Update of Food-Cobalamin Malabsorption and Oral Cobalamin Therapy

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Abstract: Cobalamin (vitamin B12) deficiency is particularly common in the elderly (>65 years of age), but is often unrecognized because its clinical manifestations are subtle; however, they are also potentially serious, particularly from a neuropsychiatric and hematological perspectives. In the general population, the main causes of cobalamin deficiency are pernicious anemia and food-cobalamin malabsorption. Food-cobalamin malabsorption syndrome, which has only recently been identified, is a disorder characterized by the inability to release cobalamin from food or its binding proteins. This syndrome is usually caused by atrophic gastritis, related or unrelated to *Helicobacter pylori* infection, and long-term ingestion of antacids and biguanides. Management of cobalamin deficiency with cobalamin injections is currently well codified, but new routes of cobalamin administration (oral and nasal) are being studied, especially oral cobalamin therapy for food-cobalamin malabsorption.

Key Words: Cobalamin, vitamin B12, cobalamin deficiency, food-cobalamin malabsorption, oral cobalamin therapy.

INTRODUCTION

Cobalamin or vitamin B12 deficiency is common in elderly patients [1], but is often unrecognized or uninvestigated because the clinical manifestations of cobalamin deficiency are subtle. However, the complications of cobalamin deficiency, particularly the neuropsychiatric and hematological [1-4], are potentially serious and therefore require investigation in all patients present with vitamin or nutritional deficiency. Classic disorders, such as pernicious anemia, are the causes of cobalamin deficiency in only a limited number of patients, especially elderly patients [4]. A more common problem is food-cobalamin malabsorption, a disorder characterized by the inability to release vitamin B12 from food or its binding proteins [4]. Since the description of this later disorder, several authors have demonstrated that oral cobalamin therapy which can be a pharmacotherapeutic option for the treatment of cobalamin deficiency [4]. This review summarizes the current knowledge on cobalamin deficiency, with a particular focus on food-cobalamin malabsorption and oral cobalamin therapy.

DEFINITION OF COBALAMIN DEFICIENCY

Literature of the last ten years has provided several definitions of cobalamin deficiency, depending mainly on the population studied and on the particular assay kits used [5-7]. Varying test sensitivities and specificities result from the lack of a precise 'gold standard' for the diagnosis of cobalamin deficiency, especially in elderly patients. The definitions of cobalamin deficiency used in this review are shown in Box **1** [7,8]. At present, cobalamin deficiency is often defined in terms of the value of serum cobalamin (<150 pmol/l or <200 pg/ml) and of homocysteine (>13 µmol/l) and methyl malonic acid (>0.4 µmol/l), two components of the cobalamin metabolic pathway. It is important to note that only methyl malonic acid is specific for the cobalamin deficiency. Increased homocysteine is also caused by folate and vitamin B6 deficiency. In the future, new serum cobalamin assay kits such as holotranscobalamin may replace older assay kits and become the standard for testing for cobalamin deficiency [9]. However, to date, little and conflicting evidence is available about the effectiveness of these new tests in real life clinical practice.

EPIDEMIOLOGY OF COBALAMIN DEFICIENCY

Epidemiological studies show that in the general population of industrialized countries cobalamin deficiency has a prevalence of around 20%, ranging from 5% to 60% depending the definition of cobalamin deficiency used [4,9]. The Framingham study demonstrated a prevalence of 12% among elderly people living in the community [10]. Other studies focusing on elderly people, particularly those who are in institutions or who are sick and malnourished, have suggested a higher prevalence of 30–40% [11,12]. Using stringent definition, we found that cobalamin deficiency had a prevalence of 5% in a group of patients followed or hospitalized in a tertiary reference hospital [8].

