

Vitamin B₁₂ Deficiency in the Elderly

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Vitamin B₁₂ deficiency is a common disorder in older adults, but its diagnostic work-up and management can be complex. In this article, we review the metabolic pathways involving vitamin B₁₂ and the various pathologies that can interfere with these pathways. This discussion provides a framework to understand the following section, which outlines an approach to the clinical examination, laboratory evaluation and treatment of subjects with suspected vitamin B₁₂ deficiency.

Key words: vitamin B₁₂, folic acid, deficiency diseases, dementia, aging.

Introduction

Vitamin B₁₂ deficiency is frequently suspected in older adults with a variety of neurologic and hematologic abnormalities. However, the diagnostic evaluation and management of such patients can be complex. Serum vitamin B₁₂ concentrations alone have limited sensitivity and specificity in the elderly.^{1,2} Our goal in this article is to outline the physiology and pathophysiology of vitamin B₁₂ metabolism, which will then permit a rational approach to the clinical examination, laboratory testing and treatment of vitamin B₁₂ deficiency. An accompanying article (see article, page 24) discusses the interdependent metabolic pathways of folate. There is now increased interest in vitamin B₁₂ and folate due to the potential role of homocysteine in a variety of cardiovascular³ and neurologic⁴ diseases.

Normal Physiology of Vitamin B₁₂

Vitamin B₁₂ is also known as cobalamin, and the terms are used interchangeably in this article. Different ligands can attach to produce chemically distinct cobalamins (e.g., cyanocobalamin, methylcobalamin), but they all share essentially identical nutritional properties.² Foods of animal origin (such as

meat and dairy products) are the primary dietary source of vitamin B₁₂. The average North American diet contains 5–15mg/day of cobalamin, more than enough to meet the traditional recommended dietary allowance of 2mg/day.² Furthermore, there are normally 2,000–5,000mg total body stores of cobalamin (which are found primarily in the liver). As a result, cobalamin deficiency on the basis of dietary insufficiency or malabsorption is rare and often takes years to develop.

Figure 1 illustrates the steps involved in vitamin B₁₂ absorption. Dietary protein (or “extrinsic factor”) binds to vitamin B₁₂ in many foods. In the acidic environment of the stomach, vitamin B₁₂ is dislodged from food protein and binds to salivary haptocorrin (previously called R binder protein). Haptocorrin prevents cobalamin from being degraded as it passes through gastric acid. As vitamin B₁₂ enters the duodenum, the neutral pH environment and pancreatic enzymes facilitate the displacement of haptocorrin. Vitamin B₁₂ then becomes attached to intrinsic factor, which is produced by parietal cells in the stomach. The cobalamin-intrinsic factor complex travels to the terminal ileum, where it is absorbed into mucosal cells via receptor-mediated endocytosis.² Within the mucosal cells,

cobalamin is picked up by transcobalamin II (TC II) and serum haptocorrins (formerly referred to as TC I and TC III), which are plasma proteins that carry cobalamin to the liver and other target organs. It is important to note that approximately 2% of vitamin B₁₂ absorption occurs in the small bowel proximal to the terminal ileum, independent of intrinsic factor and its receptor.⁵ Studies have shown that high-dose oral vitamin B₁₂ can be absorbed in significant quantities in the absence of intrinsic factor or an intact ileum.⁶

Two cobalamin-dependent biochemical reactions exist in humans and higher animals (Figures 2 and 3).^{2,7} In the first reaction, cobalamin supplies coenzymatic activity to aid in the conversion of methylmalonic acid (MMA) to succinyl-coenzyme A (succinyl-CoA). In the second reaction, both cobalamin and folate are needed to synthesize methionine. Homocysteine, a simple amino acid, is a precursor to methionine in this reaction, and its importance is discussed in detail in the accompanying article on folate. The conversion of methionine into S-adenosylmethionine is essential for proper functioning of the central nervous system.^{2,7} The other product of this reaction, tetrahydrofolate, is needed for DNA synthesis.^{2,7} As a result, areas in the body that have high cell turnover (such as the hematologic system and gastrointestinal tract) are particularly sensitive to vitamin B₁₂ or folate deficiency.

Pathophysiology

Keeping in mind the stages of vitamin B₁₂ metabolism allows us to identify the various causes of deficiency in a logical sequence (Table 1, page 20). To begin, an inadequate “tea and toast” diet is the most obvious cause of deficiency. However, pure dietary vitamin B₁₂ deficiency is rare, as it requires strict vegetarianism and must be present for several years to deplete B₁₂ reserves.

