Prevalence of cobalamin (vitamin B-12) and folate deficiency in India—audi alteram partem

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Audi alteram partem—hear the other side.

There is an emerging epidemic of cardiovascular disease in India (1). This has resulted from an unfavorable combination of conventional lifestyle-related risk factors (smoking, hypertension, diabetes, and hypercholesterolemia) and unconventional risk factors associated with metabolic syndrome X [insulin resistance, dyslipidemia, truncal (visceral) obesity, acanthosis nigricans, skin tags, and elevated homocysteine, lipoprotein(a), plasminogen activator inhibitor, and fibrinogen concentrations] (2). Homocysteine is a continuous, progressive risk factor for occlusive vascular disease (ie, higher concentrations predict higher risk) that is modifiable and likely causal. Therefore, reversible (vitamin responsive) hyperhomocysteinemia—including deficiencies of vitamin B-12 (cobalamin), folate, vitamin B-6, and thermolabile methylentetrahydrofolate reductase—are of particular interest (3).

In this issue of the Journal, Refsum et al (4, 5) report that ≈75% of a selected urban population from India (Pune, Maharashtra State) had metabolic evidence (hyperhomocysteinemia and methylmalonic acidemia) consistent with cobalamin deficiency that can only partly be explained by a vegetarian diet. Obviously, if these findings are widespread, this will have important health implications. However, anyone who has visited the Indian subcontinent cannot but be struck by the heterogeneity of the people, which encompasses racial, religious, ethnic, cultural and socioeconomic differences. This, in turn, influences dietary habits. So any nutritional study arising from India needs to be viewed within the broad context of the heterogeneity, ie, racial, religious, ethnic, cultural and socioeconomic differences, of its people.

Are there missing pieces of data that somewhat limit the study by Refsum et al? Yes. Because elevations in homocysteine and methylmalonic acid (MMA) precede overt clinical symptoms and signs of cobalamin deficiency, it is unclear how many individuals had clinically significant cobalamin deficiency and how many simply had a subclinical deficiency (3, 5, 6). Additionally, because of the limited clinical information presented, it is unclear whether subjects had neurologic manifestations of cobalamin deficiency in the absence of hematologic abnormalities. Diagnostic algorithms have consistently stressed the value of always including clinical data to improve the pretest probability that tests results indicating low serum cobalamin or low serum folate concentrations support the diagnosis of a deficiency of these vitamins (3, 5, 6). This is because these tests, by themselves, have inherent limitations in sensitivity and specificity. Moreover, without detailed clinical information, are the combined results of serum cobalamin, folate, and metabolite tests sufficiently unambiguous to accurately distinguish cobalamin deficiency from either folate deficiency or combined cobalamin and folate deficiency? Not necessarily. Cobalamin deficiency results in elevated serum MMA and homocysteine concentrations, whereas folate deficiency results in only hyperhomocysteinemia. However, the combination of a cobalamin and folate deficiency gives a profile similar to that of cobalamin deficiency alone (3, 5, 7). One way to discriminate between these 2 conditions is to show that abnormally high metabolite concentrations are restored to baseline with appropriate selective vitamin replacement (5, 7–9). Thus, in pure cobalamin deficiency, only cobalamin repletion will restore elevated MMA and homocysteine concentrations to normal. Furthermore, hyperhomocysteinemia due to pure folate deficiency can be reversed only by folate replacement. Thus, repletion of both cobalamin and folate are necessary in persons with a combination of cobalamin and folate deficiency to completely restore serum MMA and homocysteine concentrations to normal (9). In this scenario, repletion of cobalamin alone would result in a suboptimal reduction in serum homocysteine, with a further reduction to baseline concentrations accomplished only by appropriate folate repletion.

Therefore, a subclinical deficiency of cobalamin, folate, or both on the basis of elevated serum MMA, serum homocysteine, or both—when serum cobalamin and folate concentrations are normal—can only be confidently diagnosed after confirming that treatment with cobalamin, folate, or both has completely restored pretherapy metabolite concentrations to normal (6–9). This is similar in principle to that used to confirm clinically significant nutrient deficiency (3). Without such information, may confidence regarding the assignment of elevated metabolites to pure cobalamin deficiency in the subjects studied is somewhat reduced (4). Furthermore, a significant minority of other popula-

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tions with subclinical or clinical folate-responsive hyperhomocysteinemia (ie, folate deficiency) have low-normal serum folate concentrations (6). Thus, the use of a stringent cutoff of ≤5 nmol folate/L by Refsum et al to indicate folate deficiency may have resulted in the missed diagnosis of folate deficiency in subjects with a combination of cobalamin and folate deficiency whose folate concentrations were in the low-normal range (3, 6).

