Conditions and Diseases that Cause Vitamin B12 Deficiency in Elderly Patients: from Metabolism to Diseases

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Introduction

Although vitamin B12 (cobalamin) was isolated almost 60 years ago, its metabolism remains incompletely defined. In practice, cobalamin metabolism is complex and requires many processes and steps, any one of which, if not present, may lead to vitamin B12 deficiency [1,2]. The Figure 1 describes through a synthetic view the different stages of vitamin B12 metabolism used in clinical practice and the corresponding etiologies of cobalamin deficiency [3,4].

For the Practitioner, it should be noted that the clinical manifestations of vitamin B12 deficiency are very numerous, polymorphic, sometimes frustrating, of chronic evolution, or on the contrary severe, of acute revelation (Table 1) [3,4]. This is often the case in the elderly, where vitamin B12 deficiency can be described as a great simulator, in the same way as syphilis a few years ago.

The present review summarizes the current knowledge on vitamin B12 metabolism and metabolic pathways in a clinical perspective, with a focus on the etiologies of cobalamin deficiency in elderly patients.

Methodology of the Literature Search

A systematic literature search was performed on the PubMed database of the US National Library of Medicine and on Scholar Google. We searched for articles published between January 2010 and January 2020, using the following key words or associations: “vitamin B12 deficiency in elderly”, “cobalamin deficiency in elderly”, “Biermer’s disease”, “pernicious anemia”, “gastrectomy”, “food-cobalamin malabsorption”, and “cobalamin nutritional deficiency” restrictions included: English- or French-language publications; published from January 1, 2010, to January 1, 2020; human subjects; adults and elderly subjects, clinical trials or review articles.

Additional studies were obtained from references of identified studies, the Cochrane Library and the ISI Web of Knowledge. Data gleaned from international meetings were also used, as information gleaned from commercial sites on the web. Internal medicine and Hematology educational books and reference textbooks were also used, as information gleaned from international meetings.

All of the English and French abstracts were reviewed by at least two senior researchers from our research team (CAREnce en vitamine B12 [CARE B12], in the university hospital of Strasbourg, France).
Dietary vitamin B12 is absorbed in food bound to proteins and undergoes acidic gastric digestion. The released cbl is attached to the R-binder haptocorrin and transported to the intestine following pancreatic proteases processing. The unbound cbl is then associated in the gut with the gastric-produced intrinsic factor (IF). This association is necessary for intestinal cbl absorption through a complex of endocytic receptors and proteins, including the endocytic receptor cubilin (CUBN) and the apical membrane protein amnionless (AMN), which is stabilized by two other proteins, namely the receptor megalin/LRP-2 and its binding protein receptor associated protein (RAP) which also binds to cubilin. After it absorption free cobalamin reaches the systemic circulation where it associates with transcobalamin II (TCII) and subsequently the cbl-TCII complex is uptaken in cells through its binding to megalin/LRP-2 and TCII receptor (TCII-R). Intracellularly, the complex is dissociated following lysosomal digestion. Part of cbl serves as a cofactor for the methionine synthase (MS) mediated transformation of homocysteine into methionine and for methyl-tetrahydrofolate reductase-mediated formation of tetrahydrofolate (THF) a precursor of purine and pyrimidine necessary for nucleic acid synthesis. The other fraction of cbl reaches the mitochondria where it forms adenosyl-cbl, a cofactor for the methyl-malonyl mutase-mediated catabolism of methyl-malonyl coA. (C): Mutations in genes encoding the intrinsic factor, cubilin, amnionless or transcobalamin II or its receptor provoke defects in cbl absorption and/or cellular uptake which translates into functional cbl deficiency and its clinical manifestations.

Table 1. Main clinical features of cobalamin deficiency [2,3,6,14].

