Vitamin B12 and health

Milly Ryan-Harshman PhD RD Walid Aldoori MB BCh MPA ScD

ABSTRACT

OBJECTIVE To review recent evidence that suggests vitamin B12 is associated with risk reduction for some chronic diseases and birth defects.

QUALITY OF EVIDENCE A MEDLINE search from 1999 to 2007 was performed using the key word *vitamin B12*. The most relevant articles (129) dealt with cardiovascular disease, cancer, mental health, and birth outcomes; most studies presented level II evidence.

MAIN MESSAGE Vitamin B12 might confer health benefits; however, such benefits are difficult to ascertain because of the complementary functions of vitamin B12 and folic acid. Vitamin B12 might lower high homocysteine levels below a threshold level achieved by folic acid alone. Furthermore, the interactions between the nutritional environment and genotype might have an important influence on vitamin B12, chronic disease risk, and risk of neural tube defects.

CONCLUSION Vitamin B12 might help protect against chronic disease and neural tube defects, but more research, particularly in the area of nutritional genomics, is needed to determine how vitamin B12 might augment the benefits of folic acid. Some consideration should be given to the potential value of fortifying foods with vitamin B12 in addition to the current mandatory folic acid fortification of grains.

RÉSUMÉ

OBJECTIF Revoir les données récentes qui donnent à penser que la vitamine B12 est associée à un moindre risque de maladies chroniques et de malformations congénitales.

QUALITÉ DES PREUVES On a consulté MEDLINE entre 1999 et 2007 à l'aide du mot-clé *vitamin B12*. Les articles les plus pertinents (129) traitaient de maladies cardiovasculaires, cancer, santé mentale et issues natales : la plupart des études présentaient des preuves de niveau II.

PRINCIPAL MESSAGE La vitamine B12 pourrait être bénéfique pour la santé; de tels effets sont toutefois difficiles à vérifier parce que la vitamine B12 et l'acide folique ont des actions complémentaires. La B12 pourrait abaisser les niveaux d'homocystéine sous les niveaux seuils atteints par l'acide folique seule. De plus, les interactions entre l'environnement nutritionnel et le génotype pourraient avoir une influence importante sur la vitamine B12, le risque de maladie chronique et celui de malformations du tube neural.

CONCLUSION La vitamine B12 pourrait aider à protéger contre des maladies chroniques et les malformations du tube neural, mais il faudra des études additionnelles, notamment dans le domaine de la génomique nutritionnelle, pour comprendre comment cette vitamine amplifie les effets bénéfiques de l'acide folique. On devrait s'interroger sur l'intérêt d'un éventuel enrichissement en vitamine B12 des aliments s'ajoutant à l'enrichissement obligatoire des grains en acide folique actuellement en vigueur.

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Vegetarians and the elderly are at higher risk of vitamin B12 deficiency. Among the elderly, vitamin B12 deficiency occurs in about 20% of the population; more than 60% of these deficiencies are due to food-cobalamin malabsorption syndrome[1] caused by gastrointestinal problems. Deficiency related to a lack of intrinsic factor results in severe neurologic damage and life-threatening anemia; therefore, such individuals require medical treatment including vitamin B12 injections. In strict vegans, vitamin B12 deficiency is mainly caused by avoidance of foods derived from animal origin, which are the only good dietary sources of vitamin B12.

In the United States, the estimated average daily intake of vitamin B12 is about 5 µg/d for men and 3.5 µg/d for women. The recommended intake for vitamin B12 is 2.4 µg/d. Between 10% and 30% of older people are unable to absorb vitamin B12 from foods; therefore, the Institute of Medicine of the National Academies in the United States recommends that individuals older than 50 years of age consume foods fortified with B12 or supplements containing B12. This is because higher doses of vitamin B12 can result in better absorption despite gastrointestinal difficulties.[2]

Vitamin B12 deficiencies have been identified in the Americas[3] and among South Asians living in Toronto.[4] Economic status, age, and dietary choices all influence the occurrence of vitamin B12 deficiency. Generally, when anemia is present, vitamin B12 levels are measured, but recent evidence suggests that while symptoms of B12 deficiency might be subtle, it can still cause metabolic and neurologic abnormalities such as hyperhomocysteinemia, cognitive function decline, or depression.[1] The Canadian Task Force on Preventive Health Care does not recommend routine screening for vitamin B12 deficiency and makes no recommendation regarding vitamin B12 therapy for any of the above conditions.[5]

Quality of evidence

A MEDLINE search from 1999 to 2007 on the relationship between B12 and health was performed using the key word *vitamin B12.* Articles referring specifically to diseases or conditions numbered more than 200, of which 129 were most relevant, largely providing level II evidence.

