How common is vitamin B-12 deficiency?[1–3]

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ABSTRACT

In considering the vitamin B-12 fortification of flour, it is important to know who is at risk of vitamin B-12 deficiency and whether those individuals would benefit from flour fortification. This article reviews current knowledge of the prevalence and causes of vitamin B-12 deficiency and considers whether fortification would improve the status of deficient subgroups of the population. In large surveys in the United States and the United Kingdom, ≈6% of those aged ≥60 y are vitamin B-12 deficient (plasma vitamin B-12 < 148 pmol/L), with the prevalence of deficiency increasing with age. Closer to 20% have marginal status (plasma vitamin B-12: 148–221 pmol/L) in later life. In developing countries, deficiency is much more common, starting in early life and persisting across the life span. Inadequate intake, due to low consumption of animal-source foods, is the main cause of low serum vitamin B-12 in younger adults and likely the main cause in poor populations worldwide; in most studies, serum vitamin B-12 concentration is correlated with intake of this vitamin. In older persons, food-bound cobalamin malabsorption becomes the predominant cause of deficiency, at least in part due to gastric atrophy, but it is likely that most elderly can absorb the vitamin from fortified food. Fortification of flour with vitamin B-12 is likely to improve the status of most persons with low stores of this vitamin. However, intervention studies are still needed to assess efficacy and functional benefits of increasing intake of the amounts likely to be consumed in flour, including in elderly persons with varying degrees of gastric atrophy. *Am J Clin Nutr* 2009;89(suppl):693S–6S.

INTRODUCTION

Vitamin B-12 deficiency and depletion are common in wealthier countries, particularly among the elderly, and are most prevalent in poorer populations around the world. This prevalence was underestimated in the past for several reasons, including the erroneous belief that deficiency is unlikely except in strict vegetarians or patients with pernicious anemia, and that it usually takes ≈20 y for stores of the vitamin to become depleted. This article reviews the prevalence of deficiency and its underlying causes, which is relevant to assessing the potential benefits of fortifying flour with this vitamin.

DIAGNOSIS OF DEFICIENCY

A diagnosis of vitamin B-12 deficiency is usually made on the basis of serum or plasma vitamin B-12 concentration, with deficiency currently defined as a concentration < 148 pmol/L (200 pg/mL) and marginal status defined as a concentration of 148–221 pmol/L. The gold-standard indicator is elevated serum (or less commonly, urinary) methylmalonic acid (MMA). Recently, a cutoff of >210 nmol/L has been proposed, ie, the 95th percentile for vitamin B-12–replete participants with normal renal function in the National Health and Nutrition Examination Survey in the United States (1). The limitations of MMA as an indicator include the cost of analysis, the need for mass spectrometry, and, especially in developing countries, the possibility of concentrations being increased by bacterial overgrowth. Although vitamin B-12 deficiency is the major cause of elevated plasma total homocysteine (tHcy) in folate-replete populations such as in the US elderly after the folic acid fortification of flour (2), in other locations deficiencies of folate, riboflavin, and vitamin B-6 must be ruled out because these too will increase tHcy. However, if vitamin B-12 supplementation or fortification of a population group lowers tHcy, this can be used as an indicator of improved status (3). Megaloblastic anemia does not usually result from chronic, marginal depletion of the vitamin caused by low dietary intake (4) but occurs more commonly in pernicious anemia and severe vitamin B-12 deficiency (serum vitamin B-12 < 120–150 pmol/L).

PREVALENCE OF DEFICIENCY IN SURVEYS

Serum vitamin B-12 concentrations in the US population were reported in the National Health and Nutrition Examination Surveys from 1999 to 2002 (1, 5). The prevalence of deficiency (serum vitamin B-12 < 148 pmol/L) varied by age group and affected ≤3% of those aged 20–39 y, ≈4% of those aged 40–59 y, and ≈6% of persons aged ≥70 y. Deficiency was present in <1% of children and adolescents but was ≤3% in children aged <4 y (the youngest age group reported). Marginal depletion (serum vitamin B-12: 148–221 pmol/L) was more common and occurred in ≈14–16% of those aged 20–59 y and >20% of those >60 y. Plasma MMA concentrations were markedly higher after age 60 y. Of >1600 elderly (age ≥60 y) California Hispanics in the Sacramento Area Latino Study on Aging

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(SALSA), 6% had plasma vitamin B-12 in the range of deficiency and an additional 16% had marginal status, with evidence of further decline in plasma vitamin B-12 with age (6). The prevalence of vitamin B-12 deficiency (serum B-12 $\leq$ 150 pmol/L) increased substantially after age 69 y in 3 UK surveys (combined $n = 3511$); it affected about 1 in 20 people aged 65–74 y and at least 1 in 10 of those aged $\geq$75 y (7, 8).

