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Review article

# Clinical aspects of cobalamin deficiency in elderly patients. Epidemiology, causes, clinical manifestations, and treatment with special focus on oral cobalamin therapy ☆

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**Abstract**

The aim of this work was to review the literature concerning cobalamin deficiency in elderly patients. Articles were identified through searches of *PubMed–MEDLINE* (January 1990 to June 2006), restricted to: English and French language, human subjects, elderly patients (>65 years), clinical trial, review and guidelines. Additional unpublished data from our cohort with cobalamin deficiency at the University Hospital of Strasbourg, France, were also considered. All of the papers and abstracts were reviewed by at least two senior researchers who selected the data used in the study. In elderly people, the main causes of cobalamin deficiency are pernicious anemia and food-cobalamin malabsorption. The recently identified food-cobalamin malabsorption syndrome is a disorder characterized by the inability to release cobalamin from food or from its binding proteins. This syndrome is usually the consequence of atrophic gastritis, related or not to *Helicobacter pylori* infection, and of the long-term ingestion of antacids and biguanides (in around 60% of the patients). Management of cobalamin deficiency has been well established with the use of cobalamin injections. However, new routes of cobalamin administration (oral and nasal) are currently being developed, especially the use of oral cobalamin therapy to treat food-cobalamin malabsorption.


*Keywords:* Cobalamin; Cobalamin deficiency; Elderly patients; Food-cobalamin malabsorption; Oral cobalamin therapy

**Contents**



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## 1. Introduction

Cobalamin, or vitamin B12, deficiency is frequent in elderly patients [1], but it is often unrecognized or not investigated because the clinical manifestations are subtle. However, because of the potential seriousness of the complications, particularly neuropsychiatric and hematological [1–4], investigation of all patients who present with vitamin or nutritional deficiency is required. Classic disorders, such as pernicious anemia, are the cause of cobalamin deficiency in only a limited proportion of elderly patients [4]. The main cause of cobalamin deficiency is food-cobalamin malabsorption, a disorder characterized by the inability to release vitamin B12 from food or from its binding proteins [4].

We summarize here the current state of knowledge on clinical aspects of cobalamin deficiency in the elderly, with a special focus on food-cobalamin malabsorption and particularly on oral cobalamin therapy.

## 2. Definition of cobalamin deficiency

In the recent literature, several definitions of cobalamin deficiency in elderly patients have emerged, depending mainly on the populations studied and on the particular test assay kits used [5–7]. Varying test sensitivities and specificities have resulted from this lack of a precise 'gold standard', especially in elderly patients. The definitions of cobalamin deficiency used in this review are shown in Table 1 [7,8]. Currently, cobalamin deficiency is often defined in terms of the value of serum cobalamin and of homocysteine and methyl malonic acid, two components of the cobalamin metabolic pathway. 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 and in elderly patients [10].

Table 1
Definitions of cobalamin (vitamin B12) deficiency [7,8]

| Definitions of cobalamin deficiency |
|---|
| Serum cobalamin level <150 pmol/l (<200 pg/ml) and clinical features and/or hematological anomalies related to cobalamin deficiency |
| Serum cobalamin level <150 pmol/l (<200 pg/ml) at two different times |
| Serum cobalamin level <150 pmol/l (<200 pg/ml) and total serum homocysteine level >13 μmol/l or methylmalonic acid levels >0.4 μmol/l[a] |
| Low serum holotranscobalamin level |

[a] This definition is useful only in the absence of renal failure and folate and vitamin B6 deficiency because homocysteine and methylmalonic acid levels are dependent on these factors.

## 3. Epidemiology of cobalamin deficiency

Epidemiological studies have shown a prevalence of cobalamin deficiency of around 20% in the elderly population of industrialized countries (between 50% and 60%, depending on the definition of cobalamin deficiency used in the study). The Framingham study demonstrated a prevalence of 12% among elderly people living in the community [11]. Other studies focusing on elderly people, particularly those who are in institutions or who are sick, have suggested a higher prevalence of 30–40% [12,13]. Using a stringent definition (Table 1), we have found a prevalence of 5% in a group of patients followed or hospitalized in a tertiary reference hospital in France [8].

## 4. Cobalamin metabolism and functions

Cobalamin metabolism is complex and requires many processes, any one of which, if not present, may lead to cobalamin deficiency [4,14–16]. The different stages of cobalamin metabolism and corresponding causes of cobalamin deficiency are shown in Table 2 [14,16]. 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 [4,9].

A typical Western diet contributes 3–30 μg of cobalamin per day to the estimated daily requirement of between 2 and 5 μg, according to the U.S. Food and Drug Administration [17]. It has been estimated that there is a delay of between 5 and 10 years between the onset of cobalamin deficiency and the development of clinical illness, and this is a direct result of the hepatic stores (>1.5 mg) and the enterohepatic cycle [4,14]. Between 1% and 5% of free cobalamin (or crystalline cobalamin) is absorbed along the entire intestine by passive diffusion, and this is the mechanism underlying the effectiveness of oral cobalamin as a treatment for cobalamin deficiencies [18,19].

## 5. 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 [15]. Historically, in