These articles suggest the health effects of B12 deficiency might include effects on cardiovascular disease (CVD), cancer, mental health problems, and adverse birth outcomes.

B12 and cardiovascular disease

Increased plasma homocysteine levels have been recognized as an important risk factor for CVD. Supplementation with folic acid and other B vitamins, a relatively inexpensive way of reducing plasma homocysteine levels, might be a way to lower CVD risk.[6,7] Several studies have shown that folic acid in combination with B12 lowers homocysteine levels, but what has not been quantified is the contribution of vitamin B12 alone to the lowering of homocysteine levels.

One study[8] demonstrated that a supplement consisting of 5 mg folic acid and 250 µg vitamin B12 lowered fasting plasma homocysteine levels by 32% after 12 weeks in patients with coronary artery disease. In another study[9] of healthy men and women ranging in age from 70 to 93 years, daily supplementation for 4 months with 500 µg of vitamin B12, 0.8 mg of folic acid, and 3 mg of vitamin B6 significantly reduced plasma homocysteine levels ($P<.001$). The authors of the study[9] suggested that suboptimal vitamin status is an important cause of elevated homocysteine even among the healthy elderly.

Several studies have examined patient populations, such as those with type 2 diabetes and dialysis patients (who are prone to cardiovascular problems), for possible relationships between vitamin B12 and homocysteine levels. Metformin, commonly used in the treatment of type 2 diabetes, might decrease vitamin B12 levels. In a randomized trial lasting 16 weeks, Wulffele and colleagues[10] showed that metformin decreased both folic acid (7% reduction) and vitamin B12 (14% reduction) levels. The modest increase (4%) in homocysteine levels likely resulted from the alteration in folic acid and vitamin B12 status. Among hemodialysis patients who had elevated homocysteine concentrations, neither intramuscular nor intravenous doses of vitamin B12 had an effect on homocysteine levels that was independent of folic acid.[11,12] However, in a small study of pregnant women with vitamin B12 deficiency between the fourth and ninth months of gestation, a rise in homocysteine levels was observed.[13]

B12 and cerebrovascular disease

Studies of the effect of dietary intakes of vitamin B12 on risk of stroke have not yielded consistent results. One study[14] indicated that intakes of folate and vitamin B6, but not vitamin B12, were significantly associated with decreased cerebrovascular mortality, whereas intakes of folate and vitamin B12, but not vitamin B6, were inversely associated with the risk of ischemic stroke.[15] Quinlivan and colleagues[16] demonstrated that following supplementation with increasing doses of folic acid, the dependency of plasma homocysteine levels on folate diminished, and the main determinant of plasma homocysteine levels then became vitamin B12. These researchers suggested that fortification of food with both folic acid and vitamin B12 could lower homocysteine levels more effectively, providing a potential benefit in vascular disease risk reduction.

Dr Ryan-Harshman *is a registered dietitian and owner of FEAST Enterprises in Oshawa, Ont.* **Dr Aldoori** *is Medical Director at Wyeth Consumer Healthcare Inc in Mississauga, Ont.*

One study[17] suggested that stroke type is important in determining the effect of blood vitamin levels on risk. Asian men younger than 50 years of age with ischemic stroke had elevated homocysteine levels only with large-artery strokes; vitamin B12 levels were significantly lower in cases compared with controls ($P<.001$), but there were no significant differences in serum folate levels. The authors suggested that the proatherogenic effect of hyperhomocysteinemia might increase risk of stroke. Treatment of hyperhomocysteinemia with folic acid, vitamin B12, and vitamin B6 has been shown to reduce thrombin formation.[18] Overall then, elevated homocysteine levels contribute to atherosclerosis, and optimum levels of folic acid and vitamins B12 and B6 might lower both homocysteine and the risk of clot formation.

With respect to heart disease and stroke, a more detailed understanding of the metabolism of homocysteine, particularly when homocysteine levels are elevated well above normal, is needed. Also, lowering homocysteine levels with vitamin supplementation has not been shown to affect secondary prevention as measured by recurrent myocardial infarction, stroke, or death due to cardiovascular causes.[19,20] Dusitanond and colleagues note, in their study of the VITATOPS trial, that multivitamin therapy does not reduce blood levels of inflammatory biomarkers, endothelial dysfunction, or hypercoagulability; they suggest this might be because the biomarkers are not sensitive to decreases in homocysteine, because homocysteine might have different mechanisms of action, or because elevated homocysteine might be a marker for, but not a cause of, increased vascular risk.[21]

