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Hematological Disease

Cobalamin Deficiency in Older Adults

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Cobalamin (vitamin B_{12}) deficiency is particularly common in among older adults, although it is frequently undiagnosed as the clinical presentations may be subtle. However, serious complications do occur, in particular neuropsychiatric and hematological disorders. In older adults, the main causes of cobalamin deficiency are food-cobalamin malabsorption (50–60%) and pernicious anemia (30–40%). Food-cobalamin malabsorption syndrome is a disorder characterized by the inability to release cobalamin from food or its binding proteins. This syndrome is frequently associated with atrophic gastritis, which may be a result of Helicobacter pylori *infection, and long-term ingestion of antacids and biguanides. The management of cobalamin deficiency with cobalamin injections is currently well documented, however new routes of cobalamin administration (including via oral and nasal passages) are being studied. Oral cobalamin therapy is of particular interest in the management of food-cobalamin malabsorption syndrome.*

Key words: *cobalamin, vitamin B_{12}, cobalamin deficiency, food-cobalamin malabsorption, oral cobalamin therapy*

Introduction

Cobalamin (vitamin B_{12}) deficiency is particularly common in the older population,[1] although it remains frequently undiagnosed as the clinical presentations may be subtle. However, serious complications do occur, in particular neuropsychiatric and hematological disorders.[2] Therefore, the condition should be considered in all patients who present with vitamin or nutritional deficiency.

The commonest cause of cobalamin deficiency is food-cobalamin malabsorption, a disorder characterized by the inability to release cobalamin from food or its binding proteins.[3] In older adults, pernicious anemia is the second most frequent cause.[4]

This article summarizes the current knowledge on cobalamin deficiency with a particular focus on food-cobalamin malabsorption and oral cobalamin therapy.

Definition

There are several criteria used to diagnose cobalamin deficiency.[5] It is frequently defined in terms of the serum concentration of cobalamin, homocysteine and methylmalonic acid (two essential components of the cobalamin metabolic pathway) (Figure 1).[3] However, in current clinical practice there is no single test or "gold standard" used to make the diagnosis, especially among the older adults. The group of patients who present the most difficulties in diagnosis are those who develop subtle cobalamin deficiency, often without hematological abnormalities, and who thus may not receive the early treatment needed to prevent irreversible neurological damage.[5]

