Cobalamin, folic acid, and homocysteine

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Cobalamin deficiency can lead to several adverse health consequences: folate trapping in the methylation cycle and subsequent impaired DNA biosynthesis; pernicious anemia hematologically, similar to that caused by folate deficiency; elevated blood homocysteine (tHcy) (risk factor for cardiovascular disease and adverse pregnancy outcomes); and neural tube defects (NTDs). Population-wide folate status is expected to improve where folic acid fortification policies for reducing NTD occurrence are established. However, there is concern that cobalamin deficiency and its characteristic neuropathy could be masked when hematological abnormalities in risk groups such as the elderly and vegetarians are reversed through folic acid supplementation. Folate-cobalamin interactions and their impact on health are reviewed here.

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INTRODUCTION

Since the implementation of mandatory fortification of grain products with folic acid in the United States, the incidence of neural tube defects (NTDs) has been reduced,¹ folate and tHcy status have improved in the population as a whole,² and the incidence of stroke has decreased.³ Despite these reported public health benefits, there has been concern about the safety of folic acid fortification in people with underlying cobalamin deficiency or low cobalamin status. This summary focuses on the similarities in folate and cobalamin metabolism, the consequences of cobalamin deficiency, and the effect of cobalamin deficiency in elderly people and pregnant women.

COMMON FACTORS IN FOLATE AND COBALAMIN METABOLISM, AND CONSEQUENCES OF DEFICIENCY

Folate cofactors are essential in DNA and methylation cycles.⁴ The conversion of 5,10-methylenetetrahydrofolate to tetrahydrofolate in the folate

cycle provides the methyl group required to convert homocysteine to methionine. Cobalamin acts as a cofactor for methionine synthase, which catalyses this reaction. When the cobalamin supply is low, the folate destined for DNA synthesis remains trapped in the methylation cycle (the methylfolate trap hypothesis).⁵ Both folate and cobalamin deficiencies are characterized by megaloblastic anemia. Both deficiencies lead to elevated tHcy.⁶

Since folic acid (pteroylglutamic acid, the synthetic form of folate) is reduced directly to tetrahydrofolate, it escapes the metabolic block caused by insufficient cobalamin. Thus, folic acid treatment corrects the megaloblastic anemia caused by cobalamin deficiency. As a result, the hematological marker of the deficiency (anemia) is corrected, and the clinical sign of the deficiency is masked. The resulting delay in diagnosis of the deficiency can lead to irreversible neurological damage.⁷ Neurological symptoms in the absence of anemia have been reported to occur in 20–30% of cases.⁷ Both reduced folate and reduced cobalamin status are risk factors for NTDs.⁸ Elevated tHcy is a risk factor for cardiovascular disease⁹ and adverse pregnancy outcomes.

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COBALAMIN AND FOLATE DEFICIENCY IN THE ELDERLY

Although dietary cobalamin deficiency is common in vegetarians¹⁰ due to the lack of cobalamin from foods of animal origin, up to 30–40% of the elderly have malabsorption of food-bound cobalamin.¹¹ This is associated with gastric atrophy and is characterized by the inability to release cobalamin from food or from intestinal transport proteins.¹² Cobalamin deficiency due to low dietary intake, together with low intake of folate and other B vitamins, is a major public health problem in developed as well as developing countries; in the elderly, it is further complicated by gastric changes. The health problems arising from this are expected to increase in prevalence as the elderly population grows. In addition to the anemia associated with these deficiencies, impaired cardiovascular health and cognitive function may also result. Estimates of the prevalence of cobalamin deficiency in the elderly vary between studies (5–25%), primarily because different cutoffs and status indices are used.¹³

IMPACT OF INTERVENTION WITH FOLIC ACID ON INDIVIDUALS WITH UNDIAGNOSED COBALAMIN DEFICIENCY

In Europe, the intake of synthetic folic acid has been assigned an upper tolerance limit of 1000 µg/day, which has been shown to not be detrimental to health in the general population. In some countries, such as the Netherlands, the addition of folic acid to foods is prohibited.