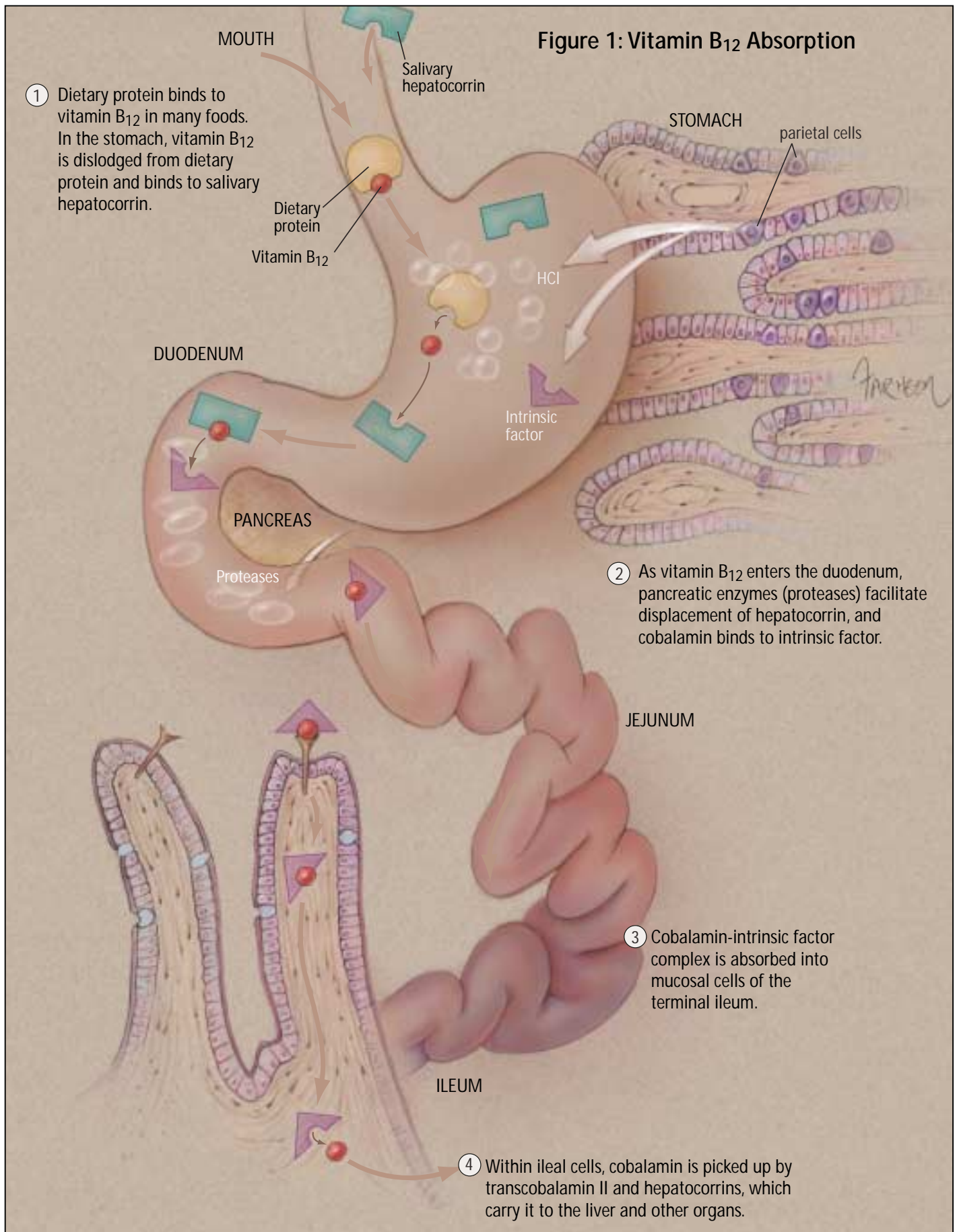
Figure 1: Vitamin B₁₂ Absorption


Figure 2: Conversion of MMA to Succinyl-CoA



Gastric disorders result in a loss of intrinsic factor and acid, leading to vitamin B₁₂ malabsorption. Gastric disorders include pernicious anemia, those resulting from gastrectomy and gastric bypass procedures, and the effects of medications (e.g., proton pump inhibitors). Pernicious anemia, or chronic atrophic gastritis, is categorized as either type A (autoimmune) or type B (non-autoimmune). *Helicobacter pylori* infection is a common cause of type B gastritis.⁸ Pernicious anemia represents a common cause of vitamin B₁₂ deficiency in the general population. In the elderly, malabsorption of cobalamin due to food protein binding may be more common than pernicious anemia, but this is controversial.^{1,2,9} There is some evidence to suggest that acid-lowering medications (e.g., histamine-2 receptor antagonists and proton pump inhibitors) may increase the risk of cobalamin deficiency.¹⁰

