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Trafficking of Cobalamin Transport Carrier Proteins in Celiac Disease

Hugh James Freeman*

UBC Hospital, 2211 Wesbrook Mall, Vancouver, BC, Canada
*Corresponding author: hugfree@shaw.ca

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Abstract Absorption of vitamin B12 is normally complex, involves multiple carriers leading to uptake of this micronutrient in the distal small intestine. Vitamin B12 is mainly from animal sources and, after ingestion, becomes complexed to haptocorrin derived from salivary glands to prevent acid destruction in the stomach. In the duodenum, pancreatic proteases hydrolyze this haptocorrin permitting vitamin B12 binding to intrinsic factor, a protein derived from gastric parietal cells. Linkage to intrinsic factor permits trafficking to the cubulin receptor in the ileum allowing entry into the enterocyte. After uptake, vitamin B12 exits the cell linking to another carrier protein in the blood, transcobalamin II. This process allows the micronutrient to circulate systemically to other cells. In celiac disease, one or more steps in this intestinal absorptive process may be impaired leading to significant neurologic, hematologic and, often poorly appreciated, further superimposed gastrointestinal effects.

Keywords: *Vitamin B12, celiac disease, absorption, Cobalamin, haptocorrin, intrinsic factor, transcobalamin*

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1. Introduction

Vitamin B12 absorption and malabsorption have been of special interest to clinician gastroenterologists and basic scientists for decades. Following some early reviews [1,2], understanding of the critical role of distinct protein carriers for vitamin B12 and trafficking of these carriers complexed to vitamin B12 within the gastrointestinal tract has dramatically evolved [3]. As a result, altered mechanisms involved in the absorption of this important micronutrient may be predicted in celiac disease, but much work still needs to be done for confirmation. In cohort studies, most diagnosed with celiac disease do not have vitamin B12 deficiency, but the frequency of those reported with this deficiency varies from approximately 4 to 8% [4]. Indeed, vitamin B12 deficiency in celiac disease may seem surprising as the major site of vitamin B12 absorption, the distal small bowel, contrasts with the proximal site of mucosal abnormalities in most with celiac disease and resultant deficiencies of other micronutrients, such as iron [5]. In this situation with more distal involvement, extensive small bowel changes would be expected with severe clinical disease. This does not usually occur. To explore possible mechanisms of vitamin B12 deficiency in adult celiac disease, a review of normal mechanisms is indicated.

Methyl-cobalamin, deoxyadenosyl-cobalamin and hydroxy-cobalamin are the major food cobalamins (vitamin B12). Cobalamin was initially crystallized in the form of cyanocobalamin [6]. Cyanocobalamin has been a major cobalamin in clinical studies even though it is sometimes described as an apparent artifact of the isolation procedure. Deficiency of vitamin B12 may result in a macrocytic anemia, impaired bone marrow production (pancytopenia with megaloblastic features), and neurological abnormalities, including degenerative spinal cord changes and peripheral neuropathy. These macrocytic and megaloblastic changes for vitamin B12 deficiency [7] are similar to changes noted with folic acid deficiency [8]. The hematologic changes reflective of rapidly turning over bone marrow precursor cells may also be observed in the epithelial cells of intestinal tract. In addition, for both deficiencies, small intestinal architecture may be altered with villus "flattening" owing to epithelial hypoplasia and a reduced crypt mitotic index (in contrast to hyperplastic changes and an increased mitotic index in untreated celiac disease).

