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Review

Excessive folic acid intake and relation to adverse health outcome

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ABSTRACT

The recent increase in the intake of folic acid by the general public through fortified foods and supplements, has raised safety concern based on early reports of adverse health outcome in elderly with low B12 status who took high doses of folic acid. These safety concerns are contrary to the 2015 WHO statement that "high folic acid intake has not reliably been shown to be associated with negative healeffects". In the folic acid post-fortification era, we have shown that in elderly participants in NHANES 1999–2002, high plasma folate level is associated with exacerbation of both clinical (anemia and cognitive impairment) and biochemical (high MMA and high Hcy plasma levels) signs of vitamin B12 deficiency. Adverse clinical outcomes in association with high folate intake were also seen among elderly with low plasma B12 levels from the Framingham Original Cohort and in a study from Australia which combined three elderly cohorts. Relation between high folate and adverse biochemical outcomes were also seen in the Sacramento Area Latino Study on Aging (High Hcy, high MMA and lower TC2) and at an outpatient clinic at Yale University where high folate is associated with higher MMA in the elderly but not in the young.

Potential detrimental effects of high folic acid intake may not be limited to the elderly nor to those with B12 deficiency. A study from India linked maternal high RBC folate to increased insulin resistance in offspring. Our study suggested that excessive folic acid intake is associated with lower natural killer cells activity in elderly women. In a recent study we found that the risk for unilateral retinoblastoma in offspring is 4 fold higher in women that are homozygotes for the 19 bp deletion in the DHFR gene and took folic acid supplement during pregnancy. In the elderly this polymorphism is associated with lower memory and executive scores, both being significantly worse in those with high plasma folate. These and other data strongly imply that excessive intake of folic acid is not always safe in certain populations of different age and ethnical/genetic background.

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1. Introduction

In the guideline entitled "The optimal serum and red blood cell folate concentrations in women of reproductive age for the prevention of neural tube defects", published in 2015, the World Health Organization (WHO) stated that "high folic acid intake has not reliably been shown to be associated with negative health effects" [1]. In this statement the WHO panel appears to have ignored those studies that were published in peer reviewed journals which have consistently shown that excessive folic acid intake is not always safe particularly as it applies to certain vulnerable segments of the population [2–4]. The evidence ignored or under-valued by this report is the substance of this review.

2. What is folic acid?

Folic acid, the fully oxidized and synthetic form of the vitamin folate found in supplements and fortified foods and not naturally in foods was first synthesized in 1945 [5]. It requires post-absorptive reduction to tetrahydrofolate (THF) for its metabolic activation. This reduction, which is required for incorporation of folic acid into body folate pools, is a two-step reaction catalyzed by dihydrofolate reductase (DHFR). The first step of this reaction, the conversion of folic acid to dihydrofolate (DHF) is extremely slow, inefficient, and easily saturated [6]. Since human liver DHFR activity is low – amounting to approximately 2% by weight of that found in rats [6], folic acid intake greater than 200 μg in a single dose is associated with the appearance of unmetabolized folic acid in plasma [7]. Although the metabolic significance of unmetabolized folic acid in plasma is not fully understood, it raises concern as it may point to disrupted one carbon metabolism due to excessive intake or aberrant interactions as explained below. Some enzymes including DHFR and methylene-tetrahydrofolate reductase are inhibited by folic acid and other folates [6,8].

3. The history of folic acid use in treatment of pernicious anemia

Excessive folic acid intake is entwined with the history and discovery of pernicious anemia (PA). Pernicious anemia is a disease caused by vitamin B12 deficiency which is primarily manifested as megaloblastic anemia, macrocytosis and neurological symptoms. Megaloblastic anemia and macrocytosis, but not the neurological symptoms, are also present in folate deficiency. This similarity between folate and vitamin B12 deficiencies with respect to hematological symptoms, stems from the participation of these two vitamins in the synthesis of thymidine in DNA and methionine. In this synthesis the methyl group from 5-methyltetrahydrofolate (5-MTHF) is transferred to homocysteine to form methionine in a reaction which is catalyzed by a methyl transferase which contains methyl-cobalamin as a coenzyme. This reaction is important in two ways. It provides de-novo synthesized methyl groups which are used for the many S-adenosylmethionine (SAM) dependent methylation reactions. It also results in the regeneration of unsubstituted tetrahydrofolate (THF) for another cycle of one carbon transfer. When this methionine synthesis is inhibited either through vitamin B12 or folate deficiencies, the entire pathway of folate metabolism, including those reactions that are involved in purine and thymidylate synthesis, is inhibited. These lead to inhibition of cell proliferation as the cells cease to divide and instead increase in size.

Folic acid was isolated and chemically synthesized in 1945 [5]. Vitamin B12 was isolated in 1948 [9] and became commercially available when isolated through bacterial fermentation until 1972 [10]. In the period between 1945 and 1972, patients with PA were often treated with large doses of folic acid in the hopea that this treatment could be associated with some relief from the hematological symptoms. There was no effect on the neurological symptoms and there are some reports that these symptoms were exacerbated [11]. Table 1 is a summary made by Savage and Lindenbaum [12] of 11 case reports involving 300 pernicious anemia patients who received various doses of folic acid and the number of those who experienced neurological relapse. One hundred and thirty five or 45% of these patients experienced neurological relapse [12]. The practice of administering folic acid to pernicious anemia patients has been discontinued, while the conduction of a placebo-controlled study in humans to test the effect of excessive folic acid in the presence of vitamin B12 deficiency is unethical and studies with animal models have been few and inconclusive [13].

4. Folic acid fortification of grain products for the prevention of neural tube defects (NTD) and the debate on the safety of folic acid

The risks of excessive folic acid intake in the presence of unrecognized vitamin B12 deficiency have been widely accepted in early years, but were questioned and doubted, mainly by advocates of food fortification with folic acid to prevent NTD [14–17]. The claim was that these case reports are inconsistent and do not amount to statistical significance.

5. Assessing risks and benefits in the aftermath of folic acid fortification

Folic fortification of grain products in the USA which was officially implemented in 1998 and was associated with a substantial

Table 1
Summary of studies of patients with pernicious anemia treated with large doses of folic acid during 1947–1951 (from Savage and Lindenbaum [12]).

Neurologica relapse or progression				
Folic acid (mg/d)	Observation time (months)	Patients (n)	Total (n)	%
3–40	12	41	3	7.3
10	0.3–17	12	3	25
5–20	12	15	4	26.7
10–15	9	14	5	15.7
2.5–50	?	20	8	40
5	48	72	32	44.4
5–10	120	36	16	44.4
2.5–15	25	22	12	54.5
≥10	24	38	28	73.7
5–600	12	10	8	80
5–40	35	20	16	80
Total		**300**	**135**	**45**