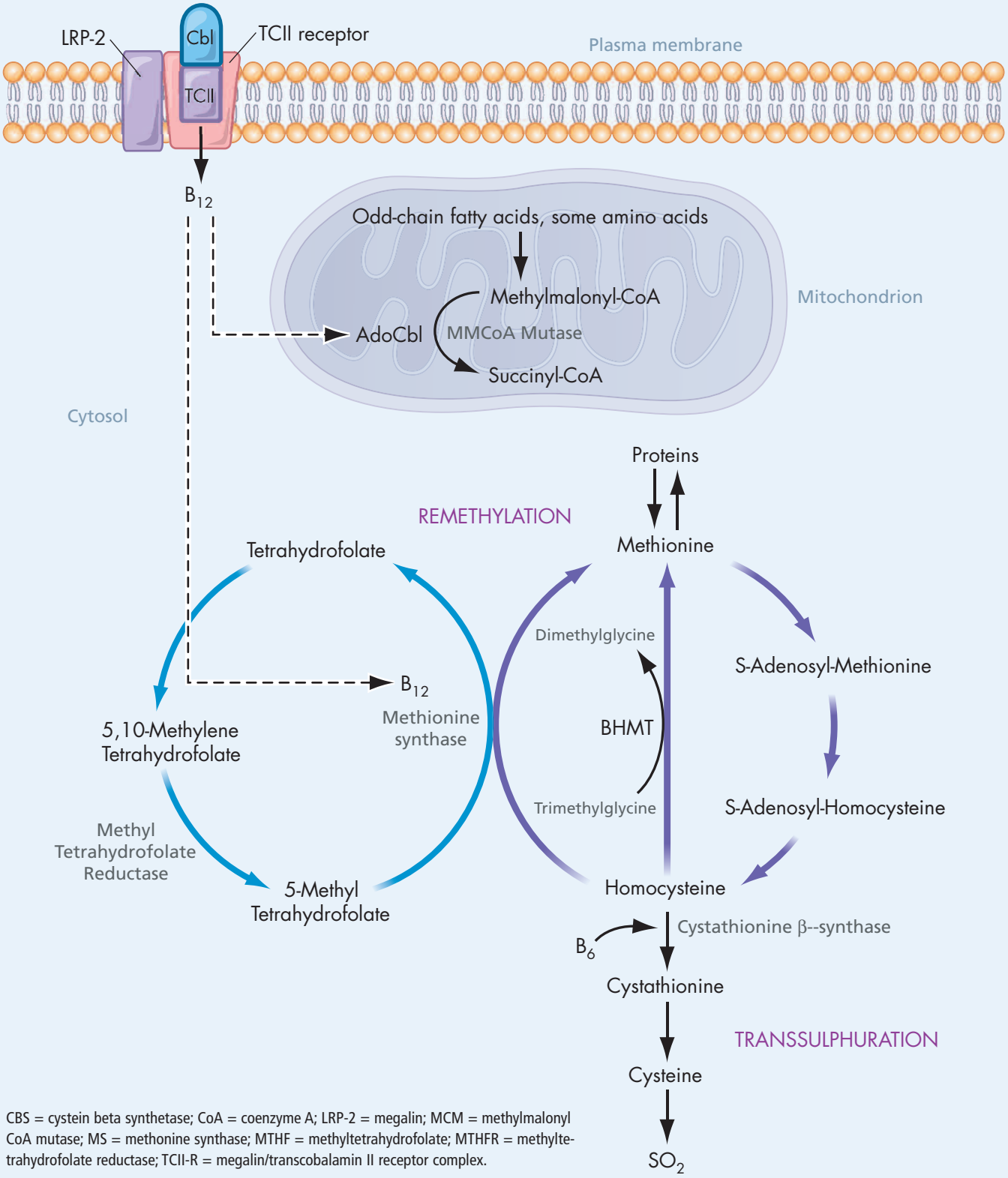
New serum cobalamin assay kits (e.g., the holotranscobalamin assay kit) are being developed to replace older versions and provide a new standard for testing.[6]

Epidemiology

Among the general population living in industrialized countries, cobalamin deficiency has a prevalence of approximately 2–20%, (depending on the definition used).[3] The Framingham study demonstrated a prevalence of 12% amongst older adults living in the community setting.[7] Other studies have focused on the older population, particularly those who are in long-term residential care or who are suffering from an acute illness or malnourishment. Figures from these studies have suggested a higher prevalence of at least 30%.[3,4]

Using strict criteria (serum cobalamin levels <150 pmol/L [<200 pg/mL] on two separate occasions), we found that cobalamin deficiency had a prevalence of 5% in a group of patients followed-up or hospitalized in a tertiary centre hospital.[3] We also documented that out of 300 consecutive patients hospitalized with anemia in our department (a tertiary reference centre), approximately 4% of cases were related to cobalamin deficiency.[8]

Figure 1:
Cobalamin Metabolism in Mammalian Cells



CBS = cystein beta synthetase; CoA = coenzyme A; LRP-2 = megalin; MCM = methylmalonyl CoA mutase; MS = methonine synthase; MTHF = methyltetrahydrofolate; MTHFR = methyltetrahydrofolate reductase; TCII-R = megalin/transcobalamin II receptor complex.

