Long-term supplementation with folic acid and vitamin B-12 has no effect on circulating uric acid concentrations in Norwegian patients with coronary artery disease

Dear Editor:

High concentrations of uric acid are associated with the occurrence of gout and are observed in concordance with other features of the metabolic syndrome, such as hypertension, impaired glucose metabolism, dyslipidemia, and obesity, and are highly associated with an increased risk of gout (1). Treatment options for hyperuricemia and gout are urgently needed because existing pharmacologic treatment is associated with side effects and low compliance (2).

In a recent issue of the Journal, Qin et al. (3) reported that treatment with enalapril together with folic acid (800 µg/d) reduced the concentration of uric acid and the risk of hyperuricemia in hypertensive patients in comparison to enalapril alone. The trial included >15,000 patients with a mean age of 60 y and a baseline uric acid concentration of 294 µmol/L. After a mean follow-up of 4.4 y, the increase in uric acid was marginally significantly less in the enalapril + folic acid group than in the enalapril group (mean difference: 4 µmol/L; risk of new-onset hyperuricemia: 0.89; 95% CI: 0.79, 0.99).

Results of a large randomized controlled study in Norway do not confirm these results. The Norwegian study was a randomized, placebo-controlled clinical study in patients with coronary artery disease or aortic stenosis (n = 3090) who received folic acid (0.8 mg/d) and vitamin B-12 (0.4 mg/d) (n = 772); folic acid, vitamin B-12, and vitamin B-6 (40 mg/d; n = 772); vitamin B-6 (40 mg/d; n = 772); or placebo (n = 780) for a median duration of 38 mo. Details of the study design and the primary outcome are described elsewhere (4). To ensure comparability with the study by Qin et al., we only present the effect of combined folic acid with vitamin B-12 compared with that of placebo. The mean age at baseline was 61 y, 80% of participants were male, the mean BMI (in kg/m²) was 26.8, and mean systolic and diastolic blood pressures were 142 and 81 mm Hg, respectively. Follow-up visits, including blood sampling, occurred after 1 mo, after 1 y, and at the end of the intervention. Serum vitamin concentrations increased in the patients assigned to the groups who received vitamins, and plasma homocysteine was reduced in the groups who received folic acid, even after 1 mo (4). At baseline, the mean uric acid concentration was 355 µmol/L, and there was a significant increase in uric acid concentrations over time, independently of vitamin supplementation or placebo treatment (P = 0.006 at 1 mo, with no further significant change at 1 y and at the end of the study; mixed-effects model; Figure 1). There was no significant effect of the folic acid + vitamin B-12 combination on the risk of hyperuricemia (serum uric acid >417 µmol/L in men and >357 µmol/L in women) at the end of the study (generalized estimating equation; OR: 1.28; 95% CI: 0.99, 1.65; P = 0.06).

The results of the Western Norway B Vitamin Intervention Trial (WENBIT) do not support the finding by Qin et al. (3) that folic acid supplementation can effectively reduce uric acid concentrations or can reduce the risk of hyperuricemia. Older investigations point to a possible inhibition of xanthine oxidase by folic acid (5); however, this was later disproved and assigned to a contaminant (pterin aldehyde) (6, 7). Thus, inhibition of xanthine oxidase by folate is unlikely to occur in vivo, even at regular folic acid supplementation at high doses.

It has previously been shown that folic acid reduces plasma homocysteine, in part by providing 5-methyltetrahydrofolate to inhibit the enzyme glycine N-methyltransferase (GNMT), which is a source of homocysteine (8). Thus, treatment with folic acid may actually increase concentrations of glycine, the substrate for GNMT as well as for uric acid production. This is in accordance with the marginally higher uric acid concentrations observed in our patients treated with folic acid plus vitamin B-12. Although we cannot exclude that our results are influenced by co-treatment with vitamin B-12, we believe that the findings by Qin et al. (3) can best be explained by chance. The temptation would have been strong to believe that simple vitamin supplementation could resolve a metabolic imbalance as complex as elevation of uric acid. In WENBIT, folic acid supplementation had neither an effect on the risk of cardiovascular events (4) nor on plasma uric acid concentrations. This suggests that folic acid cannot solve the problem of hyperuricemia and its relation to excess cardiovascular risk.

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Jutta Dierkes
Reinhard Seifert
Jesse F Gregory
Ottar Nygård

*Correspondingauthor:OttarNygård,DepartmentofNutrition,UniversityHospitalofNorthWestNorway,N-7007,Mo,Norway.

