

Vitamin B12 Deficiency: Causes, Evaluation and Treatment.

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Clinical Points:

- Deficiency of serum vitamin B12 levels can cause a variety of neurological and psychiatric disorders.
- Vitamin B12 deficiency has been reported in approximately 15% of adults older than 65 years of age. This is believed to be mainly caused by an age-related decline in intestinal absorption.
- Approximately 98% of B12 absorption is facilitated by intrinsic factor. The remaining 2% is absorbed passively.
- Oral B12 supplementation in high doses has been found to be as effective as intra-muscular vitamin B12 administration in pernicious anaemia.
- Intra-muscular B12 remains the treatment of choice in most Western countries, contrary to the prevailing evidence.

ABSTRACT

Vitamin B12 (cobalamin) deficiency is a major public health problem, particularly among the elderly population. It is known that a deficiency in serum B12 levels can cause a combination of neurological and psychiatric disorders. Therefore, in these cases successful replacement of depleted B12 levels is a necessity. Identification of B12 deficiency in elderly patients can be rather difficult as they often tend to present with neurological and neuropsychiatric symptoms despite a lack of haematological evidence showing depleted serum B12 levels. More recently, other parameters such as methylmalonyl-CoA or homocysteine (components of the cobalamin-dependent pathways) have been used as markers of B12 deficiency. Both parameters become elevated upon the onset of B12 deficiency. Several studies have shown that oral B12 replacement therapy can be equally as effective as parenteral (intra-muscular) B12 replacement. Yet, despite these publications, B12 is primarily administered to deficient patients intramuscularly. This inconvenient method of B12 replacement places a rather unnecessary demand on healthcare resources.

INTRODUCTION

The neurological disorders associated with vitamin B12 deficiency have previously been well described (1). It is known that patients with low serum B12 may have neurological complications as a result (2), in which both the central nervous system and peripheral nervous system are affected. A deficiency in vitamin B12 may cause autonomic failure (1). This review aims to discuss the causes, evaluation and treatment of a deficiency in serum B12 levels. A remarkable therapeutic trial that was previously carried out, in an effort to treat the once-fatal condition known as pernicious anaemia (common in patients with B12 deficiency), will also be discussed.

NORMAL B12 ABSORPTION

Vitamin B12 (cobalamin) plays an important role in DNA synthesis and neurological function (3). Adequate serum levels are necessary for nervous system maintenance and the development of normal red blood cells (4). Vitamin B12 cannot be synthesised in the body and must therefore be obtained from the diet. The main dietary sources of B12 are dairy products, meat (especially liver) and eggs. The acidic environment of the stomach enables the release of B12 that is bound to food (3). The free B12 is then rapidly bound by intrinsic factor (IF), a muco-polysaccharide secreted by the gastric parietal cells that line the stomach. The binding of B12 to IF occurs in the duodenum causing the formation of the IF-B12 complex (4). This complex is resistant to digestion by gastric juices. Upon reaching the terminal ileum, it binds to and is absorbed by the intestinal microvilli. In the plasma, about 20% of the absorbed B12 binds to the serum protein holotranscobalamin (Holo-TC) for transport

(5). Holo-TC is the protein that delivers bound B12 to all cells in the body. The majority of B12 (80%) circulating in the blood binds to the serum protein haptocorrin and is biologically unavailable for most cells (6). The function of haptocorrin remains unknown.

Only two enzymatic reactions are known to be dependant on B12 in humans, which are the conversion of methylmalonyl-CoA to succinyl-CoA (a necessary component of the citric acid cycle) and the conversion of homocysteine to methionine (3). The latter reaction is accompanied by the conversion of methyltetrahydrofolate to tetrahydrofolate, which is necessary for efficient DNA synthesis (6). Therefore, a deficiency in B12 can impair DNA synthesis.

CAUSES OF VITAMIN B12 DEFICIENCY

The causes of vitamin B12 deficiency can be divided into three classes: i) nutritional deficiency, ii) malabsorption syndromes and iii) other gastrointestinal (GI) causes. (7)

Nutritional Deficiency

Nutritional deficiency of B12 can occur in specific populations. The elderly, chronic alcoholics and vegans are most at risk due to the dietary deficits of B12 frequently found within these groups.

Malabsorption Syndromes

The primary example of a malabsorption syndrome is pernicious anaemia. This condition is the result of an autoimmune disease in which antibodies attack the parietal cells of the stomach, almost completely blocking the

release of IF as a result. This hindered IF release prevents the formation of the IF-B12 complex, subsequently impairing B12 absorption. Researchers now believe there is an age-associated decline in the intestinal absorption of B12 (5). Therefore, it comes as no surprise that B12 deficiency has been reported in about 15% of adults older than 65 years (3).

Other GI Causes

Although quite rare, certain GI conditions can also cause B12 deficiency. If a patient has an intestinal parasite infestation such as *Diphyllobothrium latum* (fish tapeworm) this may compete with the intestinal microvilli for the absorption of B12 (7). Similarly, if a patient has a bacterial overgrowth in the small bowel (commonly seen in those with a history of intestinal surgery), it would also compete with the ileum for the absorption of B12 (3).

EVALUATION OF VITAMIN B12 DEFICIENCY

Problems arise immediately when trying to define vitamin B12 deficiency. The scientific literature uses pmol L^{-1} while clinical laboratories use ng L^{-1} (8). It has been argued, that while serum holotranscobalamin levels may give an indication of the absorption of B12, malabsorption and deficiency are separate entities (9). Therefore, numerous attempts have been made to qualify B12 deficiency as either clinically or metabolically significant by including other parameters such as methylmalonyl-CoA or homocysteine (components of the cobalamin-dependent pathways). If these components are found to be elevated above normal it would indicate a "tissue deficiency" even if serum B12 is found to be normal (10).