Source: Adapted from Andrès E *et al.*, 2004,[4] Dali-Youcef N, *et al.*, 2009.[9]

Cobalamin Metabolism and Function

The metabolism of cobalamin is complex and is made up of many processes, defects in any one of which can lead to cobalamin deficiency.[9] The different stages of cobalamin metabolism and corresponding causes of cobalamin deficiency are shown in Figure 2. In the clinical setting, cobalamin absorption is measured imperfectly by the Schilling test.[3,5] Once metabolized, cobalamin is a cofactor and coenzyme for many biochemical reactions, including: the synthesis of deoxyribonucleic acid, methionine synthesis from homocysteine, and the conversion of propionyl into succinyl coenzyme A from methylmalonate (see Figure 1).[9]

A typical Western diet contributes 3–30 μg/d of cobalamin toward the recommended dietary allowance of 2.4 μg/d for adults.[3] There is a 5–10 year delay from the onset of cobalamin deficiency to the development of clinical manifestations, which is directly attributable to hepatic stores of cobalamin (>1.5 mg) and the enterohepatic cycle.[9] Between 1 and 5% of free cobalamin (or crystalline cobalamin) is absorbed along the entire intestine by passive diffusion.[9,10] This absorption process explains why the use of oral preparations in the treatment of cobalamin deficiency is successful.[11]

Causes of Cobalamin Deficiency

In older adults, cobalamin deficiency is classically caused by pernicious anemia (Biermer's disease).[1,3] The principal characteristics of pernicious anemia have been reported in detail in several reviews.[12,13] The diagnosis of pernicious anemia is based on the presence of intrinsic factor antibodies in the serum (specificity >98%, sensibility ~ 50%), or a finding of autoimmune atrophic gastritis on endoscopy. The presence of *Helicobacter pylori* infection in gastric biopsies excludes the diagnosis.[3,5]

Cobalamin deficiency as a result of dietary deficiency or malabsorption is rarer. Dietary causes are usually found in older people who already have a degree of malnourishment. This mainly concerns older adults living in long-term care facilities or psychiatric hospitals.[3]

Since the 1980s, there has been a decline in cases of cobalamin deficiency due to malabsorption. This is mainly due the fact that fewer surgical procedures such as total gastrectomy and resection of the terminal ileum are being performed.[3] However, there are also several diseases seen frequently in gastroenterology that may be associated with cobalamin malabsorption. These include: deficiency in the exocrine function of the pancreas after chronic pancreatitis (usually alcohol related), less commonly lymphomas and tuberculosis of the gastro intestinal tract, Crohn's disease, Whipple's disease, and celiac disease.

Food-Cobalamin Malabsorption

First described by Carmel in 1995,[14] food-cobalamin malabsorption is a syndrome characterized by the inability to release cobalamin either from food or intestinal transport proteins. It is particularly associated with hypochlorhydria, in which case the absorption of unbound cobalamin is normal. As various studies have shown, this syndrome is defined by cobalamin deficiency in the presence of sufficient food-cobalamin intake and normal Schilling test results, which rule out malabsorption or pernicious anemia.[9,15]

Table 1: Food-Cobalamin Malabsorption Syndrome

Criteria for Food-Cobalamin Malabsorption	Associated Conditions or Agents
Low serum cobalamin (vitamin B_{12}) levels	Gastric disease: atrophic gastritis, type A atrophic gastritis, gastric disease associated with *Helicobacter pylori* infection, partial gastrectomy, gastric bypass, vagotomy
Normal results of Schilling test using free cyanocobalamin labelled with cobalt 58, or abnormal results of derived Schilling test*	Pancreatic insufficiency: alcohol abuse
No anti-intrinsic factor antibodies	Gastric or intestinal bacterial overgrowth: achlorhydria, tropical sprue, Ogilvie's syndrome, human immunodeficiency virus
No dietary cobalamin deficiency	Drugs: antacids (histamine$_2$ receptor antagonists and proton-pump inhibitors) or biguanides (metformin)
	Alcohol abuse
	Sjögren's syndrome, systemic sclerosis
	Haptocorrin deficiency
	Aging or idiopathic

*Derived Schilling tests use food-bound cobalamin (e.g., egg yolk, chicken, and fish proteins).

