Does high folic acid intake affect unrecognized cobalamin deficiency, and how will we know it if we see it?\textsuperscript{1,2}

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Twelve years of mandatory food fortification with folic acid (FA), during which widespread self-supplementation pushed FA intake even higher, have nurtured questions about risks to persons with cobalamin deficiency but generated little meaningful data until just recently. In 2007 analysis of National Health and Nutrition Examination Study (NHANES) data linked higher folate concentrations with worse methylmalonic acid (MMA) and homocysteine indexes of metabolic deficiency in cobalamin-deficient adults (1). A companion analysis of an elderly NHANES cohort indicated that cognition and, curiously, anemia were also worse in that setting, whereas higher folate concentrations were associated with better cognition when cobalamin was normal (2). In this issue of the Journal, Miller et al (3) provide important confirmation of the metabolic association, but not the worse cognition, in the Sacramento Area Latino Study on Aging (SALSA).

An intervening report from Oxford found no metabolic, cognitive, or anemia associations (4). Its lack of statistical significance may reflect too few folate values above the reference interval (4.9% in its total study population compared with 26.3% in SALSA) because fortification is not mandatory and self-supplementation is limited in the United Kingdom. In fact, mean MMA and homocysteine values were also considerably higher in the study’s low-cobalamin/high-folate subjects than in those with normal folate. Interestingly, the standard deviations either approached or considerably exceeded their metabolite means in the low-cobalamin/high-folate group, which suggested that the group was metabolically diverse. Similarly wide metabolite distributions characterized the low-cobalamin/high-folate groups in NHANES and SALSA data (1, 3).

The apparent skew may hold important clues to the still undetermined meaning of the metabolic associations. The NHANES and SALSA reports hypothesized that FA causes oxidative damage to cobalamin metabolism. However, considerable precedent favors a reversed causation, if the association is indeed causal: advanced cobalamin deficiency, with its methyltetrahydrofolate accumulation, typically raises folate concentrations by 20–30% (5). The high red cell folate values (3), which should decline in cobalamin deficiency as red cell methyltetrahydrofolate exits to plasma (5), seemed incompatible but, despite high folate intakes, they were >200 nmol/L lower on average than in normal-cobalamin/high-folate subjects.

The wide spread of MMA and homocysteine values that characterized only the low-cobalamin/high-folate group in all 3 studies (1, 3, 4) suggests that this group alone contains subsets, one of which is probably severely cobalamin deficient, whereas another may have no deficiency; as can often occur despite abnormal cobalamin parameters (6). Pernicious anemia, although infrequent, is the predominant cause of clinically expressed cobalamin deficiency (5) and may plausibly explain the severely deficient group, whose 1.4% proportion in SALSA approximates the American frequency of pernicious anemia (7). Focused analyses may help.

The 3 studies’ disparate clinical outcomes, however, cannot be reconciled at present. The studies differed in many structural ways, including duration and extent of their populations’ exposure to high folate intake. The studies also had only 1–2 cognitive tests each to analyze, all of which were dissimilar.

A quandary in folate-cobalamin exploration is that observational studies cannot prove mechanisms but trials involving FA are subject to ethical constraints in cobalamin-deficient subjects. Alternative ways must be found to extract answers and resolve whether a public health problem requiring intervention exists. Future studies must identify in advance and collect all clinical and test data necessary for reliable characterization; data borrowed from broad multipurpose surveys often lack sufficient depth. The collected information must especially include optimal neurologic as well as cognitive testing. Statistical analyses can be enhanced with more clinically and pathophysiologically appropriate evaluations of group and individual data that may identify obscured subsets and reconfigured answers. Studies may also consider incorporating focused therapeutic trials with cobalamin. All this is a large task, but anything less is unlikely to suffice. The surveys must also be very large because the proportion of informative cases is typically minuscule and can inhibit stratification and subset analyses. The 1535 SALSA subjects, for example, yielded only 100 subjects (6.5%) with low cobalamin concentrations.

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tions. Only 22 subjects (1.4%) had the low-cobalamin/high-folate combination of interest, and they may require further subdivision if the metabolic association turns out to be confined to a subset with malabsorptive disease such as pernicious anemia, for example.

In anticipating studies to build on the potentially important NHANES and SALSA approaches and findings, it is also useful to explicitly note the avoidable weaknesses affecting many contemporary studies of cobalamin deficiency and probably contributing to the high frequency of conflicting outcomes. A basic underlying problem is that how cobalamin deficiency causes neurologic dysfunction is itself unknown despite many hypotheses. This makes it hard to address specific neurologic issues, such as the following: the often inverse relation between neurologic and hematologic expressions in clinically affected patients (8–10); why neurologic expression of cobalamin deficiency appears to be associated with higher folate concentrations than hematologic expression, irrespective of fortification (8, 10); and, of course, how (or whether) FA directly worsens cobalamin-deficient neurologic status, and why neurologic (like hematologic) progression can vary in the face of delayed cobalamin therapy while FA is given (5).

Misunderstandings of cobalamin pathophysiology have often posed an additional impediment. Because cobalamin deficiency lacks a diagnostic gold standard (6), surveys court substantial classification errors by using only one biochemical marker. Hematologic flaws have compromised most contemporary surveys on cobalamin and anemia (11): overall frequencies, means, correlations, and differences mislead by obscuring the important core (elderly subjects often have anemia, but cobalamin deficiency causes <5% of these anemias), inclusion of nonmacrocytic anemias dilutes and invalidates data (most cobalamin-deficient anemias are macrocytic), and analysis of mean corpuscular volumes in isolation is insufficiently informative for many reasons. Coexistence of biochemical cobalamin abnormality with anemia is disconcertingly often coincidental rather than causal (11) [>90% of cobalamin and MMA abnormalities reflect subclinical deficiency (6)]. Neurologic and cognitive tests are hard to include in large surveys and lack all specificity for cobalamin deficiency. The now prevalent tendency to focus on cognition while ignoring the probably more common myeloneuropathies can also be questioned. Malabsorption is usually central to clinically expressed cobalamin deficiency and a major determinant of the likelihood of deficiency to progress (6). Yet, malabsorption is rarely considered and never tested in contemporary surveys. Finally, misunderstandings often become embedded within interpretations that do not differentiate clinical and subclinical cobalamin deficiencies. Clinical deficiency is relatively rare, but it features anemia and neurologic dysfunction, whose progression is likely because severe malabsorption underlies most cases; its treatment is mandatory. Subclinical, purely biochemical deficiency usually shares none of those characteristics, but it far outnumbers clinical deficiency (6). Adverse FA effects have been described only in patients with clinical cobalamin deficiency arising from severe malabsorptive disease (5). None have yet been shown in subclinical deficiency. Drawing clinical conclusions without taking into account the many disparities between the 2 deficiency forms makes no more sense than formulating conclusions on fire safety from data that do not distinguish between burning houses and overheated houses.

The earlier article by Selhub et al (1) and the present study by Miller et al (3) have provided a fresh impetus with their intriguing new information. The challenges now lie in the requisite next steps toward unraveling the nature of clinical cobalamin deficiency in the era of FA fortification.

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REFERENCES

1. Selhub J, Morris MS, Jacques PF. In vitamin B12 deficiency, higher serum folate is associated with increased total homocysteine and methylmalonic acid concentrations. Proc Natl Acad Sci USA 2007; 104:19995–20000.