<table>
<thead>
<tr>
<th>Hematological manifestations</th>
<th>Neuro–psychiatric manifestations</th>
<th>Digestive manifestations</th>
<th>Other manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequent: macrocytosis, neutrophil hypersegmentation, regenerative macrocytary anemia, medullar megaloblastosis (“blue spinal cord”)</td>
<td>Frequent: polyneuritis (especially sensitive), ataxia, Babinski’s phenomenon</td>
<td>Classic: Hunter’s glossitis, jaundice, LDH and bilirubin elevation (“intramedullary destruction”)</td>
<td>Frequent: Tiredness, loss of appetite</td>
</tr>
<tr>
<td>Rare: isolated thrombocytopenia and neutropenia, pancytopenia</td>
<td>Classic: combined sclerosis of the spinal cord</td>
<td>Debatable: abdominal pain, dyspepsia, nausea, vomiting, diarrhea, disturbances in intestinal functioning</td>
<td>Under study: atrophy of the vaginal mucosa and chronic vaginal and urinary infections (especially mycosis), hypofertility and repeated miscarriages, venous thromboembolic disease, angina (hyperhomocysteinemia)</td>
</tr>
<tr>
<td>Very rare: hemolytic anemia, thrombotic microangiopathy (presence of schistocytes)</td>
<td>Rare: isolated thrombocytopenia and neutropenia, pancytopenia</td>
<td>Rare: resistant and recurring mucocutaneous ulcers</td>
<td></td>
</tr>
</tbody>
</table>
Vitamin B12 Ingestion and Related Disorders

Vitamin B12 Sources and Dietary Recommendations

Vitamin B12 is produced exclusively by microbial synthesis in the digestive tract of animals. Therefore, animal products are the main sources of cobalamin in the human diet, in particular organ meats (liver, kidney) [2–4]. Other good sources are fish, eggs and dairy products. In foods, hydroxocobalamin, methylcobalamin, and 5'-deoxyadenosylcobalamin are the main cobalamins present.

A typical Western diet contributes 3–30 µg of cobalamin per day. The Food and Nutrition Board of the US Institute of Medicine recommends dietary allowance (RAD) of 2.4 µg per day for adults [5]. The RDA did not distinguish between adults and elderly people though it is questionable whether an intake of 2.4 µg per day can maintain cobalamin status in elderly people with often poor nutrition (malnutrition, in quality and quantity), malabsorption or maldigestion.

Malnutrition, Vegetarianism and Veganism

Vitamin B12 deficiency caused by limited intake of vitamin dietary sources (which requires any animal product intake) is rare, even exceptional, in general population [6,7]. Malnutrition of cobalamin concerns especially vegans and more rarely vegetarians not supplemented by pharmacological vitamin intakes. These nutritional practices, particularly veganism this is currently fashionable in industrialized countries to purge the body and mind, especially among working people in their early 30s and in “up to date” people.

Dietary causes of cobalamin deficiency are common in elderly people who are already malnourished, such as elderly frailty patients in psychiatric hospitals [6] or those living in institutions who may consume inadequate amounts of vitamin B12-containing foods. However, an inadequate intake is not the only explanation for the common cobalamin deficiency in elderly population. Food-cobalamin malabsorption is a significant participating factor in elderly people [6].

Studies focusing on elderly people, particularly those who are in institutions or who are sick and malnourished have suggested a vitamin B12 deficiency prevalence of 30–40% (defined as low vitamin B12 blood level) [6,8]. In this setting, the Framingham study demonstrated a prevalence of 12% among elderly people living in the community [9]. Using stringent definition (presence of clinical and/or biological signs of cobalamin deficiency), we found that vitamin B12 deficiency had a prevalence of 5% in a group of patients (mean age of the patient: 72 years) followed or hospitalized in a tertiary reference hospital in France [3].

In practice, the diagnosis of malnutrition, vegetarianism or veganism is based on patient interview and a comprehensive dietary survey (at least 1 week).