2. Cobalamin Origins

Cobalamin is an essential water soluble vitamin and cannot be synthesized by mammalian species, only by microbes, primarily anaerobic species. In humans, these are mainly located in the large bowel, and since absorption of nutrients from the colon is, at best, very limited, most believe that humans are essentially entirely dependent on dietary sources from animal products, particularly liver and kidney. Strict vegetarians are at high risk for deficiency. Interestingly, it has been suggested that very

small amounts of vitamin B12 may also be absorbed by passive transport along the length of the small intestine [4], however, further studies on this route of small intestinal uptake are needed. Adults require an estimated 2 to 3 micrograms per day. Cobalamin is stored in the liver and, through an enterohepatic circulation, some biliary excretion into the small intestine occurs [3]. It is believed that mammals have only 2 vitamin B12-dependent enzymes in cells including: methionine synthase and methylmalonyl-CoA mutase [3]. However, there are many carriers involved in delivery of dietary B12 (recommended dietary allowance, 1-5 micrograms per day) to circulating blood, and ultimately, individual cells, through a multi-step process [1,2,3]. These include several anatomical sites including the salivary glands, stomach, pancreas and small intestine. As a result of this multi-carrier-mediated process, two forms of cobalamin eventually enter cells and become biologically active in humans: 5-hydroxyadenosylcobalamin and methylcobalamin, ultimately involved in fatty acid catabolism and methionine synthesis.

3. Multi-step Trafficking

This occurs before entering the circulating blood. Specific sites involved in assimilation of dietary vitamin B12 include:

1. Salivary Glands and Stomach. Cobalamin released from food is first bound largely by haptocorrin (or R-factor, previously referred to as transcobalamin I), a glycosylated protein from the salivary glands secreted in response to food ingestion [9]. It has a high affinity for cobalamin in the stomach at acid or neutral pH. Pepsin may also play a role. Haptocorrin is encoded by the TCN1 gene on chromosome 11. The essential function of haptocorrin is to protect acid-sensitive vitamin B12 as it moves through the stomach. Haptocorrin is also found in multiple fluids, including saliva, gastric and intestinal content, bile and serum.

2. Pancreas and Duodenum. In the duodenum, proteases from the exocrine pancreas rapidly release cobalamin from the haptocorrin-B12 complex as well as other ingested proteins that may be linked to cobalamin. A second binding process for cobalamin to intrinsic factor occurs in the proximal small bowel. Intrinsic factor is normally secreted by parietal cells in the gastric mucosa; intrinsic factor is encoded by the GIF gene, also on chromosome 11 [10]. This complex of cobalamin now linked to intrinsic factor traverses the small bowel to its more distal portion, the ileum.

3. Ileum. Entry into and from ileal epithelial cells into the blood stream is complex but initially depends on facilitated uptake through cubulin (only found in the kidneys and small intestine) by receptor-mediated endocytosis. Cubulin is encoded by the CUBN gene [11] and mutations in the gene may lead to an autosomal recessive megaloblastic anemia [11]. Binding to cubulin may also require calcium. Cubulin appears to be located at the bases of the villi in the distal small intestine. Interestingly, in the developing fetus, this receptor for the intrinsic factor-vitamin B12 complex may be located all along the small intestine and not only in the ileum. Within the enterocyte, evidence suggests that intrinsic factor is degraded within lysosomes, releasing cobalamin. The ATP-dependent transporter ABCC1, or MRP1 (multidrug resistance protein-1), is located in the basolateral membrane of the enterocyte and transports cobalamin out of the ileal epithelial cell.

4. Blood. After exit from the cell, cobalamin in its intact form is bound preferentially in the blood to transcobalamin II (about 20-30%) while haptocorrin binds the rest, including incomplete vitamin B12 derivatives. Transcobalamin II mediates transport of cobalamin across cells complexing with the transcobalamin II receptor. Transcobalamin II is then internalized in lysosomes and degraded by hydrolase activities releasing cobalamin for further intracellular processing.

In summary, vitamin B12 is delivered or trafficked by a series of distinct carriers to its site of action within cells. Interestingly, these cells also include the cells of the small intestine and, as noted, pathological alterations may occur in the small intestinal cells and structure [7], presumably limiting its absorptive function, including vitamin B12, as so-called “enterogenous vitamin B12 malabsorption”. Similar functional changes likely occur with folic acid deficiency [8]. In celiac disease with deficiencies of these nutrients, these added pathological changes may be superimposed on already present changes attributed to celiac disease.