Across studies in Latin America, $\approx$40% of children and adults had deficient or marginal status (9), including a nationally representative sample of women and children in the 1999 Mexican National Nutrition Survey. The reported prevalence of deficient and marginal values is much higher in African and Asian countries, eg, 70% in Kenyan school children (10, 11), 80% in Indian preschoolers (12), and 70% in Indian adults (13).

LOW INTAKE AND RISK OF DEFICIENCY

The 2 main causes of vitamin B-12 deficiency are inadequate dietary intake and, in the elderly, malabsorption of the vitamin from food. Contrary to popular belief, not only strict vegetarians (vegans) are at high risk of vitamin B-12 deficiency, and there is strong evidence that status reflects usual intake across a wide range. In the United States and Canada, the Estimated Average Requirement is 0.7–2.0 μg/d across the life span, whereas the respective Recommended Dietary Allowance is 0.9–2.4 μg/d. The vitamin is present only in animal-source foods (ASFs) or fortified foods. In the large EPIC study in the United Kingdom, intakes increased progressively with ASF intake, averaging 0.4 μg for vegans, 2.6 μg for lactoovovegetarians, 5.0 μg for those who also consumed fish, and 7.2 μg for consumers of meat (omnivores) (14). Numerous other studies on smaller population groups confirmed that both vitamin B-12 intake and serum vitamin B-12 concentrations increase progressively from vegans to lactoovovegetarians, to those who consume fish or some meat, to omnivores (15–17).

ASF intake may be restricted for cultural or religious reasons and, by many people in the world, because of low income. Food and Agriculture Organization food balance sheets reveal that most of the world's population consumes <20% of their energy as ASFs, with many countries in Africa consuming <10%, compared with >20% in wealthier regions and 40% in the United States. Predictably, lower intakes are associated with a higher prevalence of deficient and marginal serum B-12 concentrations; strong correlations were found in all studies that measured both vitamin B-12 intake and serum vitamin B-12 (10–17).

Fortified foods, especially ready-to-eat cereals, and supplements can be important sources of vitamin B-12. In the US Framingham Offspring Study, $\approx$16% of those aged 26–83 y had serum vitamin B-12 <185 pmol/L and $\approx$9% had values <148 pmol/L (18). Mean intake of the vitamin was 9 μg/d. Intake from all sources was higher in persons with serum vitamin B-12 >185 pmol/L than in those with serum vitamin B-12 <148 pmol/L, including supplements (1.5 compared with 0.4 μg/d) and fortified cereals (0.6 compared with 0.3 μg/d). Overall, plasma vitamin B-12 increased by 45 pmol/L for each doubling of intake, with response to supplements and cereals similar to that produced by other foods. In nonconsumers of supplements, for each doubling of intake, plasma vitamin B-12 was increased by 24 pmol/L with fortified cereals, 39 pmol/L with dairy products, and only 12 pmol/L with meat, fish, and poultry. Thus, it is clear that animal-source or fortified foods affect serum vitamin B-12 across the usual range of daily intake.

Plasma vitamin B-12 concentrations plateaued at intakes >10 μg/d in the Framingham Offspring Study. This is consistent with earlier observations by Chanarin (19) who summarized studies that measured vitamin B-12 absorption from radioactively labeled aqueous solutions and foods. Although >70% of the vitamin is absorbed when intake is in the range of 0.1–0.5 μg, the ileal receptors for the vitamin B-12–intrinsic factor complex become saturated with higher intakes such that absorption falls to $\approx$50% of a 1-μg dose, 15% of a 10-μg dose, and 3% of a 25–50-μg dose (**Figure 1**). The maximum amount that can be absorbed from a 5–50-μg single dose is 1.5 μg. Above 25 μg, only 1% of a dose is absorbed, by passive diffusion, which explains why the relative increase in serum vitamin B-12 is related to the log of the dose. In healthy Danish women, serum vitamin B-12 and other vitamin B-12 status indicators appeared to plateau at an intake (from food + supplements) >6 μg/d (20), but in part this is expected because of the lower efficiency of absorption of the vitamin at higher intakes.

FOOD-BOUND COBALAMIN MALABSORPTION

Malabsorption of vitamin B-12 from food is the main cause of deficiency in the elderly and explains why depletion occurs with aging. The condition is caused by atrophy of the gastric mucosa and the gradual loss of gastric acid, which releases the vitamin from food. In its early stages, gastric inflammation and elevated serum gastrin concentrations are common. In elderly persons in the Framingham Offspring Study, 24% of those aged 60–69 y and 37% of those aged $\geq$80 y had elevated serum gastrin (21). Likewise, in the SALSA Study, serum gastrin was elevated in 48% of the elderly participants with deficient plasma vitamin B-12 values, in 23% of those with marginal concentrations, and in 21% of those with normal status; overall, these concentrations were inversely correlated with plasma vitamin B-12 (6).