Sources: Adapted from Dali-Youcef N *et al.*, 2009,[9] and Andrès E *et al.*, 2005.[15]

Table 2: Main Clinical Features of Cobalamin Deficiency

Hematological	Neuropsychiatric	Digestive	Other
Frequent: macrocytosis, hypersegmentation of the neutrophils, aregenerative macrocytary anemia, LDH and bilirubin elevation, medullary megaloblastosis ("blue spinal cord") **Rare:** isolated thrombocytopenia and neutropenia, pancytopenia **Very rare:** hemolytic anemia, thrombotic microangiopathy (presence of schistocytes)	**Frequent:** polyneuritis (especially sensory involvement), ataxia, Babinski's phenomenon **Classic:** combined sclerosis of the spinal cord **Rare:** cerebellar syndromes affecting the cranial nerves including optic neuritis, optic atrophy, urinary and/or fecal incontinence **Under study:** changes in the higher functions, even dementia, stroke and atherosclerosis (hyperhomocysteinemia), parkinsonian syndromes, depression, multiple sclerosis	**Classic:** Hunter's glossitis, jaundice, LDH and bilirubin elevation ("intrame dullary destruction") **Debatable:** abdominal pain, dyspepsia, nausea, vomiting, diarrhea, disturbances in intestinal functioning Rare: resistant and recurring mucocutaneous ulcers	**Under study:** atrophy of the vaginal mucosa and chronic vaginal and urinary infections (especially mycosis), hypofertility and repeated miscarriages (connection with cobalamin deficiency under study), venous thromboembolic disease, angina (hyperhomocysteinemia), osteoporosis

LDH = L-lactate dehydrogenase.

Sources: Adapted from Stabler SP *et al.*, 1990,[2] Andrès E *et al.*, 2004,[4] Wun Chan JC *et al.*, 2006,[13] and Andrès E *et al.*, 2006.[17]

The principal characteristics of this syndrome are listed in Table 1. In theory, the investigation of choice for food-cobalamin malabsorption is the modified Schilling test (not available in clinical practice), which uses radioactive cobalamin bound to animal proteins (e.g., salmon, trout), and provides evidence of food-cobalamin malabsorption, despite the presence of a normal Schilling test.[14,15]

Food-cobalamin malabsorption has been found to be the leading cause of cobalamin malabsorption, especially in older adults.[15] In our experience (300 patients with a documented cobalamin deficiency, median age 71 years), food-cobalamin malabsorption accounted for approximately 60–70% of cases of cobalamin deficiency, whereas pernicious anemia accounted for only 15–25%.[3]

Some authors have debated the significance or even the existence of cobalamin deficiency related to food-cobalamin malabsorption because many patients have only mild clinical or hematological manifestations.[14] Several of our patients, however, developed significant features which are classically associated with pernicious anemia, including: polyneuropathy, confusion, dementia, combined medullary sclerosis, anemia, and pancytopenia.[15] Nevertheless, the "partial" nature of this form of malabsorption may result in a slower, progressive depletion of cobalamin, compared to that which occurs in complete malabsorption due to problems with the intrinsic factor–mediated absorption pathway.[9,14,15] This slower, progressive form of depletion may explain why mild or pre-clinical deficiency is associated more often with food-cobalamin malabsorption than pernicious anemia.

Atrophic gastritis is one of the principal causes of food-cobalamin malabsorption.[14,15] Achlorhydria is known to inhibit the release of cobalamin from protein food sources. Over 40% of patients over 80 years of age have gastric atrophy which may or may not be related to *H. pylori* infection.[3]