In 2006, Dr. Harold Hin and his colleagues carried out the "Banbury B12 study". This cross-sectional study examined associations of cognitive impairment, depression and neuropathy with blood measurements of B12 in elderly people. A total of 1,000 community-dwelling individuals over the age of seventy five years were examined. In this study, participants with a serum B12 concentration of less than 133 pmol L^{-1} were deemed to be B12 deficient. Low B12 concentrations were identified in 13% (125 participants) of this free-living population. Cognitive function was assessed using the Mini-Mental State Examination and a Hospital Anxiety and Depression test was used to assess depression. The results from these standard tests indicated that low B12 concentrations correlated with cognitive impairment and depression. A further finding was that participants with B12 levels in the bottom quartile had a two-fold risk of cognitive impairment, when compared to those in the top quartile. Low B12 levels were also associated with peripheral neuropathy, based on the findings that the B12 deficient participants were observed to have missing knee and ankle jerk reflexes (11).

HISTORY OF PERNICIOUS ANAEMIA TREATMENTS

B12 deficiency can cause several forms of anaemia, most notably pernicious anaemia. The story behind the earlier treatments of pernicious anaemia is a rather fascinating one. Up until the late 1920's pernicious anaemia was untreatable and fatal. Three American physiologists (William Murphy, George Minot and George Whipple)

devised the concept that food could be used to treat pernicious anaemia. The diet they constructed containing liver "in such quantities [that] seemed very outrageous" had dramatic beneficial effects on the once untreatable pernicious anaemia (12). In 1934, the three colleagues were awarded the Nobel Prize in physiology and medicine.

Despite the proven efficacy of the liver therapy, a more satisfactory method of treatment than the daily consumption of a half pound of liver was needed. An American doctor named William Bosworth Castle devised an idea that enabled him to investigate the pathophysiology of this disease. Liver seemed to be necessary for the patients' bone marrow to function properly and Castle questioned why normal people did not have to eat such large amounts of liver to stave off pernicious anaemia. He attained permission from his supervisor (the aforementioned Dr. Minot) to carry out a rather unusual therapeutic trial. This investigation required Castle to consume 300g of rare hamburger steak daily for ten days. An hour after eating (thereby ensuring the gastric juices were adequately mixed with the ingested food), he would then regurgitate his stomach contents and incubate them until they had liquefied. Castle then directly administered the mixture to the stomach of patients suffering from pernicious anaemia via a flexible tube. Amazingly a clinical improvement and a reticulocyte increase were observed in all of the patients tested. Castle proposed a theory that an "intrinsic factor" is secreted by the stomach of normal healthy individuals which is required for the formation of an "anti-pernicious anaemia complex [from an] extrinsic factor", present in beef and liver (13).

The B12 molecule was first isolated in its cyano-form in 1948 (14) and was then identified as the active component of the "extrinsic factor" proposed by Castle. The chemical structure of the B12 molecule was later confirmed, using x-ray crystallography by Dorothy Hodgkin in 1956. She was subsequently awarded the Nobel Prize in chemistry for her significant findings.

CURRENT TREATMENTS OF B12 DEFICIENCY

B12 supplementation is now widely used for the treatment of B12 deficiency (4). Currently, most B12 deficient individuals are treated with an intramuscular B12 injection. (4) This is highly surprising, considering case-series and case-control studies, dating as far back as the early fifties, have shown oral B12 supplementation to be equally as effective as intra-muscular B12 administration (15). Recent studies have also reached similar conclusions. For example, in 1998, Kuzminski et al. performed a randomised trial on 38 vitamin B12 deficient patients. Participants received either oral or intra-muscular B12 supplementation for 120 days. Differences dosages were administered to each group. Patients in the oral supplementation group received daily dosages of 2,000 mcg of B12 for 120 days, whereas patients in the parenteral group were intramuscularly injected with 1,000 mcg on days 1, 3, 7, 10, 14, 21, 30, 60 and 90. Once the 120 days had elapsed, haematological testing revealed that patients in the orally supplemented group had considerably higher serum B12 levels than those the intra-muscularly injected group (16).

The transport mechanism for absorption of oral B12 that has been proposed by researchers is that B12 can actually be absorbed both actively (upon binding to IF) and passively (without binding to IF) (17). It is now known that B12 is primarily absorbed actively but the passive mechanism accounts for 1-2% of absorption (17). Therefore, it is believed that oral replacement therapy can be as effective as parenteral supplementation, provided that B12 is administered at a sufficient dose (3).

There are disadvantages associated with intra-muscular B12 supplementation when compared with oral B12 supplementation. Firstly, injections can be quite painful and distressful for patients and can therefore become a considerable source of work for healthcare professionals (18). Secondly, injections must be administered in either a healthcare facility or in the home of the patient, by a visiting healthcare professional (19) which can place a demand on healthcare resources that may be avoided with oral supplementation.

It remains highly surprising that oral B12 supplements are rarely prescribed to B12 deficient patients, despite the evidence. This is most likely because many clinicians are unaware that oral B12 supplementation can be as effective as intramuscular injections, provided they are taken in sufficiently high dosages (3). Only Canada and Sweden have successfully reversed their method of treatment from parenteral to oral supplementation, which now accounts for 73% of B12 replacement in these countries (20).

SUMMARY

Healthcare professionals should be made aware that high-dose oral supplementation can be equally as effective as intramuscular injection, when used to treat patients with a B12 deficiency. The oral method of supplementation has been shown to be safe, cost effective and well-tolerated by patients (21). This form of treatment would be less distressful for patients and far less resource-consuming on the healthcare system.

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