Food-Cobalamin Digestion

Physiology of Cobalamin Absorption

Dietary cobalamin, which is bound to proteins in food, is released in the acidic environment of the stomach where it is rapidly complexed to the binding protein and transporter haptocorrin (HC), also referred to as the R-binder or transcobalamin I (Figure 1) [1,10]. About 80% of circulating vitamin B12 are bound to HC and serum cobalamin levels show positive correlation to serum HC concentrations.

Although some unexplained low serum cobalamin concentrations were reported to be caused by mild to severe HC deficiencies, these abnormalities were not accompanied by clinical manifestations of cobalamin deficiency [11,12].

Cobalamin continues its route in the gastrointestinal track and dissociates from HC under the action of pancreatic proteases, followed by its association in the intestine with the intrinsic factor (also known as the S-binder) which is essential for ileal absorption of cobalamin (Figure 1) [1,10]. The intestinal absorption of cobalamin into the enterocytes takes place in the terminal ileum via intrinsic factor receptor cubilin. The amount of acid secretion in the gastrointestinal tract plays a critical role in binding of cobalamin to its transporting proteins.

Indeed, homozygous nonsense and missense mutations in the gene encoding the gastric intrinsic factor GIF were reported to cause hereditary juvenile cobalamin deficiency [13]. This metabolism step is also implicated in the physiopathology of the so called Biermer’s disease (see the next section) [1].
Food-Cobalamin Malabsorption

Food-cobalamin malabsorption (FCM) is a syndrome characterized by the inability of the body to release cobalamin from food or intestinal transport proteins (“maldigestion”), particularly in the presence of hypochlorhydria (Figure 1) [14,15]. Ralph Carmel first characterizes FCM in cases of subtle cobalamin deficiencies [15]. In our experience, this syndrome accounted for 60 to 70% of cases of mild to severe vitamin B12 deficiency in elderly patients [16]. To our opinion, this is the first cause of vitamin B12 deficiency in the elderly, along with Biermer’s disease. The principal characteristics of this syndrome are listed in Table 2.

Table 2. Food-cobalamin malabsorption syndrome [14].

<table>
<thead>
<tr>
<th>Criteria for food-cobalamin malabsorption</th>
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</thead>
<tbody>
<tr>
<td>• Low serum cobalamin (vitamin B12) levels</td>
</tr>
<tr>
<td>• Normal results of Schilling test using free cyanocobalamin labeled with cobalt-58 or abnormal results of derived Schilling test ‡</td>
</tr>
<tr>
<td>• No anti-intrinsic factor antibodies</td>
</tr>
<tr>
<td>• No dietary cobalamin deficiency</td>
</tr>
<tr>
<td>• Presence of an associated conditions or agents (e.g., atrophic gastritis, <em>Helicobacter pylori</em> infection, partial gastrectomy, gastric by-pass, pancreatic insufficiency (alcohol abuse), intestinal bacterial overgrowth, long term anti-acid agents (proton-pump inhibitors) or biguanides (metformin) intake</td>
</tr>
</tbody>
</table>

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

FCM is caused primarily by atrophic gastritis [14]. Other factors that contribute to FCM are: chronic infection with *Helicobacter pylori* and intestinal microbial proliferation, situations in which cobalamin deficiency can be corrected by antibiotic treatment [14,17]; long-term ingestion of anti-acid agents such as H2-receptor antagonists and proton-pump inhibitors (e.g., omeprazole, pantoprazole, esomeprazole, etc.), particularly among patients with Zollinger-Ellison syndrome (gastrinoma) [18], and long term intake of biguanides (metformin) [19,20]. In addition, other FCM inducers include: chronic alcoholism, especially in malnourished patients; surgery or gastric reconstruction (e.g., bypass surgery for obesity, partial gastrectomy for benign gastric tumor or malignant gastric tumors, etc.); partial exocrine pancreatic failure (e.g., chronic alcohol intake, cystic fibrosis, etc.); and rarely Sjögren’s syndrome and systemic sclerosis or HIV [14].