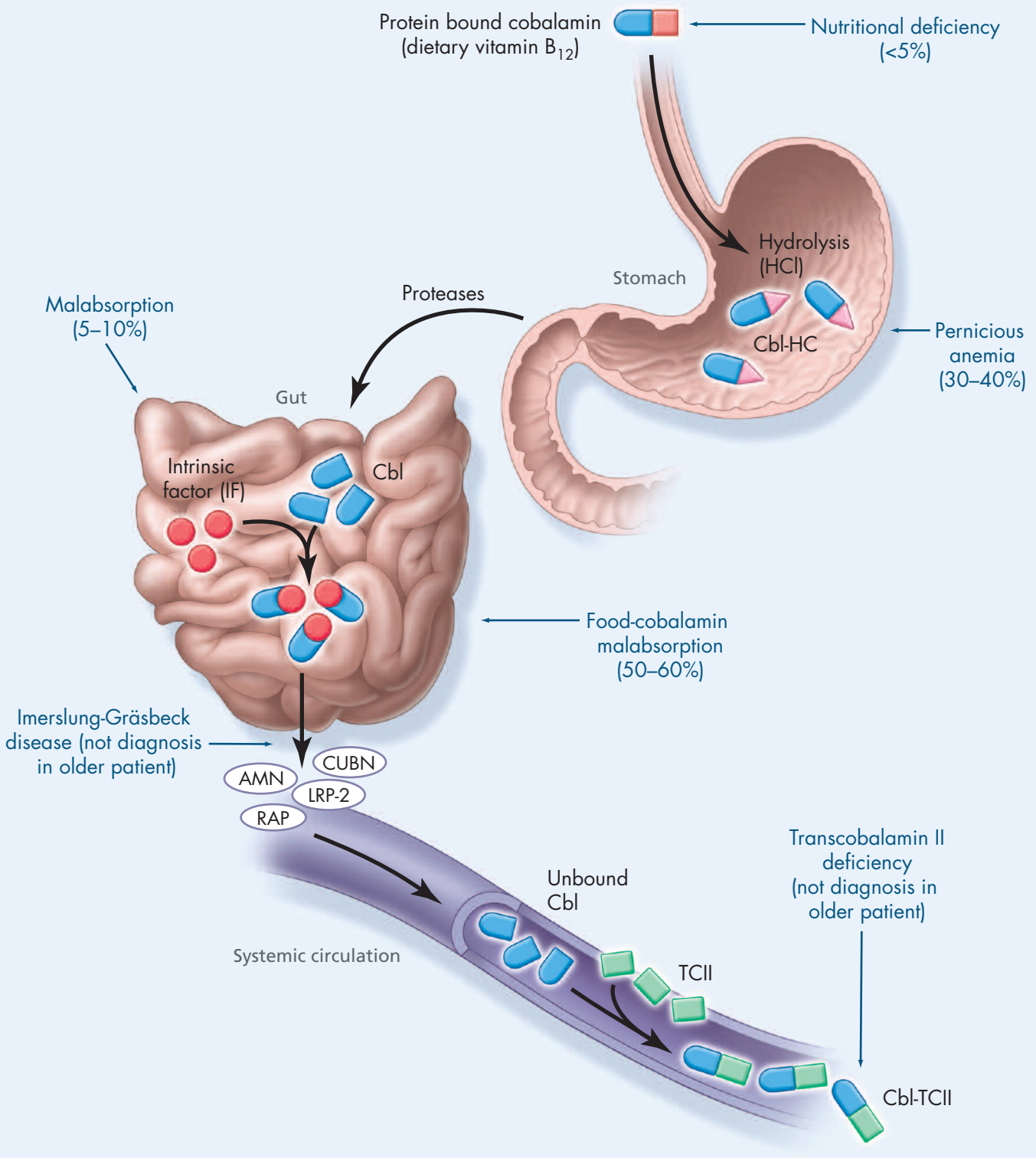
Other factors that contribute to food-cobalamin malabsorption in older people are listed in Table 1.[14–16] These include: chronic carriage of *H. pylori* and intestinal microbial proliferation; long-term ingestion of certain drugs such as antacids (including H_2 receptor antagonists and proton pump inhibitors) or biguanides (metformin); chronic alcoholism; surgery or gastric reconstruction (e.g., bypass surgery for obesity); partial pancreatic exocrine failure; and Sjögren's syndrome or systemic sclerosis. In our experience, atrophic gastritis (with or without *H. pylori* infection) and long-term metformin or antacid use are the major causes, seen in 30 and 20% of patients respectively.[15,16]

Clinical Presentations of Cobalamin Deficiency

The principal clinical features of cobalamin deficiency are described in Table 2. There is a wide range of pathology of varying degrees of severity, ranging from common sensory neuropathy and isolated anomalies of macrocytosis and hypersegmentation of neutrophils, to more severe conditions such as combined sclerosis of the spinal cord, hemolytic anemia and pancytopenia.[2,3,13,17] In the aforementioned series of 92 patients with food-cobalamin malabsorption,[15] we found at least one clinical sign or hematological abnormality in 70% and 76% of patients respectively.