Food-bound cobalamin malabsorption is diagnosed when an individual has normal absorption of crystalline vitamin B-12 using a Schilling test, no antibodies to intrinsic factor or other tests positive for pernicious anemia (which is defined as vitamin B-12 malabsorption due to loss of gastric intrinsic factor secretion), and no acid-suppressing medications or gastric surgery

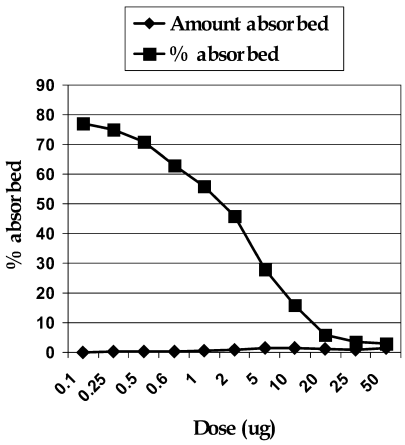

FIGURE 1. The efficiency of absorption of a single oral dose of vitamin B-12 across a range of intakes. Based on data from reference 19.

but impaired absorption of the vitamin when administered bound to egg or chicken serum (22). Because a normal Schilling test also means that intrinsic factor secretion and function are normal, reabsorption of biliary vitamin B-12 is maintained and depletion of the vitamin will progress slowly, over years. Importantly, however, a longitudinal study revealed that serum vitamin B-12 declined between ages 70–81 y in elderly Swedish men, and for reasons not understood, the decline was most evident in those with lower serum values initially (23). It seems reasonable to assume that entering later life with low stores of the vitamin for whatever reason, including low dietary intake, would increase the risk that deficiency would result from chronic food cobalamin malabsorption.

The causes of food cobalamin malabsorption are uncertain. Carmel (24) summarized data from 9 studies in the United States and found that the condition was present in ≈40% of patients with unexplained low serum vitamin B-12 concentrations. Not all of those patients were elderly, and some had other risk factors such as gastric resection. In a subsequent comparison of 43 normal elderly and 159 elderly persons with low serum cobalamin (22), malabsorption affected primarily those aged ≥60 y and was not clearly related to markers of gastric function (eg, serum gastrin). *Helicobacter pylori* infection was present in 78% of those with severe malabsorption, in 50% with mild malabsorption, and in 44% with normal absorption, but any effect of *H. pylori* was independent of its association with atrophic gastritis and gastric acid production; *H. pylori* infection is generally accepted as being the main cause of chronic atrophic gastritis and affects ≈50% of those aged ≥60 y in industrialized countries and a far greater proportion in developing countries. Elevated serum gastrin was a significant predictor of malabsorption but was not elevated in two-thirds of those who had malabsorption. Malabsorption was more prevalent in Hispanics and blacks, which was not explained by their higher prevalence of *H. pylori* infection.

The low gastric pH that occurs as a result of gastric atrophy can also increase bacterial overgrowth in the upper intestine, which results in less absorption of protein-bound (but not crystalline) vitamin B-12. A short course of treatment with tetracycline reversed protein-bound vitamin B-12 malabsorption in elderly persons with atrophic gastritis (25). High doses of H_2-receptor antagonists (eg, >1000 μg/d cimetidine) or proton pump inhibitors (eg, 20–40 mg/d omeprazole) inhibit food cobalamin absorption (the latter by 70%) by reducing gastric acid secretion (26, 27). However there is little evidence that deficiency of vitamin B-12 will result from short-term use of these medications. Gastric bypass or resection can also produce vitamin B-12 deficiency. The influence of polymorphisms in proteins that transport the vitamin is not well established, but the 776G>C polymorphism in transcobalamin, for which 20% of the population is homozygous, is associated with higher MMA and lower *trans* cobalamin concentrations (28).