The incidence of clinical cobalamin deficiency before and after fortification with folic acid does not appear to have been studied systematically in countries that have introduced mandatory fortification. It has been estimated that a dietary intake 400 times greater than the recommended nutrient intake for cobalamin may be needed to correct cobalamin deficiency caused by food-bound malabsorption of cobalamin.¹⁴ The fortification of flour with cobalamin to improve status in people aged 65 years and over may not be a feasible option, as the effect of population exposure to such high doses is unknown. Masking anemia among a small number of patients with high pharmacological folic acid doses (5–15 mg/day) has been shown.¹⁵ Both plasma folate and cobalamin were strong predictors of tHcy in the European SENECA study.¹⁶

INTERACTION BETWEEN FOLATE AND COBALAMIN STATUS

Recently, intramuscular cobalamin injections were shown to normalize elevated tHcy, methylmalonic acid and 5-methyltetrahydrofolate/total folate ratio, and mild macrocytosis in a subject with baseline cobalamin defi-

ciency but adequate folate status and no anemia. This was considered proof of the methyl trap hypothesis.¹⁷ The higher rate of cognitive decline observed in participants with higher folate in the Chicago Health and Aging Project was proposed to have been due to the masking of cobalamin deficiency by high folate intake.¹⁴ A slower rate of cognitive decline was observed in participants with higher cobalamin intake. There is also evidence that folic acid supplementation reduces tHcy until a point is reached at which cobalamin becomes a limiting factor for further homocysteine reduction.¹⁸

PREGNANCY

Circulating levels of tHcy are reduced by approximately 36% of nonpregnant values by midnormal pregnancy¹⁹ and return to nonpregnant levels towards the end of the last trimester in the absence of folic acid supplementation.²⁰ Elevated tHcy has been associated with pregnancy complications affecting both maternal health and pregnancy outcome, e.g., preeclampsia,²¹ placental abruption,²² preterm delivery,²³ NTDs,²⁴ congenital heart defects,²⁵ Down syndrome,²⁶ and intrauterine growth retardation.²⁷ Both elevated tHcy²⁸ and low folate status²⁹ have been associated with recurrent miscarriage. Both low maternal folate and cobalamin status are risk factors for NTDs.⁸ Other adverse pregnancy outcomes associated with low cobalamin status are preterm birth,²³ intrauterine growth retardation,²⁷ and very early recurrent miscarriage.³⁰ Future studies will establish whether elevated tHcy is the cause or simply a biomarker of the complications associated with it. If its reduction were to benefit maternal and fetal health in situations of elevated tHcy during pregnancy, combined folic acid and cobalamin treatment could be considered.

Blood cobalamin concentration drops during normal pregnancy.³¹ This may be a physiological response to pregnancy. Clinically significant cobalamin deficiency meriting intervention during pregnancy has only been reported in pregnant women with traditionally vegetarian diets.³² However, if maternal cobalamin status is compromised as a result of pregnancy, it might impair both maternal and fetal cobalamin status during the ensuing lactation period, as reported in vegetarian mother-child pairs³³ and in developing countries.³⁴ Little risk of cobalamin deficiency during lactation was reported in healthy, well-nourished women.³⁵ However, elevated methylmalonic acid, a metabolic marker of cobalamin deficiency, was detected in 4 of 72 exclusively breastfeeding mothers during the first 4 months of lactation. Mothers with reduced cobalamin reserves at the start of lactation might benefit from cobalamin supplementation, especially if cobalamin status is compromised

while folate status is maintained or enhanced in the presence of fortification.

CONCLUSION

Older adults are at increased risk of cobalamin deficiency compared with younger adults and children. Early detection and treatment of cobalamin deficiency is important to prevent cognitive decline and neuropsychiatric disorders. In elderly populations, low cobalamin status is also associated with high tHcy concentrations. Low cobalamin status, low folate status, and high tHcy have all been associated with pregnancy complications. Studies are required to address the efficacy of combinations of folic acid and cobalamin supplementation/fortification in women of child-bearing age and in the elderly.

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Declaration of interest. The authors have no relevant interests to declare.

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