Cobalamin deficiency appears to be more common in patients with chronic

Figure 2:
Cobalamin Absorption and Metabolic Pathway



AMN = amnionless; Cbl = cobalamin; Cbl-HC = cobalamin haptocorin complexe ; CUBN = cubulin; LRP-2 = megalin; RAP = receptor associated protein; TCII = transcobalamin II.

Sources: Adapted from Andrès E et al., 2004,[4] and Dali-Youcef N, et al., 2009.[9]

Table 3: Experience of Oral Cobalamin Therapy for Food-Cobalamin Malabsorption at the University Hospital of Strasbourg, France

Study Characteristics	Therapeutic Modalities	Results
Open prospective study of well-documented cobalamin deficiency related to food-cobalamin malabsorption (*n* = 10)	Oral crystalline cyanocobalamin: 650 µg/d for at least 3 mo	Normalization of serum cobalamin levels in 80% of patients Significant increase of Hb levels (mean of 1.9 g/dL) and decrease of mean ECV (mean of 7.8 fL) Improvement of clinical abnormalities in 20% of patients No adverse effects
Open prospective study of low cobalamin levels not related to pernicious anemia (*n* = 20)	Oral crystalline cyanocobalamin: 1,000 µg/d for at least 1 wk	Normalization of serum cobalamin levels in 85% of patients No adverse effects
Open prospective study of well-documented cobalamin deficiency related to food-cobalamin malabsorption (*n* = 30)	Oral crystalline cyanocobalamin: between 250 and 1,000 µg/d for 1 mo	Normalization of serum cobalamin levels in 87% of patients Significant increase of Hb levels (mean of 0.6 g/dL) and decrease of ECV (mean of 3 fL); normalization of Hb levels and ECV in 54% and 100% of patients, respectively Dose effect—effective dosage of cobalamin ≥500 µg/d No adverse effects
Open prospective study of low cobalamin levels not related to pernicious anemia (*n* = 30)	Oral crystalline cyanocobalamin: between 125 and 1,000 µg/d for at least 1 wk	Normalization of serum cobalamin levels in all patients with at least a dosage of ≥250 µg/d Dose effect—effective dosage of cobalamin ≥500 µg/d No adverse effects
Open prospective study of low cobalamin levels related to pernicious anemia (*n* = 10)	Oral crystalline cyanocobalamin: 1,000 µg/d for at least 3 mo	Significant increase of serum cobalamin levels in 90% of patients (mean of 117.4 pg/mL) Significant increase of Hb levels (mean of 2.45 g/dL) and decrease of ECV (mean of 10.4 fL) Improvement of clinical abnormalities in 30% of the patients

ECV = erythrocyte cell volume; Hb = hemoglobin.

Source: Adapted from Andrès E *et al.,* 2009,[11] and Andrès E *et al.,* 2004.[15]

Key Points

Cobalamin deficiency is particularly common in older adults but is often undiagnosed due to its subtle clinical manifestations.

In older adults, the main causes of cobalamin deficiency are pernicious anemia and food-cobalamin malabsorption.

Food-cobalamin malabsorption is a syndrome characterized by the inability to release cobalamin from food or its binding proteins, and is commonly caused by atrophic gastritis, which may or may not be related to *Helicobacter pylori* infection, and/or long-term ingestion of antacids and biguanides.

New routes of cobalamin administration (via oral and nasal passages) are being studied, in particular, oral cobalamin therapy for food-cobalamin malabsorption.

neurological conditions, such as dementia, Alzheimer's disease, stroke, Parkinson's disease, and depression; however, it is unclear if these represent causal relationships.[3,10,18] In our own studies in which we administered cobalamin to patients with dementia, no clinical improvement was observed.[3,11] Other studies have had similar results.[19,20] At this time, a causal role of cobalamin in these conditions remains speculative.

