Vitamin Supplement

Serum unmetabolized folic acid in a nationally representative sample of adults ≥60 years in the United States, 2001–2002

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Folic acid is a compound that does not occur naturally in food but is added as a fortificant and dietary supplement. When it is ingested it is converted into forms of reduced folate that are identical to those arising from ingestion of naturally occurring folate in foods; however, some folic acid may appear unmetabolized in the serum (1, 2). Very little is known about its metabolism and biological effects. Folic acid fortification increased dietary intakes of folic acid (3) and blood folate levels in the United States (4). Some (5–9) but not all (10–12) research suggests that high folic acid intakes may promote the growth of pre-existing cancers or malignant lesions.

Material and methods

The National Health and Nutrition Examination Survey (NHANES) is a nationally representative, cross-sectional survey of the US population. During 2001–2002, UMFA and 5-methyltetrahydrofolic acid (5-methylTHF), the major circulating folate form in serum, were assayed in participants who fasted a mean of 8 hours ($n=1121$ individuals, ≥60 years) using a revised affinity/HPLC method with electrochemical (coulometric) detection (13, 14). Other biochemical parameters measured were serum folate, red blood cell (RBC) folate, serum vitamin B12, and plasma homocysteine and methylmalonic acid (MMA).

Results

Unmetabolized folic acid (UMFA) was detected in 38% of the population (15), with a mean concentration of 4.4±0.6 nmol/L (median 1.2±0.2 nmol/L). The group with detectable UMFA (+UMFA) included a significantly higher proportion of folic acid supplement users than those without it (−UMFA; 60 vs. 41%). The +UMFA males and females had higher supplemental and total (food+supplements) folic acid intakes than their −UMFA counterparts. Serum folate, 5-methylTHF, and vitamin B12 concentrations were also higher in the +UMFA group, while there was no differences in RBC folate, homocysteine, or MMA concentrations. The distribution of the −UMFA group was approximately equal across quartiles of 5-methylTHF concentrations. However, the distribution of +UMFA in their serum increased with increasing quartile of 5-methylTHF concentrations (Fig. 1A). A similar trend was observed in total folic acid intake quartiles (Fig. 1B).

Conclusions

Folic acid intakes do not entirely explain the variability in the presence or persistence of UMFA in this US population, suggesting that genetic differences in its metabolism may also be involved. More research is needed to determine the factors associated with circulating UMFA in folic acid fortified-populations. Given the

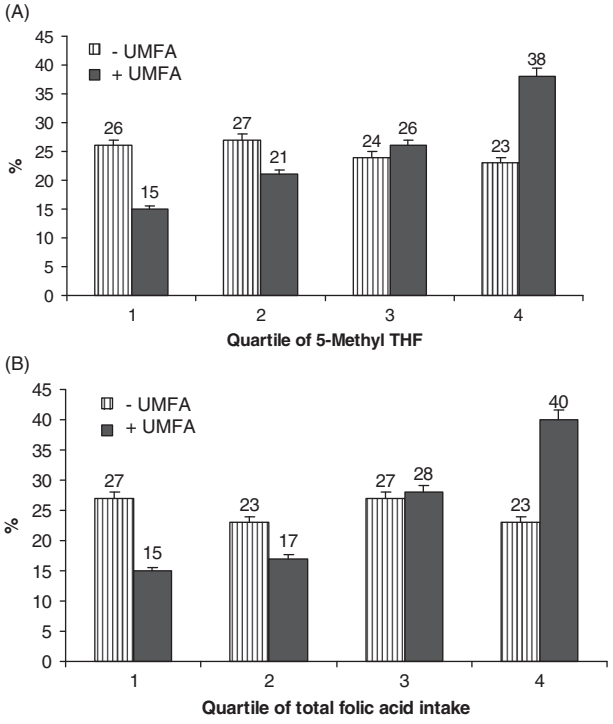

Fig. 1. The percentage of US adults (≥60 years) without (−UMFA) and with (+UMFA) detectable concentrations of unmetabolized serum folic acid by quartiles of serum 5-methyltetrahydrofolate (5-methylTHF) concentrations (A), quartiles of total folic acid intake (B).

possibility that excessive folic acid exposure may be associated with adverse effects such as promoting progression of certain cancers and its possible associations with anemia, macrocytosis, and cognition (16), understanding the association between folic acid intake (dietary and supplemental) and serum UMFA is important. Monitoring of UMFA may therefore be warranted.

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