

Food-Cobalamin Malabsorption: A Controversial Etiology of Symptomatic Vitamin B12 Deficiency

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Opinion

Until the 1990s, the main causes of cobalamin (vitamin B12) deficiency in adults are Biermer's (also called Addison' disease or pernicious anemia) and malabsorptions [1]. Thanks to progress made during the last 15 years in the understanding of cobalamin metabolism, new physiopathological concepts have emerged, including a new medical concept: the "food-cobalamin malabsorption" [2]. This new clinical syndrome was found to be the leading cause of symptomatic cobalamin deficiency in a number of recently published series [3-5]. However, controversies persist in the scientific literature about his real involvement in severe cobalamin deficiency. In fact, some clinicians believe that this disorder is responsible only on "subtle" B12 deficiency [6]. In this editorial, we sought to detail our personal perception and experience of this food-cobalamin malabsorption in clinical practice.

Food-cobalamin malabsorption is a medical disorder characterized by the inability to release cobalamin from food or its carrier proteins [7]. Cobalamin is found exclusively in food, and daily intake requirements range from 2 to 5 µg [8]. The dissociation of vitamin B12 from food or its carrier proteins and its release as "unbound" cobalamin are essential prerequisites for its binding to intrinsic factor and in fine its intestinal absorption, through the cubulin receptor [2]. Thus to our opinion, the syndrome of food-cobalamin malabsorption refers in clinical practice to all vitamin B12 deficiencies that are related

to pre-absorption steps of cobalamin ("maldigestion" not "malabsorption") [8].

The Table 1 summarizes the main characteristics of the food-cobalamin malabsorption [4,8]. This syndrome was described by Carmel and Dawson in the 1990s [7,8]. In some cobalamin-deficient patients, these authors observed conflicting results when employing a "modified" Schilling test, which uses radioactive cobalamin bound to altered animal proteins (e.g., egg yolk, chicken, salmon), and the normal Schilling, which uses free radioactive vitamin B12 (unbound) [7]. The original description was made by Doscherholmen et al. in 1973, but was not pursued [9]. However, to date, Schilling test or its variant (modified Schilling), the gold standard to establish the diagnosis, were not available in clinical practice. Thus to our opinion, food-cobalamin malabsorption nowadays is a diagnosis of exclusion [8].

As illustrated in the Table 1, several causes of cobalamin malabsorption have been reported, the most common being age, atrophic gastritis, *Helicobacter pylori* infections, and the intake of proton pump inhibitors, H2-receptor antagonists, or metformin [4,7,8]. In an American study including 202 subjects, Latino-American or Afro-American race, advanced age, and *H. pylori* infection were shown to be independent risk factors for FCM. Some studies revealed a female preponderance, though this still needs to be confirmed [10].

Diagnostic criteria for food-cobalamin malabsorption syndrome	
1.	Serum cobalamin levels <200 pg/ml
2.	Normal "standard" Schilling test (using free cyanocobalamin labelled with cobalt-58) or abnormal "modified" Schilling test (using protein-bound radioactive cobalamin) ‡
3.	No dietary cobalamin deficiency (intake >2 µg per day)
4.	Associated causes:
-	Atrophic gastritis, chronic <i>H. pylori</i> infection, gastrectomy, gastric by-pass
-	Exocrine pancreatic insufficiency (alcohol abuse...)
-	Chronic alcohol abuse
-	Intake of antacids (H2-receptor antagonists or proton pump inhibitors) or biguanides (metformin)
-	Microbial overgrowth, AIDS
-	Sjögren's syndrome, scleroderma

-	"Idiopathic" or related to age
†:	The presence of the first three items is necessary for the diagnosis of food-cobalamin malabsorption syndrome.
‡:	The "modified" Schilling test uses food-bound cobalamin (e.g. egg, chicken and fish proteins...); test not available in clinical routine.

Table 1: Characteristics of food-cobalamin malabsorption syndrome according to Andrès et al. [4,8]†.

In our experience, the clinical manifestations of food-cobalamin malabsorption are not very different from those of cobalamin deficiencies associated with other causes, e.g. Biermer's disease [8,11]. However, it should be emphasized that Carmel first believed that food-cobalamin malabsorption was associated with moderate cobalamin deficiency, leading to only "subtle" clinical symptoms ("subtle cobalamin deficiency") [6]. Our published data contradicts this assertion, as illustrated in Table 2 [4,12]. It is to note that Schilling test was used in the majority of our patients, with normal results of this test (with and with administration of intrinsic factor). The classic hematological abnormalities encountered include aregenerative macrocytary anemia and other less common, though more severe, hematological abnormalities as: intramedullar hemolysis, thrombopenic purpura, myelodysplasia, medullar aplasia, early-stage pseudo-leucosis, or pseudo-thrombotic microangiopathy [4,12]. Neuropsychiatric abnormalities are also common clinical manifestations of the food-cobalamin malabsorption, and may occur even if hematological abnormalities do not develop. Combined scleroses of the spinal cord, peripheral neuropathies, or cognitive dysfunctions are frequent manifestations [4,12]. Besides the aforementioned manifestations, those related to the age of the patient or the etiology of malabsorption should also be considered.

Clinical features of food-cobalamin malabsorption syndrome	
Mean age years	76 ± 8
Sex ratio (women/men)	2
Symptomatic patients	
Clinically	70%
Biologically	76%
Main clinical manifestations	
Sensitive polyneuropathy	45%
Cognitive disorders	23%
Asthenia	21%
Main biological manifestations	
Macrocytosis	53%
Anaemia	21%
Leucopenia	11%
Thrombocytopenia	9%
Pancytopenia	6.50%

Table 2: Profile of 92 patients with cobalamin deficiency secondary to food-cobalamin malabsorption syndrome [4,12].

According to our own experience, the prevalence of cobalamin deficiency among hospitalized patients approaches 5%, with food-cobalamin malabsorption accounting for 50% to 60% of cases (in a population of quiet elderly patients) [8]. Thus, we believe that food-cobalamin is one of the main etiologies of symptomatic cobalamin deficiency in adult patient.

In this situation, we have documented the usefulness of oral cobalamin therapy [13,14]. Since 1995, numerous clinical trials confirmed the non-inferiority of the oral route (with cyanocobalamin between 125 to 1000 µg per day) as compared to the parental route in the treatment of food-cobalamin malabsorption, as evidenced by a normalization of hematological abnormalities and regression of clinical symptoms, particularly neuropsychiatric manifestations, in the majority of patients [15,16]. In a study, Kaptan et al. also showed that *H. pylori* eradication was sufficient to correct cobalamin deficiency [17].

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