Treatment

Parenteral Administration

The classic treatment for cobalamin deficiency, particularly when the cause is not dietary related, is parenteral administration. In most countries, intramuscular injections (in the form of cyanocobalamin and, more rarely, hydroxo- or methylcobalamin) are prescribed.[3,5,21] However, protocols concerning both dosage and schedule of administration vary considerably between different institutions.

In Canada, as in France, the recommended practice is to build up vitamin stores and correct low serum cobalamin levels rapidly, particularly in cases of pernicious anemia. The treatment involves the administration of 1,000 μg/d of cyanocobalamin for 1 week, followed by 1,000 μg/wk for 1 month, followed by 1,000 μg/month, which usually continues as a life long treatment.[3]

In the U.S. and U.K., doses ranging from 100 to 1,000 μg/month (or every 2–3 months when hydroxocobalamin is given) are used for the duration of the patient's lifetime.[21]

Hydroxocobalamin may have several advantages over other preparations due to better tissue retention and storage.[3–5] Additionally, recent research has studied the possibility of oral cobalamin supplementation through food fortification.

Oral Cobalamin Therapy

In cases of cobalamin deficiency (with the exception of those due to nutritional deficiency), alternative routes of cobalamin treatment have been used, including oral and nasal administration.[9,11,21] These routes of administration have been proposed as a way of avoiding the discomfort, inconvenience, and cost of monthly injections.[11]

Our working group has developed an effective oral treatment for food-cobalamin malabsorption and pernicious anemia using crystalline cobalamin (cyanocobalamin).[11] Our initial studies of oral cobalamin treatment (open, nonrandomized studies) are described in Table 3. All our patients who were treated orally corrected their cobalamin levels and at least two thirds corrected their hematological abnormalities.[11] Moreover, one third of patients also showed an improvement in clinical symptoms while assigned to oral treatment. In most cases of food-cobalamin malabsorption, a "low" cobalamin dose (i.e., 125–1,000 μg/d of oral crystalline cyanocobalamin) was used.

These findings are in accordance with the results from two prospective randomized controlled studies which compared oral cobalamin treatment with intramuscular cobalamin therapy.[22,23] A systematic review of randomized-controlled trials by the Vitamin B_{12} Cochrane Group supports the efficacy of oral cobalamin therapy, with a dose of between 1,000 and 2,000 μg given initially as a daily prescription and then weekly thereafter.[24] In this analysis, serum cobalamin levels increased significantly in patients treated with oral cobalamin and both groups of patients (receiving oral and intramuscular treatment) showed signs of neurological improvement. Nevertheless, to our knowledge, the effect of oral cobalamin treatment in patients presenting with severe neurological disease has not yet been adequately documented. Hence until further research has been carried out, parenteral cobalamin therapy is still to be recommended in such patients.[11]

Treatment with oral cobalamin preparations has, however, not yet been fully validated in current clinical practice-in particular the low doses used and the long-term efficacy.[11] In a randomized controlled trial, double-blind, dose-finding trial, Eussen *et al.* found that the lowest dose of oral cyanocobalamin required to normalize mild cobalamin deficiency is approximately 200 times the recommended dietary allowance of approximately 3 μg/d (i.e., >500 μg/d).[25]

Nevertheless, it can be proposed that ongoing supplementation should be con-

Clinical Pearls

The management of cobalamin deficiency with cobalamin injections is currently well documented, but new routes of cobalamin administration (via oral and nasal passages) are being studied, in particular oral cobalamin therapy for food-cobalamin malabsorption.

tinued until any associated factors are corrected (e.g. by discontinuing the use of certain medications or by treating *H. pylori* infection or pancreatic exocrine failure). This may result in lifelong administration, or, where applicable, sequential administration.[11,26]

Conclusion

We have discussed several different aspects of cobalamin deficiency, including food cobalamin malabsorption syndrome as well as the different modalities of treatment, with a special focus on oral cobalamin therapy. However, many clinically diagnosed cases of cobalamin deficiency remain unexplained and further research focusing on the absorption of vitamin B_{12} will pave the way for new approaches towards the investigation, diagnosis and treatment of cobalamin deficiency.

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