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Box 1.   Definitions of Cobalamin (Vitamin B12) Deficiency [7,8]

- Serum cobalamin levels <150 pmol/L <u>and</u> clinical features and/or hematological anomalies related to cobalamin deficiency
- Serum cobalamin levels <150 pmol/L (<200 pg/ml) on 2 separate occasions
- Serum cobalamin levels <150 pmol/L <u>and</u> total serum homocysteine levels >13 μmol/L <u>or</u> methylmalonic acid levels >0.4 μmol/L (in the absence of renal failure and folate and vitamin B6 deficiencies)
- Low serum holotranscobalamin levels <35 pmol/L

COBALAMIN METABOLISM AND FUNCTION

The different stages of cobalamin metabolism and corresponding causes of cobalamin deficiency are shown in Table **1** [4,13-15]. Absorption depends mainly on intrinsic factor, which is secreted by the gastric mucosa. Intrinsic factor binds cobalamin forming a complex that is absorbed by the terminal ileum. This mechanism is responsible for at least 60% absorption on oral cobalamin [13-15]. Cobalamin metabolism is complex and requires many processes, any one of which, if not present, may lead to cobalamin deficiency [4,13-15]. Once metabolized, cobalamin is a cofactor and coenzyme in many biochemical reactions, including DNA synthesis, methionine synthesis from homocysteine and conversion of propionyl into succinyl coenzyme A from methyl malonate [4,8,9]. A typical Western diet contributes 3–30 μg of cobalamin per day towards the recommended dietary allowance set by the Food and Nutrition Board of the Institute of Medicine (US) of 2.4 μg/day for adults and 2.6 to 2.8 μg/day during pregnancy [16]. It has been estimated that there is a delay of 5 to 10 years between the onset of cobalamin deficiency and the development of clinical illness, this is a direct result of the hepatic stores (>1.5 mg) and the enterohepatic cycle [4,13]. Of particular interest is the observation that between 1% to 5% of free cobalamin (or crystalline cobalamin) is absorbed along the entire intestine by passive diffusion. This absorption explains the mechanism underlying oral cobalamin oral treatment of cobalamin deficiencies [17,18].

CLASSICAL CAUSES OF COBALAMIN DEFICIENCY

Fig. (**1**) presents the principal causes of cobalamin deficiency in 172 elderly patients (median age: 70 years) hospitalized in the university hospital of Strasbourg, France [14]. In elderly patients, cobalamin deficiency is classically caused by pernicious anemia or Biermer's or Addison's disease [1,11]. The principal characteristics of pernicious anemia have been reported in detail in several reviews [19-21]. Cobalamin deficiency caused by dietary deficiency or malabsorption is rarer. Dietary causes of deficiency are limited to elderly people who are already malnourished, such as elderly patients living in institutions (they may consume inadequate amounts of vitamin B12-containing foods) or in psychiatric hospitals (strict vegetarian) [4,13]. Since the 1980s, the malabsorption of cobalamin has become rarer, owing mainly to the decreasing frequency of gastrectomy and surgical resection of the terminal small intestine [4,8, 14]. Several disorders commonly seen in gastroenterology practice might, however, be associated with cobalamin malabsorption. These include deficiency in the exocrine function of the pancreas after chronic pancreatitis (usually alcoholic), lymphomas or tuberculosis (of the intestine),

Table 1.   Stages of Cobalamin Metabolism and Corresponding Causes of Cobalamin Deficiency [13,15]

| Stages and Actors in Cobalamin Metabolism	Causes of Cobalamin Deficiency
Intake solely through food	– Strict vegetarianism (patients who are sick in institutions or in psychiatric hospitals)
Digestion brings into play: – Haptocorrin – Gastric secretions (hydrochloric acid and pepsin) – Intrinsic factor – Pancreatic and biliary secretions – Enterohepatic cycle	– Gastrectomies – Pernicious anemia – Food-cobalamin malabsorption
– Absorption brings into play: – Intrinsic factor – Cubilin, amionless – Calcium and energy	– Ileal resections and malabsorption – Pernicious anemia – Food-cobalamin malabsorption
Transport by transcobalamins	– Congenital deficiency in transcobalamin II
Intracellular metabolism based on various intracellular enzymes	– Congenital deficiency in various intracellular enzymes
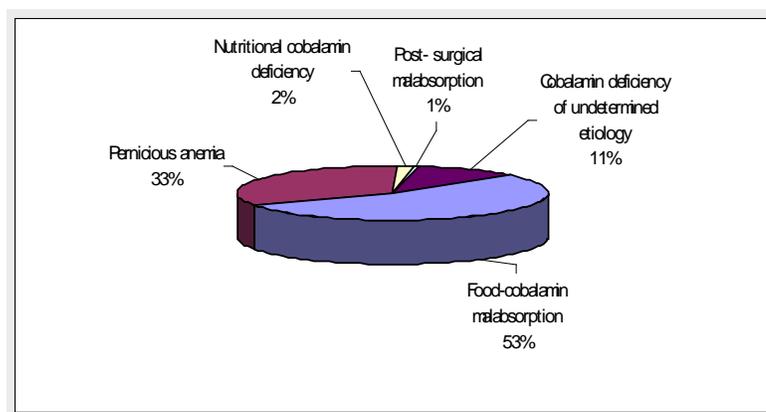
Fig. (1). Causes of cobalamin deficiency in 172 elderly patients [14].