Disorders of the intestinal lumen may result in cobalamin deficiency through either malabsorption (e.g., pancreatic insufficiency) or competitive uptake (e.g., bacterial overgrowth, fish tapeworm infestation). Disorders of the ileum specifically lead to malabsorption of the cobalamin-intrinsic factor complex. Examples include surgical resection, Crohn's ileitis and the effects of medications such as colchicine.²

Although uncommon, congenital transcobalamin II deficiency has been identified and is associated with impaired cobalamin metabolism.²

Clinical Features of Vitamin B₁₂ Deficiency

Areas that have high cell turnover (such as the hematologic system and gastroin-

testinal tract) are particularly sensitive to vitamin B₁₂ deficiency. Consequently, clinical manifestations of deficiency associated with the macrocytic anemia include fatigue, palpitations and pallor. As well, gastrointestinal involvement may produce a smooth beefy red tongue, angular cheilitis, stomatitis and diarrhea.

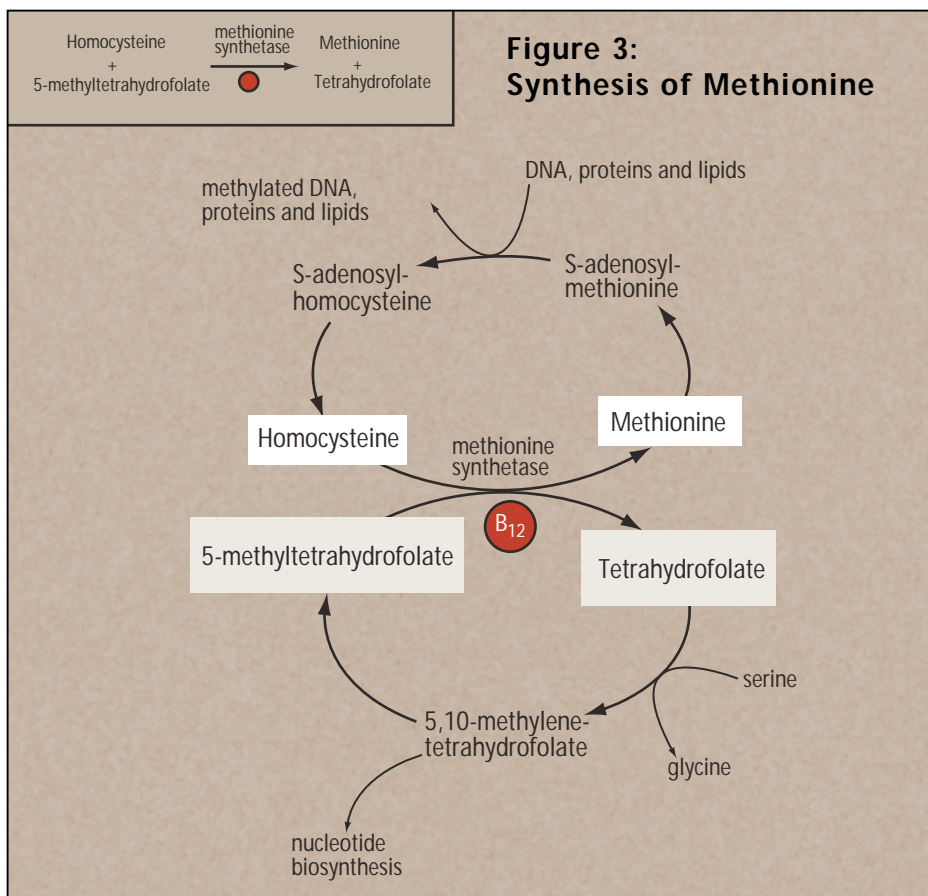
The neurologic manifestations of cobalamin deficiency are well detailed in a large case series.¹¹ The authors of this report found that paresthesia and ataxia were common early manifestations of deficiency. A wide spectrum of neurologic syndromes was identified, includ-

ing muscle weakness (often worse in the lower extremities), hypo- or hyperactive reflexes, spasticity (a late sign), optic neuropathy (leading to reduced visual acuity and visual field defects), dementia, psychoses and mood disorders. Multiple neurologic syndromes were often documented in individual patients.¹¹ It is important to note that the neurologic manifestations of cobalamin deficiency commonly occur in the absence of hematologic signs, particularly if supplementary folate is being taken.¹² Conversely, some patients with vitamin B₁₂ deficiency present with purely hematological involvement and no neurological manifestations.