What is also not known is at what level the inflammatory process of atherosclerosis exceeds the ability of any supplement to reverse negative consequences. This, in fact, is the greatest difficulty researchers face when attempting to ascertain nutritional benefits in secondary prevention trials. Recent studies have shown that vitamin B12 with other B vitamins reduces insulin resistance in patients with metabolic syndrome[22] and markers for oxidative stress and inflammation[23,24]; however, 2 randomized clinical trials showed no effect of B vitamins on venous thrombosis,[25,26] and a meta-analysis found no benefit regarding the progression of atherosclerosis.[27]

B12 and cancer

Synthesis and repair of DNA is a well-known function of folic acid. Ames[28] notes that folate deficiency, and possibly vitamin B12 and B6 deficiencies, are related to cancer via the incorporation of uracil, rather than the appropriate base, into human DNA, resulting in chromosomal breaks.

A small study[29] provided some evidence of a modest relationship between intake of B vitamins and cervical cancer. A case-control study among Hawaiian women suggested a protective role for B vitamins in cervical cancer, owing to a reduction in premalignant cervical lesions with high nutrient intakes.[30]

Some evidence exists for interactions among micronutrient intake levels, genotype, and cancer. Different forms of the methylenetetrahydrofolate reductase (MTHFR) gene carry different risks of colon cancer. The CC genotype with low micronutrient intake carries the highest risk of colon cancer. Slattery et al[31] reported that high intakes of folate, vitamin B6, and vitamin B12 were associated with a 30% to 40% risk reduction in colon cancer among those with the TT genotype relative to those with the CC genotype and low intakes. An earlier study[32] using data from the Nurses' Health Study did not find an inverse association between the TT variant of the MTHFR gene and diet with respect to colorectal adenoma, the immediate precursor of colorectal cancer. Other data from participants in the Physicians' Health Study and the Health Professionals Follow-up Study indicated that an interaction between the variant MTHFR genotype and risk of colorectal cancer was apparent, but for the methionine synthase variant, only a nonsignificant decrease was observed. No relationship was observed between vitamin B12 and either variant genotype.[33]

Overall, differences observed regarding genotype, micronutrient intakes, and colorectal cancer are not very strong. Relationships between dietary intakes, genotypes, and certain cancers are plausible; however, the field of nutritional genomics is in its infancy, and more research is needed to determine if any interactions observed are valid.

B12 and mental health

Researchers have postulated that biochemical factors such as homocysteine might be involved not only in heart disease, but also in brain function. Therefore, the relationship of B vitamins and homocysteine to cognitive function is under investigation. Homocysteine concentrations, but not vitamin B12, were associated with a decline in cognitive performance in a normal aging population.[34] In another study, B vitamins (2 mg folic acid plus 1 mg vitamin B12) lowered plasma homocysteine concentration by 30% in those with dementia or mild cognitive impairment, but no effect on cognitive function was observed.[35] Some studies have shown that folic acid might be more important to cognitive function than vitamin B12,[36] but B12 supplementation has been shown to improve symptoms indicative of delirium[37] or to improve some functions in patients with cognitive impairment,[38] even when the underlying condition of dementia remains unchanged. A systematic review of vitamin B12 and cognition concluded that the evidence is currently insufficient to show that B12 improves the cognitive function of people with dementia.[39]

Meins and colleagues found that patients with Alzheimer disease who had lower than normal vitamin B12 levels showed more frequent behavioural and

psychological symptoms of dementia than patients with normal values.[40] Engelborghs et al[41] did not find a correlation between serum vitamin B12 levels and behavioural and psychological symptoms of dementia in Alzheimer disease patients, but did find a correlation between serum vitamin B12 and frontotemporal dementia.

Vitamin B12 deficiency rises with age, but only about 10% of those with low vitamin B12 also have low folate levels.[42] Therefore, given the prevalence of both vitamin B12 deficiency and mental disability among the elderly, supplementation with vitamin B12 might reduce the risk of age-associated mental disability or improve the quality of life among those with dementia, but more studies are needed to determine how biologically important vitamin B12 might be.

Hyperhomocysteinemia, vitamin B12 deficiency, and impaired 1-carbon metabolism due to genetic polymorphism have also been associated with depression.[43,44] Hintikka and colleagues found that higher vitamin B12 levels were significantly associated with a better outcome for treatment of major depression, suggesting that vitamin B12 supplementation could be used to augment antidepressant treatments.[45]

As a therapeutic agent on its own, however, vitamin B12 is unlikely to substantially alter cognitive function or depression, though it has been shown to lower homocysteine levels. In fact, the most recent studies[46-49] show no benefit of vitamin B12 in trials lasting from 6 months to 2 years. Future studies should be designed to examine the nutritional, rather than the pharmacologic, benefits of vitamin supplementation in conjunction with pharmacotherapy.