Crohn's disease, Whipple's disease, and uncommonly celiac disease [11,15]. Food-cobalamin malabsorption has been found to be the leading cause of cobalamin malabsorption, especially in elderly patients [4,8,11,22]. In our studies [14,23], in which we have now followed more than 300 patients with a documented cobalamin deficiency, food-cobalamin malabsorption accounts for about 60–70% of the cases of cobalamin deficiency in elderly patients, whereas pernicious anemia accounted for only 15–25%.

FOOD-COBALAMIN MALABSORPTION

First described by Carmel in 1995 [22], food-cobalamin malabsorption is a syndrome characterized by the inability of the body to release cobalamin from food or intestinal transport proteins, particularly in the presence of hypochlorhydria, where the absorption of "unbound" cobalamin is normal ("maldigestion"). In our experience, this syndrome accounted for 60 to 70% of cases of cobalamin deficiency in elderly patients [14,15]. This syndrome is characterized by cobalamin deficiency in the presence of sufficient food-cobalamin intake and a normal Schilling test ruling out malabsorption or pernicious anemia (diagnostic of exclusion) [14,22,23]. Thus in this syndrome, patients can absorb "unbound" cobalamin through intrinsic factor or passive diffu-

sion mechanisms. Thus the recognition of the syndrome permits new developments of oral cobalamin therapy [4]. The principal characteristics of this syndrome are listed in Table **2**. Authors supporting the existence of this syndrome have employed a modified Schilling test, which uses radioactive cobalamin bound to animal proteins (e.g. salmon, trout) and reveals malabsorption when the results of a standard Schilling test are normal [4,14,23].

Some authors have speculated about the reality and significance of cobalamin deficiency related to food-cobalamin malabsorption [4], because many patients have only mild clinical or hematological features. However, several of the patients we have described in a recently published study [14] had serious features classically associated with pernicious anemia, including polyneuropathy, confusion, dementia, medullar-combined sclerosis, anemia and pancytopenia. Nevertheless, the partial nature of this form of malabsorption may produce a more slowly progressive depletion of cobalamin than does the more complete malabsorption engendered by disruption of the intrinsic factor-mediated absorption. The slower progression of depletion probably explains why mild, preclinical deficiency is more frequently associated with food-cobalamin malabsorption than with pernicious anemia [4,14].

Table 2.   Food-Cobalamin Malabsorption Syndrome [4,14,15]

Criteria for Food-Cobalamin Malabsorption	Associated Conditions or Agents
– Low serum cobalamin (vitamin B12) levels – Normal results of Schilling test using free cyanocobalamin labeled with cobalt-58 or abnormal results of derived Schilling test ‡ – No anti-intrinsic factor antibodies – No dietary cobalamin deficiency	– Gastric disease: atrophic gastritis, type A atrophic gastritis, gastric disease associated with *Helicobacter pylori* infection, partial gastrectomy, gastric by-pass, vagotomy – Pancreatic insufficiency: alcohol abuse – Gastric or intestinal bacterial overgrowth: achlorhydria, tropical sprue, Ogylvie's syndrome, HIV – Drugs: antacids (H2-receptor antagonists and proton pump inhibitors) or biguanides (metformin) – Alcohol abuse – Sjögren's syndrome, systemic sclerosis – Haptocorrine deficiency – Ageing or idiopathic