Laboratory Testing

The laboratory evaluation of vitamin B₁₂ deficiency is complex. An excellent review of this topic is available elsewhere.² Here, we will highlight some of the more common issues.

Essentially there are two parts to the laboratory investigation: evaluating vita-



min B₁₂ status, and finding the cause of B₁₂ deficiency.² Tests aimed at establishing the diagnosis of vitamin B₁₂ deficiency include the serum vitamin B₁₂ concentration, several hematologic parameters (the mean corpuscular volume [MCV] and peripheral blood smear) and metabolite measurements (MMA and homocysteine). Tests aimed at determining the cause of deficiency include autoantibody assays (antiparietal cell and anti-intrinsic factor antibodies) and the Schilling test.

Serum cobalamin levels have limited sensitivity and specificity in the elderly, and published estimates of these values vary widely, due in part to the lack of a consistent gold standard for diagnosis in individual studies.² Up to 50% of subjects with elevated MMA and/or homocysteine levels have serum cobalamin concentrations above the conventional cutoff of two standard deviations below the mean in a normal population.¹ Causes of falsely normal serum cobalamin levels include myeloproliferative disorders, liver disease, recent supplementation with vitamin B₁₂ and intestinal bacterial overgrowth (as the bacteria produce biologically inactive cobalamin analogues).² In general, however, cobalamin concentrations below 74pmol/L (100pg/mL) are 90% specific for the diagnosis of deficiency.²

Should vitamin B₁₂ be measured in all patients presenting with dementia? The arguments for and against such a strategy are complex. In practice, the Canadian Consensus Conference on Dementia recommended that vitamin B₁₂ should be considered an optional test in the evaluation of dementia, indicated if "proprioceptive loss, peripheral neuropathy or a macrocytic anemia accompany cognitive decline".¹³ In contrast, the more recent American Academy of Neurology practice parameter for the diagnosis of dementia suggested that vitamin B₁₂ levels should be included in the routine assessment of elderly subjects with suspected dementia, because vitamin B₁₂ deficiency is common in this population.¹⁴

Hematologic parameters alone are of limited value. In addition to the megaloblastic anemia of vitamin B₁₂ deficiency, there are many other causes of an elevated MCV. These include folate deficiency, medications (e.g., zidovudine [AZT]), myelodysplastic disorders, liver disease, alcohol abuse and hypothyroidism. Traditionally, peripheral blood smears are emphasized in the diagnostic work-up, and may demonstrate oval macrocytes and hypersegmented neutrophils. In practice, however, the independent contribution of these findings to the diagnosis of deficiency appears to be low.²

Serum and urine MMA and serum total homocysteine assays exist to aid in the diagnosis of cobalamin deficiency, although MMA may not be widely available in Canadian centres. Of note, elevations in both metabolite levels would be expected in subjects with cobalamin deficiency (Figures 2 and 3), while only homocysteine levels would rise in subjects with folate deficiency.² Hypovolemia and renal insufficiency can also cause elevations of both MMA and homocysteine, and deficiency of pyridoxine (vitamin B₆) can raise homocysteine levels. After excluding these conditions, an elevated metabolite level in the setting of a borderline cobalamin level (e.g., 140–180pmol/L) is strongly suggestive of early cobalamin deficiency. Following serial MMA and/or homocysteine levels can be valuable in assessing the response to treatment in vitamin B₁₂ deficiency; metabolite levels usually normalize within seven to 14 days of treatment.²

There are several autoantibodies that can be detected in subjects with pernicious anemia, including antiparietal cell and anti-intrinsic factor antibodies. Antiparietal cell antibodies are found in approximately 85% of patients with pernicious anemia, but these antibodies are non-specific and can also be detected in patients with autoimmune endocrinopathies and 3–10% of the healthy population.² In contrast, anti-intrinsic factor antibodies have low sensitivity but high specificity (i.e., not

every patient with pernicious anemia carries them, but they are rarely found in people without pernicious anemia). Assays to measure these autoantibodies are available in many larger centres in Canada.