Although the reference ranges for serum cobalamin, folate, homocysteine, and MMA concentrations were presumably based on those of a healthy Caucasian population, there are well-recognized racial and ethnic differences in what are considered to be normal concentrations (10). Therefore, it would be ideal to know what values are considered normal in this particular Indian population. But this poses yet another set of problems. If a large percentage of a population of apparently non-vitamin-deficient individuals, on the basis of normal serum cobalamin and folate concentrations, has a subclinical vitamin deficiency, the reference ranges for serum MMA and homocysteine that indicate “normalcy” would be much higher than in a population without a subclinical vitamin deficiency. Yet, such concentrations would not be optimal to promote health. One rational approach would be to develop optimal reference standards for metabolite concentrations, specific to a population, whereby apparently healthy subjects have been treated with folate, cobalamin, and vitamin B-6 to completely normalize any metabolites that may have been elevated as a result of a subclinical deficiency. Such a reference range for serum MMA and homocysteine (generated from post-vitamin treated subjects) would represent the optimal reference standard for this cohort against which metabolite concentrations of other subjects can be compared.

These issues of normalcy and the need to develop optimal reference standards for metabolite concentrations in specific populations in whom a large percentage may have a subclinical vitamin deficiency are not simply theoretical within populations in India. It has been known for >3 decades that vegetarians in India have lower serum cobalamin concentrations than do nonvegetarians, with the lowest concentrations being in vegans (11). This is because cobalamin is only produced in nature by cobalamin-producing microorganisms; therefore, humans must receive cobalamin in their diets—primarily from meats and less so from eggs and dairy products (3). Given the advantage of hindsight, many hematologically normal control subjects in earlier studies of the nutritional status of vegetarians with low cobalamin concentrations would likely now be classified as cobalamin deficient on the basis of sophisticated clinical tests such as vitamin-responsive electroencephalographic changes (5) or after metabolic testing before and after cobalamin replacement (7–9). Although data from Kerala State, India, indicate that healthy subjects had homocysteine concentrations of ≈11 μmol/L (12), this observation probably reflects the vast differences in race, culture, ethnicity, and much higher literacy rates (of 99%) that in turn influence the consumption of a vitamin-replete diet in this region.

Folate deficiency has traditionally been linked to poverty, which (by Indian standards) afflicts ≈33% of the population of India (1). A recent World Bank report on the crisis of malnutrition in India highlighted the fact that one-half of all children aged <4 y are malnourished, 30% of all newborns are underweight, and 60% of all women are anemic (13). Therefore, any discussion of cobalamin deficiency in India immediately raises the question of whether folate deficiency, which consistently accompanies poverty and malnutrition, has become an uncommon cause of megaloblastic anemia. Although some studies suggest that this is the case (14, 15), nagging questions remain about whether these patients with megaloblastic anemia had a combination of cobalamin and folate deficiency. In these studies, folate status was assessed in all subjects by measuring serum folate concentrations. However, serum folate concentrations are highly labile to the extent that a low serum folate concentration can be rapidly normalized shortly after consumption of a single, nutritious, folate-rich meal while hospitalized (3). Because all subjects were hospitalized during the evaluation of their anemia (13, 14), it is possible that any underlying folate deficiency could easily have been rapidly (and inadvertently) corrected if the blood was tested after such an in-hospital meal (3). In these same patients, however, the portion of the elevated serum homocysteine concentration due to folate deficiency would not have returned to normal until after 1 wk (7). Thus, if these patients also had a cobalamin deficiency, the clinician would erroneously link a low serum cobalamin concentration with elevated serum homocysteine and MMA concentrations and conclude that the patients had a cobalamin deficiency alone, when in fact they had both cobalamin and folate deficiencies. Thus, underrecognition of a combined cobalamin and folate deficiency is particularly likely in studies in which there is no prospectively defined protocol in place that explicitly mandates that serum folate concentrations be assessed by venipuncture before in-hospital food intake.

Finally, the article by Refsum et al reminds us of yet another facet of cobalamin nutrition. Apart from the intrinsic morbidity accompanying cobalamin deficiency and the accompanying adverse risk effects of hyperhomocysteinemia, cobalamin deficiency also increases the susceptibility to infectious diseases, particularly tuberculosis (16), which affects 14 million persons annually in India and results in 1 death from tuberculosis each minute (1).

On the basis of these considerations, the Ministry of Health of the Government of India should urgently initiate studies to comprehensively define the prevalence of cobalamin and folate deficiencies throughout India. If cobalamin and folate deficiencies are confirmed in a large enough percentage of the Indian population to be judged a major public health problem, forces must be galvanized to curb this nutritional epidemic of potentially mammoth proportions.

REFERENCES

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