It is to note that in case of FCM, patients can absorb “unbound” cobalamin through intrinsic factor or passive diffusion mechanisms [10,14]. Thus the recognition of the syndrome permits new developments of oral cobalamin therapy using free crystalized cobalamin that is readily absorbed [21].

In practice, the diagnosis of FCM is to date based on the exclusion of the main others causes of vitamin B12 deficiency, in connection with the fact that the Schilling’s test is no longer currently available [4]. Health care providers need to be aware of FCM, since it is easy to treat and treatment can prevent serious late consequences of vitamin B12 deficiency.

### Vitamin B12 Absorption

**Physiology**

Absorption depends mainly on Intrinsic Factor (IF), which is secreted by the gastric mucosa. IF binds cobalamin forming a complex that is absorbed by the terminal ileum (Figure 1) [1,10]. This mechanism is responsible for at least 60% absorption on oral cobalamin [1]. This complex is located at the apical side of brush-border membranes (BBMs) of polarized epithelia, such as the intestinal apical BBM.

It consists of the intrinsic factor-vitamin B12 receptor named cubilin, a 460 kDa peripheral membrane glycoprotein, encoded by the *CUBN* gene which was mapped to chromosomal region 10p12.33-p13 [22], and the 48 kDa amnionless (AMN) protein encoded by the *AMN* gene, a gene localized on human chromosome 14 [23]. In this setting, the human megalin/gp330/LRP-2 receptor, encoded by the LRP-2 gene located on chromosome 2q24-q31 [24], may play an important role in the stability of the cubilin/AMN complex [10, 25–29]. It is noteworthy that the interaction of these factors is Ca2+-dependent [26–29].

Cubilin and megalin are also expressed in the apical side of proximal kidney tube and are considered responsible for cobalamin reuptake into the circulation [10].

**Biermer’s or Addison’s Disease**

In adults, vitamin B12 deficiency is classically caused by Biermer’s also named Addison’s disease, formerly known...
as “pernicious anemia” [30,31]. This disorder is an autoimmune disease characterized by: the destruction of the gastric mucosa, especially fundal, associated with a primarily cell-mediated auto-immune process; and the presence of various antibodies, especially anti-intrinsic factor antibodies and gastric parietal anti-cell antibodies that target the H+/K+ ATPase α and β subunits [30,31]. Pernicious anemia has a genetic component [30]. In this context, pernicious anemia is associated with other immunologic diseases such as Sjögren’s syndrome, Hashimoto’s disease, type 1 diabetes mellitus, and celiac disease [30,32].

In our experience, Biermer’s disease accounted for 30 to 40% of cases of cobalamin deficiency in adults, and more than 60% in severe vitamin B12 deficiencies [4]. In this later situation, hematological (e.g., macrocytic anemia) or psycho-neurological manifestations (e.g., medullar combined sclerosis) are commonly observed [32]. In practice, the diagnosis of Biermer’s or Addison’s disease is based on the presence of intrinsic factor antibodies in serum (specificity > 98% and sensitivity around 50%) or biopsy-proven autoimmune atrophic gastritis (Table 3) [1,30]. The presence of *H. pylori* infection in gastric biopsies is an exclusion factor.

**Table 3. Biermer’s or Addison’s disease [1,30,32].**

<table>
<thead>
<tr>
<th>Criteria for Biermer’s disease (pernicious anemia)</th>
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<tbody>
<tr>
<td>• Low serum cobalamin (vitamin B12) levels</td>
</tr>
<tr>
<td>• Abnormal results of Schilling test using free cyanocobalamin labeled with cobalt58 ‡</td>
</tr>
<tr>
<td>• Presence of anti-intrinsic factor antibodies (sensibility of 50%, specificity &gt;98%)</td>
</tr>
<tr>
<td>• Presence of an auto-immune gastritis (especially fundal), with absence of <em>Helicobacter pylori</em> in the status phase of the disease</td>
</tr>
<tr>
<td>• Associated conditions: auto-immune disorders (e.g., Sjögren’s syndrome, Hashimoto’s disease, type 1 diabetes mellitus, and celiac disease)</td>
</tr>
<tr>
<td>• Predisposition of gastric cancer</td>
</tr>
</tbody>
</table>

‡ Schilling test is not used anymore in clinical practice.