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

Food-cobalamin malabsorption is caused primarily by atrophic gastritis [14]. Over 40% of patients older than 80 years of age have gastric atrophy that might or might not be related to *Helicobacter pylori* infection [11,24]. Other factors that contribute to food-cobalamin malabsorption in elderly people include chronic carriage of *H. pylori* and intestinal microbial proliferation (in which case cobalamin deficiency can be corrected by antibiotic treatment) [24,25]; long-term ingestion of antiacids, including H_2-receptor antagonists and proton-pump inhibitors [26,27], particularly among patients with Zollinger-Ellison syndrome [28,29], and biguanides (metformin) [30-32]; chronic alcoholism; surgery or gastric reconstruction (e.g. bypass surgery for obesity); partial pancreatic exocrine failure [4,14], and Sjögren's syndrome or systemic sclerosis [33] (Table **2**). In a series of 92 elderly patients (mean age: 76 years) with food-cobalamin malabsorption [14], we have reported at least one of these associated conditions or agents in 60% of the patients. These conditions mainly include atrophic gastritis (± *H. pylori* infection) in 30% of the patients and long-term metformin or antacid intake in 20% of the elderly patients.

CLINICAL MANIFESTATIONS OF COBALAMIN DEFICIENCY

The clinical manifestations are highly polymorphic and of varying severity, ranging from milder conditions such as tiredness, common sensory neuropathy, atrophic glossitis (Hunter's glossitis) and isolated anomalies of macrocytosis or hypersegmentation of neutrophils, to severe disorders, including combined sclerosis of the spinal cord, hemolytic anemia and even pancytopenia [2,14,34-36]. Frequently, neurologic signs and symptoms precede hematologic abnormalities or continue to be isolated. Several new studied or established manifestations of cobalamin deficiency are described in Table **3**. In the aforementioned series of 92 patients with food-cobalamin malabsorption [14], we have found at least one clinical feature and hematological abnor-

malities, 70% and 76% of the patients respectively. Cobalamin deficiency appears to be more common among patients who have a variety of chronic neurologic conditions such as dementia, Alzheimer's disease, stroke, Parkinson's disease and depression, although it is unclear if these are causal relationships [4,37]. In our own studies in which we administered cobalamin to patients with dementia, improvement was not observed [8,14]. Other studies have had similar results [18,38]. At this time a causal role of cobalamin in these conditions remains speculative.

CLASSICAL TREATMENT OF COBALAMIN DEFICIENCY

The classic treatment for cobalamin deficiency, particularly when the cause is not dietary deficiency, is parenteral administration—usually by intramuscular injection—of this vitamin (in the form of cyanocobalamin and, more rarely, hydroxocobalamin) [1,17,18,34]. In France, the recommended practice is to build up the tissue stores of the vitamin quickly and correct serum cobalamin hypovitaminosis, particularly in the case of pernicious anemia. The treatment involves the administration of 1,000 µg of cyanocobalamin per day for 1 week, followed by 1,000 µg per week for 1 month, followed by 1,000 µg per month, normally for the rest of the patient's life [8,11,19]. In USA and UK, dosages ranging from 100 to 1,000 µg per month (or every 2-3 months when hydroxocobalamin is given) are used during the rest of the patient's life [4,17].

ORAL COBALAMIN THERAPY

In cases of cobalamin deficiency other than those caused by nutritional deficiency, alternative routes of cobalamin administration have been used: oral [17,18,39-45] and nasal [46,47]. These other routes of administration have been proposed as a way of avoiding the discomfort, inconvenience and cost of monthly injections. Our working group has developed an effective oral treatment of food-cobalamin

Table 3.   Main Clinical Features of Cobalamin Deficiency [2,4,14,15,34-36]

Hematological Manifestations	Neuro-Psychiatric Manifestations	Digestive Manifestations	Other Manifestations
– **Frequent**: macrocytosis, neutrophil hypersegmentation , aregenerative macrocytary anemia, medullar megaloblastosis ("blue spinal cord") – **Rare**: isolated thrombocytopenia and neutropenia, pancytopenia – **Very rare**: hemolytic anemia, thrombotic microangiopathy (presence of schistocytes)	– **Frequent**: polyneuritis (especially sensitive), 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, dementia, stroke and atherosclerosis (hyperhomocysteinemia), parkinsonian syndromes, depression, multiple sclerosis	– **Classic**: Hunter's glossitis, jaundice, LDH and bilirubin elevation ("intramedullary destruction") – **Debatable**: abdominal pain, dyspepsia, nausea, vomiting, diarrhea, disturbances in intestinal functioning – **Rare**: resistant and recurring mucocutaneous ulcers	– **Frequent**: – Tiredness, loss of appetite – **Under study**: atrophy of the vaginal mucosa and chronic vaginal and urinary infections (especially mycosis), hypofertility and repeated miscarriages, venous thromboembolic disease, angina (hyperhomocysteinemia)