EFFECT OF FOOD-BOUND COBALAMIN MALABSORPTION ON ABSORPTION OF VITAMIN B-12 FROM FORTIFIED FOODS

In the United States and other industrialized countries, the main reason to fortify flour with vitamin B-12 is to improve the status of the elderly. It is assumed that most elderly persons with impaired absorption of the vitamin from food can still absorb the crystalline vitamin added as a fortificant to flours, and in fact elderly persons are advised to consume a higher proportion of their vitamin B-12 intake as fortified foods and supplements. By definition, diagnosis of food-bound cobalamin malabsorption requires normal absorption of free cobalamin, so a person with this condition should be able to absorb crystalline vitamin B-12 added as a fortificant to food or in supplements. However, in a small proportion of elderly persons, gastric atrophy may have progressed to a stage in which intrinsic factor production is impaired so that they cannot absorb the vitamin from any source, including fortified foods. Although pernicious anemia is clearly most prevalent in the elderly, it is still relatively uncommon. A study in California found that 1.9% of 729 free-living persons aged ≥60 y had undiagnosed pernicious anemia defined as an abnormal Schilling test or positive antiintrinsic factor antibodies, and that their vitamin B-12 depletion was still relatively mild (29). It is possible, although untested, that some elderly persons have a moderate degree of impairment of crystalline vitamin B-12 absorption but have not progressed to pernicious anemia. Some evidence for this was obtained in the SALSA Study in which elderly persons in the highest quartile of serum gastrin needed a significantly higher intake of crystalline vitamin B-12 to achieve the same serum vitamin B-12 concentrations as those in the lowest quartile (21).

Testing the ability of the elderly to absorb high doses, eg, >100 μg, is not useful for answering the question of efficacy of food fortification because ≈1% of a high dose will be absorbed by passive diffusion, independently of gastric function or intrinsic factor. A recent report by the Flour Fortification Initiative recommended that where vitamin B-12 fortification is practiced, 2 μg/100 μg of flour should be added (30). The main constraint on the level of fortification is the cost of the vitamin used in premixes, not safety or sensory changes in the product. On the basis of an average flour consumption of ≈150 g/d in the United States, the relevant question becomes the efficiency of absorption from intakes ≈3 μg/d. In the Netherlands, subjects aged 50–65 y were assigned randomly to consume bread fortified with 9.6 μg vitamin B-12 and 138 μg folic acid daily or unfortified bread for 12 wk (31). Fortification increased serum folate by 45% and serum vitamin B-12 by 49%, and the proportion of subjects with serum vitamin B-12 <133 pmol/L decreased from 8% to 0%. Although the study showed that bread made with vitamin B-12–fortified flour can increase serum concentrations of the vitamin, the level of fortification was high and elderly persons with baseline serum concentrations <118 pmol/L (ie, those who may have had more severe gastric atrophy and/or preclinical pernicious anemia) were excluded. Only one study has measured the effect of low doses on elderly persons (≥70 y) with serum vitamin B-12 <162 pmol/L and defined as having "food vitamin B-12 malabsorption" (32). They were given a daily dose ranging from 2.5 to 80 μg in water after breakfast for 30 d. The authors concluded that serum vitamin B-12 increased as a linear function of the log of the dose, and 5.9 μg/d was needed to increase serum vitamin B-12 by 37 pmol/L (50 pg/mL). There was no effect on MMA or tHcy. Unfortunately, food cobalamin malabsorption was defined as a normal Schilling test accompanied by some type of gastric problem or pernicious anemia (2 cases) so malabsorption may or may not have been present; furthermore, the serum vitamin B-12 response was highly variable across the few lower intakes tested, the study was too short to determine an optimal dose, and the dose was not provided in food.

POTENTIAL IMPACT OF FLOUR FORTIFICATION ON THE PREVALENCE OF VITAMIN B-12 DEFICIENCY

In wealthier countries, vitamin B-12 fortification of flour is most likely to lower the prevalence of inadequacy in the elderly, in those who consume low amounts of ASFs and fortified cereals, and in nonusers of supplements. Flour fortification would not be an effective way to supply vitamin B-12 for those with pernicious anemia, which affects 2–4% of the US population depending on ethnicity. Such patients require intermittent intramuscular injections with the vitamin or high-dose (eg, 500–1000 μg/d) oral supplements (31). The prevalence of pernicious anemia increases with age and, although the undiagnosed condition was found in a very low proportion of elderly in one study, this needs to be confirmed in a larger population sample. The proportion of elderly persons with impaired ability to absorb vitamin B-12 from fortified food needs to be tested, although it is likely to be relatively small.

In poor countries, flour fortification would potentially improve vitamin B-12 status in a much larger proportion of the population because of low usual intake of the vitamin in ASFs. Here individuals could benefit across the life span, although it could be especially beneficial for pregnant and lactating women, children, and the elderly. Confirming the efficacy of different levels of addition of the vitamin to flour on vitamin B-12 status and functional outcomes in different populations, including the elderly in different stages of gastric atrophy, should be a research priority. (Other articles in this supplement to the Journal include references 33–36.)

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