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Opinion paper

Critical evaluation of lowering the recommended dietary intake of folate

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SUMMARY

We evaluated the recommendation of the Austrian, German, and Swiss Societies for Nutrition of lowering dietary folate intake from 400 to 300 μg dietary folate equivalents/d. A dose–response relation exists between folate intake or plasma level and disease risk within the normal range. Improving folate status can prevent between 30% and 75% of neural tube defects. A prepregnancy plasma folate of >18.0 nmol/L (mean 26.1 nmol/L) is associated with low total homocysteine (tHcy) (<10.0 μmol/L) and optimal prevention of birth defects. Because the closure of the neural tube occurs in the first 8 weeks after conception, women with low prepregnancy folate intake cannot achieve maximal risk reduction.

The Austrian, German, and Swiss Societies for Nutrition recommend that young women should additionally supplement with 400 μg folic acid at least 4 weeks before conception. This short time window is not sufficient to achieve optimal plasma folate and tHcy levels in the majority of women. Factors affecting the relation between folate intake and blood biomarkers are total folate intake, baseline plasma folate, time available for supplement use, dose and form (folic acid or methyl folate), genetic polymorphisms, physiological and lifestyle factors.

Lowering the recommended dietary folate intake may have important public health consequences. Elderly people and young women are at risk for diseases related to folate shortage. Reducing birth defects through supplementation of folic acid remains a poor option, as <20% of young women (i.e., in Germany) supplement with the vitamin. Recommending adequate food folate intake is crucial for reaching the target protective plasma folate levels in the population.

1. Introduction

Personalized nutrition aims at promoting disease prevention. Maintaining optimal serum concentrations of folate (vitamin B9) necessary for disease prevention has become ever more important. The Dietary Reference Intake (DRI) of folate for adults has been set by the Institute of Medicine (IOM) of the U.S. National Academy of Sciences to 400 μg dietary folate equivalents (DFEs).[1] The nutrient's Recommended Dietary Allowance (RDA) was defined on the basis of the lowest amount of folic acid (FA) that can reverse anemia.[1,2] Later on, it has been shown that folate intake and serum levels are negatively related to plasma concentrations of total homocysteine (tHcy).[3] DFEs of 400 μg daily can maintain favorable plasma concentrations of tHcy. FA is the synthetic form of the vitamin that is used in supplements and fortified foods. A dose of 400–800 μg of FA is recommended for women of childbearing age from at least 4 weeks before to at least 8 weeks after conception to reduce the risk of neural tube defects (NTDs) in the baby.

Until recently, the DRI for folate in three German-speaking countries (Austria, Germany, and Switzerland) was 400 μg/d. The Austrian, German, and Swiss Societies for Nutrition have very recently lowered the recommended folate intake to 300 μg/d. The recommendation to supplement FA prepregnancy has not been changed. Nevertheless, lowering folate intake does not promote health on a population level and is not consistent with the current evidence on the relation between folate intake, tHcy, and disease risk. This review aims at a literature-based estimation of the

Abbreviations: DFEs, dietary folate equivalents; DHFR, dihydrofolate reductase; DRI, Dietary Reference Intake; EAR, Estimated Average Requirements; FA, folic acid; MCV, mean corpuscular volume (MCV); MTHFR, methylenetetrahydrofolate reductase; NTD, neural tube defect; RDA, Recommended Dietary Allowance; THF, tetrahydrofolate; L-5-methylTHF, 5-methyltetrahydrofolate; tHcy, total homocysteine; UL, tolerable upper intake level.

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optimal intake of folate (dietary or dietary plus supplemental) necessary for achieving optimal blood markers and risk reduction of diseases. Table 1 summarizes the most important health-related facts about folate.

2. Serious limitations in the new recommendation to lower the population reference intake of folate from 400 to 300 μg DFEs/d

The RDA is the level assumed to meet the requirements for 95% of healthy subjects within each life stage and sex group. The Estimated Average Requirements (EAR) are expected to satisfy the needs of 50% of the people in that age and sex group. The RDA is calculated from the EAR based on intake data available from the population. The Austrian, German, and Swiss Societies for Nutrition have recently revised the intake recommendations for the nutrient folate[4] (http://www.dge.de/pdf/ws/Referenzwerte-2013-Folat.pdf). The modified recommendations cannot promote population health for the following reasons:

1. Determining nutrient intake consistently between studies and countries depends on the alignment of food composition databases and analytical methods that are used to estimate food contents.[e1] Folate content in plants is rather low; a significant amount is lost during food processing[e2,e3]; and the bioavailability of folate from food is limited. Moreover, methodological difficulties cause underestimation or overestimation of the actual dietary folate intake.[1,e4] New estimates of folate intake in the German National Intake Survey Study (National Verzehrstudie II, NVSII, 2012) showed a median intake of approximately 200 μg/d DFEs.[4] The dietary folate intakes in the German NVSII study are not consistent over time. Intake data in the NVSII 2012 depended on 2 × 24-h recalls, and the computation was performed by using Bundeslebensmittelschlüssels (BLS-version 3.02). An earlier publication from the same study in 2008 reported using Diet Interview Software for Health Examination Studies (DISHES) and BLS II.4. The two ways of data analyses depended on different food tables. The latest report from the German NVSII showed median folate intakes in men and women of 207 and 181 μg/d DFEs, respectively (n = 13,753, age 15–80 years).[4] One earlier report from almost the same collective (2008) showed median folate intakes of 283 and 252 μg/d DFEs for men and women (n = 15,371, age 14–80 years), respectively (28% higher than the 2012 report; http://www.mri.bund.de/fileadmin/Institute/EV/NVSII_Abschlussbericht_Teil_2.pdf). The comparability of the intakes calculated by using different databases has not been evaluated. Plasma folate and tHcy were not measured in the German NVSII study. Systematic or random failure due to the alignment of food composition databases should be first clarified by validating folate intake against plasma folate and tHcy in the same set of subjects.
2. The recommendations to lower folate requirements were based on three outdated studies[2,5,6] that do not consider age- and sex-specific requirements, which is against the principal definition of the RDA. Victor Herbert (1962) has defined daily requirement as FA sufficient to maintain normality and prevent megaloblastic anemia in three healthy women who were placed on a folate-deprived diet for 3 months.[2] The study concluded that 50 μg FA/d (=100 μg DFEs) is able to prevent anemia based on serum folate and changes in hematologic tests. Milne et al. studied 40 men at the beginning (age 19–54 years), and only 19 men remained at the end of the study (after 6–8 months).[6] The participants received a diet that was poor in both folate (200 μg DFEs/d) and iron (16.8 mg/d).[6] Serum folate declined from 18.8 to 16.5 nmol/L, and serum ferritin declined by almost 50%. Folate and iron requirements for men and women may be different. For example, serum ferritin in men was 60.1 mg/L, which is much higher than values expected in young women.[6] Moreover, folate requirements may be low in the presence of dietary iron restriction. In the study by Milne et al., maintaining normality was based on 6–8 months experimental folate deficiency and blood count, or serum folate levels.[6] The tHcy was not measured and DNA methylation or clinical outcomes were not tested.[6] In a third study, Sauberlich et al. investigated the effect of folate depletion in 10 nonpregnant women (age 21–40 years).[5] The study consisted of 28 days of depletion (intake 0) followed by 64 days of repletion.[5] During the depletion phase, serum folate declined from 24.9 to 7.9 nmol/L (−68%).[5] Despite the severe decline in serum folate, none of the participating women developed anemia within 1 month.[5] No marked changes in blood count were observed. Deoxyuridine suppression test (H3-thymidine incorporation into lymphocyte DNA) and hypersegmentation of neutrophils were tested; however, these tests are neither sensitive nor specific for folate deficiency. Because of their serious limitations, the studies by Milne et al. and Sauberlich et al. were judged as equivocal and were not considered for defining the RDA by the IOM.[1]
3. The new recommendations of the Austrian, German, and Swiss Societies for Nutrition assume that serum folate levels of ≥10 nmol/L and whole blood folate levels of ≥340 nmol/L are

Table 1
Health-related aspects of folate (vitamin B9).

Folate	Facet
International recommendation for Dietary Reference Intake (DRI), adults	400 μg DFEs.
Recommended daily folate supplementation for women of childbearing age	400–800 μg (FA or L-5-methylTHF) on top of folate supply with foods.
Dietary sources	Fresh green vegetables (spinach and broccoli), fruits, starchy vegetables, beans, whole grains and liver.
Folate status blood markers	Serum/plasma folate (short term marker, marker to follow-up repletion or depletion); whole blood folate (storage or long-term marker); plasma tHcy (depends also on vitamins B12, and B6, and renal function).
Determinants of folate status markers	Higher requirements (example in pregnancy), age, genetic polymorphisms in folate metabolizing enzymes, malabsorption, medications, status of related nutrients (B12, B6, B2, betaine), food processing and storage, lifestyle factors (smoking, alcohol).
Available folate forms as supplements	L-5-methylTHF (natural form), folic acid (synthetic form).
Natural folate forms in the diet	Polyglutamates: mostly derivatives of 5-methylTHF and THF.
Folate deficiency causal-relationship to diseases	Neural tube defects, brain development, depression, dysregulation of DNA-methylation that may cause cancer, genetic and epigenetic modifications that are linked to age-related diseases.
UL of food folate	There is no upper limit.
UL for folic acid	1 mg/d.

UL: upper tolerable level, DFEs: dietary folate equivalents, tHcy: total homocysteine, THF: tetrahydrofolate.