It is important to note that of Biermer’s disease require a long term gastric follow-up (upper-endoscopy with biopsies, every year in case of gastric lesions or every 2 to 5 years in the absence of detectable lesion), because this disorder favors the emergence of various cancers of the stomach [1,4].

**Cobalamin Malabsorption**

Since the 1980s, the prevalence of vitamin B12 malabsorption declined, especially in elderly patient, owing mainly to the decreasing frequency of gastrectomy (due to the provision of antacid drugs) and terminal small intestine surgical resection [4,10]. However, several disorders commonly seen in clinical practice might, to date, be associated with cobalamin malabsorption [10]. These disorders include: exocrine pancreas’ function deficiency following chronic pancreatitis (usually alcoholic), lymphomas or tuberculosis (of the intestine), celiac disease, Crohn’s disease, Whipple’s disease, and uncommon celiac disease [4].

In practice, the diagnosis is based on patient interview (personal surgical history), a full clinical examination and digestive explorations in doubt.

**Genetic Disorders of Cobalamin Malabsorption**

In this setting, the Imerslund-Gräsbeck syndrome or megaloblastic anemia due to selective cobalamin malabsorption with proteinuria is a vitamin B12 deficiency leading to megaloblastic anemia, usually revealed in childhood, and is corrected by parenteral administration of vitamin B12 [10,34–39]. To our knowledge, no data of the Imerslund-Gräsbeck is available in elderly patients. This is also the case for mutations in CUBN, wisch were reported to cause hereditary megaloblastic anemia 1 (MGA1), a rare autosomal recessive disorder affecting human subjects with neurological symptoms and juvenile megaloblastic anemia [34–36]. Moreover, mutation in AMN was also reported in recessive hereditary MGA1 [10,36] and hence was demonstrated to be crucial for a functional cobalamin-IF receptor [10].

**Rational of Oral Cobalamin Therapy**

Of particular interest for the practitioner in this section of malabsorption is the observation that about 1 to 5% of free vitamin B12 (or crystalline cobalamin) is absorbed along the entire intestine by passive diffusion [10]. This absorption explains the mechanism underlying oral
cobalamin treatment of vitamin B12 deficiencies [39]. Our working group has developed an effective oral treatment for FCM [40] and pernicious anemia [41] using crystalline cobalamin (cyanocobalamin) (Table 5). Oral cobalamin has been proposed as a way of avoiding the discomfort, inconvenience and cost of monthly injections.

Table 4. Definitions of cobalamin (vitamin B12) deficiency [3,4,6,10,14].

- Serum cobalamin levels <150 pmol/l and clinical features and/or hematological anomalies related to cobalamin deficiency.
- Serum cobalamin levels <150 pmol/l (<200 pg/ml) on two separate occasions.
- Serum cobalamin levels <150 pmol/l and total serum homocysteine levels >13 mmol/l or methyl–malonic acid levels >0.4 mmol/l (in the absence of kidney failure or atheroma and of Methylene Tetra Hydro Folate Reductase (MTHFR) deficiency and in the absence of folate and vitamin B6 deficiencies).
- Low serum holotranscobalamin levels <35 pmol/l.

Table 5. Recommendations for oral vitamin B12 treatment [39].

<table>
<thead>
<tr>
<th>Pernicious anaemia</th>
<th>Intake deficiency and food-cobalamin malabsorption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parenteral administration (intramuscular)</td>
<td>Cyanocobalamin: 1,000 µg per day for 1 week than 1,000 µg per week for 1 month than 1,000 µg per each month, for life (1,000 to 2,000 µg per day for at least 1 to 3 months in case of severe neurological manifestations)</td>
</tr>
<tr>
<td>Oral administration</td>
<td>Cyanocobalamin: 1,000 µg per day for life*</td>
</tr>
</tbody>
</table>

*: The effect of oral cobalamin treatment in patients presenting with severe neurological manifestations has not yet been adequately documented.

