetes, compared with only 26% with hyperhomocysteinemia and 12% with diabetes in those without CKD. Individuals who were homozygous for the *MTHFR* C677T polymorphism, a genetic variant that expresses an enzyme with reduced 5-methyltetra-hydrofolate synthesis activity, exhibited the greatest reduction in serum homocysteine following folic acid–enalapril treatment because their baseline levels of circulating homocysteine were higher. This finding is consistent with other studies suggesting that the current recommended dietary intake for folate may not be adequate for individuals homozygous for the *MTHFR* 677T variant when homocysteine lowering is used as the functional biomarker to assess folate status.⁴

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Importantly, the folic acid–enalapril combination was more effective in reducing rates of renal dysfunction in individuals with CKD (odds ratio [OR], 0.44; 95% CI, 0.26-0.75) compared with enalapril treatment alone, with the primary outcome measure being a prespecified level of decline in the estimated glomerular filtration rate (eGFR).³ The folic acid–enalapril treatment significantly reduced other measures of renal dysfunction in addition to the 21% reduction in risk for the primary outcome compared with the enalapril-only group. These included secondary outcome measures of rapid decline in renal function (OR, 0.67; 95% CI, 0.47-0.96) and a composite event measure (OR, 0.62; 95% CI, 0.43-0.90); both were significantly reduced in the group receiving the folic acid–enalapril combination compared with the enalapril group. There was no evidence for primary prevention of CKD in either arm of the study.

Hyperhomocystenemia is a common finding in patients with CKD. However, folic acid–induced reductions in serum homocysteine levels did not affect kidney function in other studies.^{5,6} Xu et al hypothesized that these differences may be owing to the inclusion of other B vitamins, including vitamin B₁₂, in previous vitamin supplementation trials on renal function. Also, the level of folic acid supplementation varied markedly among these trials. The study by Xu et al administered folic acid at levels below 1 mg/d, whereas other studies administered folic acid at much higher levels. Dose may be an important modifier of efficacy and toxic effects, especially for specific clinical populations. For example, in patients with diabetic nephropathy, subjects receiving 2.5 mg/d folic acid, 25 mg/d vitamin B₆, and 1 mg/d vitamin B₁₂ exhibited greater decreases in serum homocysteine than did those receiving placebo, but kidney function (measured by eGFR) unexpectedly decreased more in the treatment group than in the placebo group.⁵ In a related study, patients with advanced kidney or end-stage renal diseases were treated with 40 mg/d folic acid, 100 mg/d vitamin B₆, and 2 mg/d vitamin B₁₂ daily. There was no effect of treatment on all-cause mortality, stroke, or amputation of lower extremities compared with placebo.⁶ Folic acid is a synthetic, provitamin form of folate that is processed to natural folate by the enzyme dihydrofolate reductase. Very high intakes of folic acid may result in saturation of dihydrofolate reductase activity. Folic acid binds tightly to the folate receptor (FR α), a glycoprotein that is anchored to the cell membrane of epithelial cells. It is possible that because FR α is expressed in the kidney, the kidney may be more harmed by unmetabolized folic acid, especially in subjects with kidney disease or impaired kidney function, as observed in a population with diabetic nephropathy.⁵ Folic acid–induced nephrotoxic effects has been demonstrated in mouse models.⁷

Another major difference among the CKD trials was the use of enalapril in the study design by Xu et al.³ The results of this study demonstrated that enalapril interacts with folate in human physiology, as enalapril treatment alone in the absence of supplemental folic acid increased serum folate by 5.1 ng/mL (to convert ng/mL to nmol/L, multiply by 2.266), with a modest decrease in serum homocysteine (0.2 μ M). While the mechanisms for this interaction are unknown and should be explored, this drug-nutrient interaction may underlie the secondary prevention of renal function decline observed in this study.

Dietary reference intakes are established to give guidance for adequate intake levels of essential nutrients for healthy individuals, but there is increasing awareness that these

recommendations may not apply to populations with chronic disease.⁸ Currently for adults in the United States, median daily intake of folic acid from fortification is estimated to be less than half the level administered in CSPPT.⁹ Clinical conditions that are known to alter nutritional status indicators include diseases and states of chronic inflammation, cancer and chronic use of certain pharmaceuticals. This study spotlights the need to better understand the effect of nutrients on disease prevention and disease management.

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