4. Intracellular Vitamin B12 Effects

The intracellular metabolism of vitamin B12 has been previously reviewed by others and has been well defined [3]. Methyl-cobalamin is a cofactor for the methionine synthase enzyme. Owing to its activity, the methyl group in methyltrahydrofolate is transferred to homocysteine resulting in methionine and tetrahydrofolate. Methionine is converted to s-adenosyl methionine, critical for phospholipid biosynthesis. Tetrahydrofolate is a free form of folate for purine synthesis. If this reaction becomes impaired, folate is trapped as methyltetrahydrofolate with less tetrahydrofolate available for DNA synthesis leading to megaloblastic cellular changes, including anemia. In addition, less methionine for phospholipid synthesis leads to neuron demyelination. Finally, homocysteine accumulates leading to endothelial dysfunction and cardiovascular disease with homocystinuria.

Adenosyl-cobalamin is a cofactor for methylmalonyl-CoA mutase important in the conversion of methylmalonyl-CoA to succinyl-CoA critical in 2 metabolic pathways: the citric acid cycle and heme synthesis. Accumulation of methylmalonyl-CoA may result in neuron demyelination and methylmalonic aciduria.

5. Malabsorption of Vitamin B12

Only limited information is available on the causes of vitamin B12 malabsorption in adult celiac disease. Most nutrient deficiencies leading to anemia in celiac disease appear to be related to iron and folic acid since these are mainly absorbed in the proximal small intestine [6]. Other micro-nutrients including vitamin B12 as well as minerals,

copper and zinc, may be associated with anemia in celiac disease [12,13,14]. For vitamin B12, one or more of sites in the absorptive process may be altered in celiac disease. In contrast to Crohn's disease of the ileum (with vitamin B12 deficiency) or after surgical resection of the ileum, histopathological changes in the ileum in celiac disease appear to be limited. Celiac disease usually affects the proximal small bowel, extending distally to a variable extent with healing in a reverse direction on a gluten-free diet [15,16]. Intra-epithelial lymphocytosis in endoscopic mucosal biopsies from the ileum has been noted [17] and may provide a clue to celiac disease changes in more proximal biopsies, however, it is not clear if functional changes related to vitamin B12 absorption result. Added study is needed.

Concomitant atrophic gastritis or gastritis with mucosal glandular atrophy may be present in some with celiac disease. Most are related to Helicobacter, however, autoimmune gastritis may also occur reducing the parietal cell mass. This may substantially alter the milieu of the stomach with less acid and an altered microbiome. In addition, reduced availability of the intrinsic factor may lead to an inability to transport vitamin B12 to terminal ileal receptors. Additional studies are needed to determine if pernicious anemia *per se* [5], like other autoimmune disorders previously been reported in celiac disease [18], actually occur sufficient to lead to significant vitamin B12 deficiency.

In some celiac patients, particularly with protein starvation, pancreatic exocrine insufficiency may be present [19,20]. In this setting, vitamin B12 may hypothetically remain complexed to haptocorrin. Linkage with intrinsic factor may be limited or not occur. Instead, vitamin B12 may only be utilized by luminal microbes. Similarly, if bacterial overgrowth occurs concomitantly in celiac disease, vitamin B12 may by consumed by these bacteria and not be available for linkage to luminal proteins critical for trafficking.

Most disorders that specifically involve ileal receptors usually occur in the paediatric population (eg., Imerslund's syndrome) and likely be recognized early in life. In some adults, however, transfer of vitamin B12 from the ileal enterocyte may not occur because of a deficiency of transcobalamin II. As a result, vitamin B12 may be trapped within the enterocyte with vitamin B12 possibly only released at the time of shedding into the lumen for bacterial action.

While vitamin B12 deficiency has been described in celiac disease, this appears to be uncommon. Presumably, this deficiency is due to an impairment in one or more of the processes involved, particularly involving different transport protein carriers. Further exploration of factors involving the gastrointestinal lumen is needed.

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