FIGURE 1 Serum uric acid concentrations in patients who received folic acid (0.8 mg/d plus 0.4 mg cyanocobalamin/d; n = 768) or placebo (n = 779) for a period of 38 mo at baseline and after 1 mo, 1 y, and 38 mo of treatment. Values are means ± SDs. B12, vitamin B-12.
From the Departments of Clinical Medicine (JD, e-mail: jutta.dierkes@uib.no) and Clinical Science (ON), University of Bergen, Bergen, Norway; the Department of Heart Disease, Haukeland University Hospital, Bergen, Norway (RS and ON); and the Food Science and Human Nutrition Department, University of Florida, Gainesville, FL (JFG).

REFERENCES


Reply to J Dierkes et al.

Dear Editor:

Our substudy of the China Stroke Primary Prevention Trial (CSPPT) (1) showed that folic acid therapy reduced the concentration of serum uric acid (UA) in a hypertensive population. The post hoc analysis of the Western Norway Vitamin Intervention Trial (WENBIT), however, did not find any significant effect of folic acid + vitamin B-12 treatment on the risk of hyperuricemia. This discrepancy could be due to important differences in the study design and population characteristics between the 2 studies. First, our analysis enrolled 15,364 participants with a mean follow-up of 52 mo, whereas the WENBIT group, which was used for the comparison, included 1552 patients with a median duration of 38 mo. Assuming that the difference between the B-vitamin group and placebo is 4 μmol/L (1), given a type I error rate of 5%, a sample size of 1600 in a 1:1 ratio would lead to a power of ~20%. Furthermore, the study participants in WENBIT had coronary artery disease or aortic stenosis, whereas the CSPPT participants were hypertensive patients without major cardiovascular conditions.

Another important difference between the CSPPT and WENBIT is the treatment regimen. Our study used a low dose of folic acid (0.8 mg/d) without combination with other B vitamins, whereas the WENBIT participants received combined treatment with both folic acid (0.8 mg/d) and vitamin B-12 (0.4 mg/d). Our recent meta-analysis (2) indicated that there might be a greater beneficial effect associated with folic acid therapy in trials without or with a low-dose use (<0.18 mg/d) of vitamin B-12. Another study suggested that the combination of folic acid, vitamin B-12, and vitamin B-6 compared with placebo resulted in a greater decrease in estimated glomerular filtration rate and an increase in cardiovascular disease (CVD) among patients with diabetic nephropathy (3). Along these lines, the CSPPT showed that folic acid alone (0.8 mg/d) reduced the risk of chronic kidney disease progression, especially in those with chronic kidney disease (4). Taken together, available data raised a concern that the beneficial effect of folic acid on UA could be offset by the toxicity associated with a high dose of vitamin B-12.

Moreover, the discrepancy between the CSPPT and WENBIT could be due to differences in the use of medications between the participants. It has been shown that treatment with lipid-lowering drugs may affect UA concentrations (5). A meta-analysis also found that the benefit of folic acid therapy was greater in trials with a lower proportion of participants who used statins (RR: 0.77; 95% CI: 0.64, 0.92) (6). The percentage use of lipid-lowering drugs at baseline was ~88% in the WENBIT, compared with 0.8% in the CSPPT. Due to the exclusion of participants with major CVD, the CSPPT had a low percentage usage of lipid-lowering drugs, making it more likely to observe the independent effect of folic acid therapy on UA reduction. In addition, all participants in our study were treated with angiotensin-converting enzyme inhibitors (ACEIs), whereas only one-third of participants in WENBIT received ACEIs. Albert et al. (7) reported a significant interactive effect between ACEIs and folic acid therapy in reducing CVD risk ($P = 0.03$), which suggests another possible explanation.

As a clinical trial, our study is not able to explain the biological mechanism underlying the effect of folic acid therapy. Previous studies have shown several potential mechanisms (1). In addition to the inhibition of xanthine oxidation, folic acid can effectively lower total homocysteine, which, in turn, decreases intracellular S-adenosylhomocysteine, a potent inhibitor for most S-adenosyl-methionine–dependent methyltransferases. S-adenosyl-homocysteine may induce marked DNA damage and release purine nucleotides that result in the production of UA. Consistently, 2 recent meta-analyses of randomized trials (2, 8) indicated that folic acid therapy significantly reduced the risk of stroke and overall CVD. There was a significant dose-response association between the degree of total homocysteine reduction and the intervention effect on CVD (8).

Overall, findings from our 2 previous studies (1, 9) provided consistent evidence that enalapril + folic acid therapy, compared with enalapril alone, can reduce UA concentrations among hypertensive adults with elevated UA. Our findings, if further confirmed in future studies, may offer a simple, safe, and effective way to lower UA, in particular among hypertensive patients residing in low-folate regions.

Xianhui Qin
Youbao Li
Fan Fan Hou
From the National Clinical Research Center for Kidney Disease, State Key Laboratory of Organ Failure Research, Guangdong Provincial Institute of Nephrology, Division of Nephrology, Nanfang Hospital, Southern Medical University, Guangzhou, China (e-mail: ffhouguangzhou@163.com).

REFERENCES