B12 and birth outcomes

Adequate folate has been shown to reduce the incidence of neural tube defects (NTDs), and recent evidence has shown that fortification has improved outcomes in Canada.[50] Some researchers have suggested, however, that adequate vitamin B12 levels might also be necessary. In India, where much of the population is vegetarian and known to be deficient in vitamin B12, folate alone might have limited benefits. Improving vitamin B12 intakes might result in higher functioning of the enzyme methionine synthase that converts homocysteine to methionine.[51]

A systematic review of the literature[52] indicated that a moderate association might exist between maternal B12 status and the risk of NTDs, but that a large observational study would be necessary to further elucidate this relationship.

Families at risk for NTDs might have genetic variations that impair the metabolism of folate and vitamin B12. A mutation in the MTHFR gene or low vitamin B12 levels, in combination with a polymorphism in methionine synthase reductase (the enzyme that activates B12-dependent methionine synthase), has recently been shown to increase the risk of NTDs by up to 5 times.[53] Other work[54] also suggests that the interrelationships between genotypes and enzyme activity might increase the risk of spina bifida.

Others have suggested that the transport of vitamin B12 to tissues by transcobalamin II (TC II) might be affected by genetics. Afman and colleagues[55] noted that genetic variation in the TC II gene probably causes a reduced affinity for vitamin B12. Supplementation with B12 might raise TC II levels, increasing cellular vitamin B12, and decreasing homocysteine, which is higher in mothers of children with NTDs.

An interaction between nutrition and genotype that affects 1-carbon metabolism could be the reason for differences in abnormal birth outcomes worldwide. Gueant and colleagues[56] noted that polymorphisms in MTHFR and MTRR (methionine synthase reductase) are

EDITOR'S KEY POINTS

- Recently, there has been increased interest in the role of vitamins in maintaining health. While much attention has been focused on vitamin D, this article looks at a vitamin deficiency that occurs in 1 out of 5 older persons: vitamin B12 deficiency.
- While vitamin B12 deficiency can occur secondary to inadequate intake (eg, some vegetarians), in older persons it is due mostly to food-cobalamin malabsorption syndrome.
- Because of the complementary functions of vitamin B12 and folic acid, it can be difficult to determine the health benefits of vitamin B12 in isolation. It appears that vitamin B12 might help in preventing neural tube defects and chronic diseases, particularly through its effect on homocysteine levels.

POINTS DE REPÈRE DU RÉDACTEUR

- Le rôle de la vitamine B12 dans le maintien de la santé a récemment suscité un renouveau d'intérêt. Alors qu'on s'intéresse beaucoup à la vitamine D, cet article porte sur une déficience vitaminique rencontrée chez une personne âgée sur 5: la déficience en vitamine B12.
- La déficience en vitamine B12 peut résulter d'une alimentation inadéquate (par ex. chez certains végétariens), mais chez le vieillard, elle est principalement due au syndrome de malabsorption de la cobalamine alimentaire.
- Parce que la vitamine B12 et l'acide folique ont des fonctions complémentaires, il peut s'avérer difficile de déterminer les avantages de la vitamine B12 seule. On croit que la vitamine B12 aide à prévenir les malformation du tube neural et certaines maladies chroniques, notamment en agissant sur les niveaux d'homocystéine.

associated with higher risk of Down syndrome in North America, Ireland, and the Netherlands, while other polymorphisms might be predictors of either Down syndrome or NTDs in Sicily, France, and Great Britain.

Conclusion

Although at least 1 study has shown that vitamin B12 augments the role of folic acid in the homocysteine–cardiovascular disease pathway, its biological significance has been difficult to assess. A fortification scheme for vitamin B12 like that of folic acid in flour might lower homocysteine levels more effectively, but physicians should at least ensure that their patients older than 50 are receiving adequate intakes of vitamin B12 from foods fortified with B12 or supplements containing B12.

Vitamin B12 levels might modestly influence the development of cancer owing to genetic polymorphisms. The new field of nutritional genomics is expected to generate valuable information about nutrient-gene interactions and chronic disease.

Some behavioural or psychological indices related to dementia and depression might improve with B12 supplementation, which should be recommended in conjunction with pharmacotherapy.

Competing interests

Dr Ryan-Harshman *received a grant from Wyeth Consumer Healthcare Inc to co-author this article, and* **Dr Aldoori** *is an employee of Wyeth Consumer Healthcare Inc.*

Correspondence to: **Dr Milly Ryan-Harshman**, *FEAST Enterprises, 947 Oshawa Blvd N, Oshawa, ON L1G 5V6; telephone 905 728-8875; e-mail* **ryanharshman@rogers.com**

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