12-1-2016

Folic acid supplementation and chronic kidney disease progression

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In contrast to prior studies demonstrating no benefit or even increased harm from B vitamin supplementation in patients with chronic kidney disease, a large randomized trial from China recently demonstrated small but statistically significant reductions in the risk of first stroke and chronic kidney disease progression with the addition of folic acid to enalapril in adults with hypertension. Differences in the study population and study intervention may explain these discordant results.

Refers to: Xu X, Qin X, Li Y, et al. Efficacy of folic acid therapy on the progression of chronic kidney disease. The renal substudy of the China Stroke Primary Prevention Trial. *JAMA Intern Med.* 2016;176:1443–1450.

Kidney International (2016) **90,** 1144–1145; http://dx.doi.org/10.1016/j.kint.2016.09.019

Despite the strong association between hyperhomocysteinemia and chronic kidney disease (CKD), previous studies have demonstrated no benefit of homocysteine-lowering therapy with B vitamin supplementation to prevent cardiovascular events or CKD progression.[1–4] In fact, the Diabetic Intervention with Vitamins in Nephropathy trial demonstrated harm with high-dose B vitamins in adults with diabetic nephropathy, particularly among those with lower estimated glomerular filtration rate (eGFR).[3] In contrast, a recent large, randomized trial demonstrated small but statistically significant reductions in the risk of stroke and CKD progression with folic acid supplementation in a hypertensive population without dietary fortification of folic acid.[5,6] How should we interpret these discordant results?

The China Stroke Primary Prevention Trial (CSPPT) randomized 20,702 adults with hypertension and no prior history of cardiovascular disease or stroke to enalapril 10 mg daily versus enalapril 10 mg in fixed-dose combination with folic acid 0.8 mg daily.[5] Use of additional antihypertensive agents was allowed; the most commonly used agents were calcium channel blockers and hydrochlorothiazide. Blood pressure control was similar in both treatment arms throughout the trial. Although other traditional cardiovascular and CKD risk factors were not excluded by protocol, diabetes and hyperlipidemia were rare. The primary results of the CSPPT demonstrated a small but statistically significant reduction in the risk of fatal or nonfatal stroke with the combination of enalapril and folic acid, as well as a reduction in the composite cardiovascular outcome.[5]

The CSPPT Renal Substudy included 15,104 participants with eGFR $\geq$ 30 and $<$ 60 ml/min/1.73 m^2, in whom serum creatinine and dipstick proteinuria were measured at baseline and exit visits.[6] Approximately 11% of substudy participants had preexisting CKD as defined by eGFR 30 to 60 ml/min/1.73 m^2 or the presence of dipstick proteinuria. The primary CKD outcome was a 30% decline in eGFR to a level $<$ 60 ml/min/1.73 m^2 in participants with a baseline eGFR $\geq$ 60 ml/min/1.73 m^2, a 50% decline in participants with a baseline eGFR 30 to 60 ml/min/1.73 m^2, or the development of end-stage renal disease. Over a median of 4.4 years of follow-up, the primary outcome occurred in 2.5% and 2.1% of participants randomized to enalapril alone and enalapril plus folic acid, respectively (adjusted odds ratio 0.79, 95% confidence interval 0.62–1.00). There was a significant interaction between treatment arm and CKD status, with a more pronounced benefit of folic acid supplementation observed in participants with CKD at baseline (adjusted odds ratio 0.44, 95% confidence interval 0.26–0.75).

The authors acknowledged a number of important limitations that should be considered when interpreting these results. Most

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importantly, although there was a very low rate of loss to follow-up in the parent trial (0.3%), 14% of participants in the substudy were excluded from the CKD outcome analysis because of missing data on the CKD outcome. Second, the primary CKD outcome was defined using a single measure of eGFR at baseline and end of study, and the CKD subgroup was also defined based on a single measure of eGFR and dipstick proteinuria. Third, adherence to study medication was low in both treatment groups. Overall, fewer than 70% of CSPPT participants were eligible for inclusion in the per-protocol analysis, and 14% of participants discontinued study medication during the trial. Results of the per-protocol analysis were similar to the results of the intention to treat analysis for the primary outcome of stroke, but a similar analysis was not reported for the CKD outcome.[5]

Another potential limitation, a lack of generalizability, is also one of the important differences between the CSPPT and prior studies that may help to explain the discordant results. Enrollment in the CSPPT took place exclusively in China, in a region without mandatory folic acid fortification of grain, which has been implemented in many countries to reduce the risk of neural tube defects. It is possible that the benefits of folic acid supplementation only extend to patients with inadequate dietary intake, consistent with a prior metaanalysis that showed a benefit of folic acid supplementation for stroke prevention only in populations without dietary fortification.[7] As such, the CSPPT results may be important in other settings in which folic acid fortification has not been implemented, including many African nations with a high prevalence of CKD.

In addition to this difference in the study population, the study intervention in the CSPPT also differed from prior studies. Folic acid supplementation was given alone, and the use of other B vitamins was excluded by protocol in the CSPPT. The current results support the safety of folic acid supplementation in patients with CKD. The harm associated with B vitamin supplementation in prior studies has been hypothesized to result from the use of cyanocobalamin, leading to accumulation of cyanide and the renally excreted metabolite thiocyanate in patients with low GFR.[8] These new results are consistent with the suggestion that folic acid and methylcobalamin should replace cyanocobalamin in future studies of B vitamin supplementation.

CONCLUSIONS FOR NEPHROLOGY PRACTICE

Should these new results change clinical practice in nephrology? Although the absolute risk reduction for CKD progression was only 0.4% in the overall population, the absolute risk reduction in the CKD subgroup was 3.5% (number needed to treat = 29). Pending the results of confirmatory trials, nephrologists in settings without mandatory folic acid fortification may consider folic acid with or without methylcobalamin supplementation as reasonable adjunctive therapy in patients with CKD. For patients with early CKD who do not need to restrict their intake of potassium or phosphorus, this could come in the form of a healthy diet rich in natural sources of folate, an intervention that is likely to have other benefits in patients with CKD and increased cardiovascular risk.

DISCLOSURE

All the authors declared no competing interests.

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