The Schilling test is most often used to determine the cause of vitamin B₁₂ deficiency. Although interpretation of the test can be difficult,² we will outline the basic procedure. Initially, a dose of non-labeled cobalamin is given intramuscularly (thereby bypassing any potential absorptive problem). This intramuscular cobalamin "saturates" the body stores, thereby facilitating excretion of a standard dose of radiolabeled cobalamin given orally during the first stage of the test. The percentage of this radiolabeled cobalamin that is excreted in a 24-hour urine collection is then measured. If the results of this first stage are abnormal (i.e., the excretion is low), a second stage is per-

Table 1
Selected Causes of Vitamin B₁₂ Deficiency

1. Dietary insufficiency – strict vegetarianism
2. Gastric disorders – pernicious anemia (types A and B) – food protein-bound cobalamin malabsorption – gastrectomy/gastric bypass – medications leading to achlorhydria (e.g., proton pump inhibitors)
3. Disorders of the intestinal lumen – pancreatic insufficiency – bacterial overgrowth (e.g., blind loop, diverticulae) – fish tapeworm (<i>D. latum</i>)
4. Disorders of the ileum – surgical resection, radiation – Crohn's disease – medications (e.g., colchicine)
5. Impaired utilization or metabolism – congenital transcobalamin II deficiency

formed three to seven days later, using a combination of another dose of labeled cobalamin and intrinsic factor. If excretion during stage 1 is abnormal, it suggests that there is dietary deficiency, protein-bound cobalamin malabsorption or congenital TC II deficiency. If excretion is low during stage 1 but improves during stage 2, the most likely explanation is a deficiency of intrinsic factor (i.e., pernicious anemia, prior gastrectomy). If excretion during both stages 1 and 2 are abnormal, possible interpretations include the presence of ileal disease, pancreatic insufficiency, competitive parasitic uptake (e.g., bacterial overgrowth, fish tapeworm infestation) or renal insufficiency. Inadequate urine collections can confound the results of the Schilling test at various stages.²

Treatment

With respect to non-deficient subjects, the U.S. Institute of Medicine has recently recommended that adults older than 50 years should consume a majority of the new recommended dietary allowance of vitamin B₁₂ (2.4mg/day) in its synthetic form rather than in its food form. This recommendation arose from concerns over malabsorption of protein-bound cobalamin.⁹

In subjects with established vitamin B₁₂ deficiency, cobalamin supplementation is universally accepted. Hematologic abnormalities nearly always correct with supplementation. Neurologic disease related to cobalamin deficiency may improve within several weeks, especially if abnormalities are detected early. Unfortunately, neurologic damage, particularly central nervous system injury, does not improve with treatment in many subjects. At the very least, however, further progression is avoided, and so cobalamin supplementation is still warranted.

Whether to use the traditional monthly intramuscular route or oral supplements is controversial. Recall that approximately 2% of vitamin B₁₂ absorption occurs independent of

intrinsic factor and its ileal receptor. As a result, large oral doses of cobalamin can provide adequate serum levels, even in subjects with pernicious anemia. Evidence suggests that changing all patients from parenteral to oral therapy would result in a significant cost savings to our health care system and would improve patient satisfaction.¹⁵ Interestingly, a significant number of patients without documented deficiency report symptom improvement with injections, and state that they would actively seek a physician to continue administering parenteral cobalamin.¹⁶

Caution must be exercised when treating patients with megaloblastic anemia due to folate and cobalamin deficiency. If folate supplementation is provided, the hematologic abnormalities may correct, but without cobalamin potentially irreversible neurologic damage may progress.² One clue to such a problem would be persistently elevated MMA levels. There is some concern that the recent fortification of cereals with folate may lead to masking of such cases of vitamin B₁₂ deficiency in the elderly.¹ If there is no response of the anemia to supplementation of both folate and cobalamin, coexistent iron deficiency should be considered (which, along with the folate and cobalamin deficiencies, may also be secondary to small intestinal malabsorption).

Conclusions

Older patients frequently present with abnormal vitamin B₁₂ levels. It is important to have an appreciation of the normal physiology of vitamin B₁₂ in order to understand the mechanisms of deficiency. This understanding permits a logical approach to the evaluation and treatment of deficiency states. ♦

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