Cobalamin Transport to Blood and Tissues

Physiology

After vitamin B12 is absorbed at the BBM-blood barrier, it dissociates from the intrinsic factor and reaches the systemic circulation where it associates with transcobalamin II (TCII) (Figure 1) [1,10,38]. The kidney represents an essential organ were body vitamin B12 stores are maintained and studies demonstrated that the kidney regulates plasma vitamin B12 levels by maintaining a pool of unbound cobalamin that can be released in case of vitamin B12 deficiency [10,42]. The tissular cobalamin-TCII complex uptake is achieved through megalin (LRP2)- and transcobalamin II receptor (TCII-R)-mediated endocytosis which plays a crucial role in cobalamin homeostasis [32,43].

Following cobalamin-TCII cellular uptake, TCII undergoes lysosomal digestion, which allows cobalamin separation from TCII and its cytoplasmic transfer. It has been estimated that there is a delay ranging from 5 and 10 years between the onset of cobalamin deficiency and the appearance of clinical manifestations, due to large hepatic stores (> 1.5 mg) and the enterohepatic cycle ensuring re-absorption of the vitamin in the gastrointestinal tract [1,10]. Also the reabsorption of TCII-bound cobalamin in the proximal tubules limits the loss of B12 in urine.

The average vitamin B12 content is approximately 1.0 mg in healthy adults, with 20–30 µg found in the kidneys, heart, spleen and brain. Estimates of total vitamin B12 body content for adults range from 0.6 to 3.9 mg with mean values of 2–3 mg. The normal range of vitamin B12 plasma concentrations is 150–750 pg/ml, with peak levels achieved 8–12 hours after ingestion of a single dose of the vitamin.

Part of the cobalamin serves as a cofactor for methionine synthase-mediated homocysteine catabolism into methionine and methyltetrahydrofolate reductase (MTHFR)-mediated formation of the vitamin B9 biologically active form, tetrahydrofolate, which is then involved in the synthesis of purines and pyrimidines (Figure 1) [10,44]. In clinical practice, several of these molecules are implicated in the definitions of vitamin B12 deficiency (Table 4). The other part of vitamin B12 is transferred to the mitochondria where it is transformed into
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adenosyl-B12, an important cofactor in methylmalonyl-coenzyme A mutase-mediated formation of succinyl-CoA from methylmalonyl-CoA, the product of odd-chain fatty acid and some amino acid catabolism. Hence, cobalamin deficiency will cause homocysteine accumulation, increased methylmalonyl-CoA levels and decreased MTHFR activity. These changes are translated into several abnormalities including folate deficiency and subsequent inhibition of purines and pyrimidines formation essential for RNA and DNA synthesis [10,38].

Genetic Disorders of Cobalamin Transport

It is worth mentioning that TCII is responsible for the cellular uptake of B12 in most tissues and that TC deficiency is associated with severe megaloblastic anemia [10,44] and developmental disorders (see the review in [44]). To our knowledge, no data of these genetic disorders is available in elderly patients, the last of these appearing in the newborn or in the child.

Conclusion

In this paper, we presented the main etiologies of vitamin B12 deficiency in elderly patients, in relation to different steps of the cobalamin transport and metabolism. However to date, many causes of cobalamin deficiency remained unknown. These causes include mainly mutations in genes encoding important proteins of the cobalamin transport or metabolic pathway. Nevertheless, “new” cause may be described in clinical practice, as the food-cobalamin malabsorption (maldigestion) with new actors or clinical practice (e.g., H. pylori, anti-acid drugs, metformine).

Acknowledgment

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References


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