malabsorption [41-44] and for pernicious anemia [48] using crystalline cobalamin (cyanocobalamin). Our principal studies of oral cobalamin treatment (open, not randomized studies) are described in Table **4** [41-44,48]. These data confirm the previously reported efficacy of oral crystalline cyanocobalamin, especially in food-cobalamin therapy [18,36, 39]. All of our patients who were treated orally corrected their vitamin B12 levels and at least two-thirds corrected their hematological abnormalities [41-44,48]. Moreover, one-third of patients experienced a clinical improvement on oral treatment. In most cases of food-cobalamin malabsorption "low" cobalamin doses (i.e. 125–1,000 µg of oral crystalline cyanocobalamin per day) were used.

This data is in accordance with the results of the two prospective randomized controlled studies comparing oral cobalamin with intramuscular cobalamin therapy [17,40]. An evidence-based analysis by the *Vitamin B12 Cochrane Group* also supports the efficacy of oral cobalamin therapy, with a dose between 1,000 and 2,000 µg given initially daily and then weekly [49]. In this analysis, serum vitamin B12 levels increased significantly in patients receiving oral vita-min B12 and both groups of patients (receiving oral and intramuscular treatment) had neurological improvement.

In a randomized, parallel-group, double-blind, dose-finding trial, Eussen *et al.* showed that the lowest dose of oral cyanocobalamin required to normalize mild cobalamin deficiency is more than 200 times the recommended dietary allowance of approximately 3 µg daily (i.e. >500 µg per day) [50]. The procedure for oral cobalamin treatment has, however, not been completely validated yet in real life, particularly the long-term efficacy [51]. To date, as several authors suggest, oral cobalamin therapy remains one of "medicine's best kept secrets" [52]. Nevertheless, the following can be proposed: ongoing supplementation until associated disorders is corrected (e.g. by halting the ingestion of the offending medication or exogenosis, or by treating *H. pylori* infection or pancreatic exocrine failure), lifelong administration or, when applicable, sequential administration [4,14].

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Table 4.   Experience of oral Cobalamin Therapy for Food-Cobalamin Malabsorption in the University Hospital of Strasbourg, France

Study Characteristics (Number of Patients)	Therapeutic Modalities	Results	Ref.
Open prospective study of well-documented vitamin B12 deficiency related to food-cobalamin malabsorption (n = 10)	Oral crystalline cyanocobalamin: 650 µg per day, during at least 3 months	– Normalization of serum vitamin B12 levels in 80% of the patients – Significant increase of hemoglobin (Hb) levels (mean of 1.9 g/dL) and decrease of mean erythrocyte cell volume (ECV) (mean of 7.8 fL) – Improvement of clinical abnormalities in 20% of the patients – No adverse effect	[42]
Open prospective study of low vitamin B12 levels not related to pernicious anemia (n = 20)	Oral crystalline cyanocobalamin: between 1000 µg per day during at least 1 week	– Normalization of serum vitamin B12 levels in 85% of the patients – No adverse-effect	[43]
Open prospective study of well-documented vitamin B12 deficiency related to food-cobalamin malabsorption (n = 30)	Oral crystalline cyanocobalamin: between 1000 and 250 µg per day, during 1 month	– Normalization of serum vitamin B12 levels in 87% of the 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 the patients, respectively – Dose effect - effectiveness dose of vitamin B12 ≥500 µg per day – No adverse-effect	[41]
Open prospective study of low vitamin B12 levels not related to pernicious anemia (n = 30)	Oral crystalline cyanocobalamin: between 1000 and 125 µg per day during at least 1 week	– Normalization of serum vitamin B12 levels in all patients with at least a dose of vitamin ≥250 µg per day – Dose effect - effectiveness dose of vitamin B12 ≥500 µg per day – No adverse-effect	[44]
Open prospective study of low vitamin B12 levels related to pernicious anemia (n = 10)	Oral crystalline cyanocobalamin: 1000 µg per day, during at least 3 months	– Significant increase of serum vitamin B12 levels in 90% of the 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	[48]

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