Chapter 19
Why Food Fortification with Vitamin B12 Is Needed?

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Key Points

- Vitamin B12 plays a functional role in a variety of organs and body systems. The list of conditions that are affected by vitamin B12 deficiency either directly or indirectly is growing.
- In some countries two factors can contribute to vitamin B12 deficiency, namely, changes in dietary pattern among segments of the population within the higher socioeconomic strata and the existence of poverty which leads to a low consumption of animal products (particularly red meat).
- There is an increasing prevalence of low vitamin B12 level in different segments of the general population.
- Vitamin B12 deficiency has various and serious health effects.
- The early detection of vitamin B12 deficiency is essential in order to prescribe opportune treatments.
- In order to prevent serious health problems, routine fortification with vitamin B12 should be seriously considered.

Keywords Vitamin B12 • Cobalamin • Vitamin B12 deficiency • Vitamin B12 routine fortification • Malignancy and vitamin B12 • Quality of life

Abbreviations

MRI Magnetic resonance imaging
RAS Recurrent aphthous stomatitis

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Introduction

There are many articles indicating the increasing prevalence of low vitamin B12 (also called cobalamin) status in different segments of the general population [1–7]. The early detection of vitamin B12 deficiency is essential in order to prescribe opportune treatments, and there is evidence that such deficiencies are more common than would be expected. Vitamin B12 deficiency frequently occurs in individuals with dietary patterns that exclude animal food products and patients who are unable to absorb vitamin B12. Vitamin B12 deficiency has many causes, and pernicious anemia has been described as a widespread cause of this. Recent studies on vitamin B12, including the description of novel etiologies of vitamin B12 deficiency, have added to our understanding of this essential dietary component. For example, vitamin B12 deficiency can arise not only from insufficient dietary intake [8] but also from food-cobalamin malabsorption syndrome [9]. The latter is characterized by the failure to release vitamin B12 from food or a deficiency of intestinal vitamin B12 transport proteins or both, due to chronic overgrowth of *Helicobacter pylori* [10] and intestinal microbial proliferation. Changes in gut flora can arise from antibiotic treatment, long-term ingestion of biguanides (metformin) [11, 12], and antacids, including H2-receptor antagonists and proton-pump inhibitors [13] (mainly among patients with Zollinger–Ellison syndrome [14]). There are also genetic vitamin B12 metabolism diseases as Imerslund–Grasbeck syndrome which is a selective vitamin B12 malabsorption with proteinuria [15]. Chronic alcoholism, surgery (e.g., bypass surgery for obesity), and partial pancreatic exocrine failure can also contribute to vitamin B12 deficiency. Overall, this demonstrates that new approaches to the identification and treatment of subjects with vitamin B12 deficiency may be needed.

Persons with vitamin B12 deficiency may be asymptomatic. However, vitamin B12 deficiency should be suspected in patients presenting with myelopathy, cognitive decline, neuropathy, psychiatric disturbances, or specific hematological signs and symptoms.

In the following an attempt is made to demonstrate the critical role of vitamin B12 by surveying and analyzing available reports, as well as reporting the clinical experiences of the main author (IV).

Vitamin B12 Responsiveness in the Clinical Setting

Vitamin B12 influences the bone marrow, skin and the peripheral and central nervous systems, mucous membranes, bones, and blood vessels, as well as the normal development of children. Numerous studies emphasize the health problems of nutritional vitamin B12 deficiency and an obligation for the clinical, biochemical, and metabolic monitoring of infants born to mothers suffering from vitamin B12 deficiency. Dietary deficiencies of vitamin B12 for the period of pregnancy and lactation may result in health problems in exclusively breastfed children. Physical examination of these children has revealed failure to thrive, muscular hypotonia, irritability, anorexia, unusual movements, and psychomotor retardation. Laboratory analysis shows hematological pathology, such as a macrocytic anemia, a low level of vitamin B12, a high level of homocysteine and methylmalonic acid (MMA). Magnetic resonance imaging (MRI) of the brain reveals spread fronto-temporoparietal atrophy and problems of myelination [16]. Several researches have shown a relationship between maternal vitamin B12 status and birth weight, and one study extended those findings directly in terms of neonatal vitamin B12 status and birth weight. Vitamin B12 status in the mother was correlated to neonatal vitamin B12 status as determined by cord serum vitamin B12 level. In addition, low neonatal vitamin B12 levels are adversely associated with low birth weight [17].

Children have particular nutritional requirements in comparison with adults. Growth, tissue differentiation and maturation, whole body accretion of macro- and microcomponents, enhanced energy expenditure, and higher rates of protein turnover explain these differences. Dietary deviations and/or an imbalance between demand and supply will thus raise the risk of nutritional deficiencies along with

Table 19.1 Demographic, clinical, and nutritional characteristics of the patients by vitamin B12 levels

Characteristic	Low B12 levels (≤160 pg/mL) (*n* = 03)	Low-normal B12 Levels (161–300 pg/mL) (*n* = 64)	Normal B12 levels (>300 pg/mL) (*n* = 42)
	Number (%)		
Female sex	65 (63)	44 (69)	29 (69)
Age group (*years*)			
18–40	52 (50)	34 (53)	22 (52)
41–60	38 (37)	26 (40)	12 (29)
>60	13 (13)	4 (6)	8 (19)
Symptoms and signs			
Impaired vibration sense	37 (36)*	10 (16)	2 (5)
Impaired position sense	18 (17)**	0	0
Hyperactive tendon reflexes	25 (24)**	9 (14)	2 (5)
Extensor plantar response	14 (14)***	3 (5)	0
Impaired sensation	28 (27)****	8 (12.5)	4 (10)
Hypoactive tendon reflexes	12 (12)	5 (8)	3 (7)
Optic atrophy	5 (5)	0	0
Fatigue	14 (14)	9 (14)	4 (10)
Recurrent strokes	2 (2)	0	0
Mental disturbances[a]	27 (26)	12 (19)	5 (12)
Meat consumption (*per week*)			
<50 g	42 (41)*	9 (14)***	0
51–100 g	39 (38)****	23 (36)	8 (19)

*$P < 0.001$ compared with normal B12 level group
**$P < 0.005$ compared with normal B12 level group
***$P < 0.02$ compared with normal B12 level group
****$P < 0.05$ compared with normal B12 level group
[a]Obtundation, impaired concentration, memory loss, disorientation, psychosis

Table 19.2 Laboratory findings in patients with low or low-normal vitamin B12 levels

Laboratory findings	Low B12 level (≤160 pg/mL) (*n* = 103)	Low-normal B12 level 161–300 pg/m (*n* = 64)
	Number (%)	
Anemia[a]	58 (56)	35 (54)
Iron deficiency[b]	20 (19)	14 (22)
Macrocytosis[c]	23 (22)	11 (17)
Low serum folate levels[d]	19 (18)	6 (9)

[a]Hemoglobin <14 g/dL in men or <12 g/dL in women
[b]Iron level <59 μg/dL in men or <37 μg/dL in women
[c]Mean corpuscular volume >94 fL
[d]Serum folate level <3.5 ng/mL

consequent health problems. Thus, if dietary restrictions are needed for children with medical conditions (e.g., procedures on the intestine, food allergies, or intolerances), particular attention must be paid to avoiding micronutrient deficiencies such as vitamin B12 [18]. This is because children are very vulnerable to the deficiency of this vitamin (e.g., see (INCECIK2010, ABDELGAWADA2002)) with long-term consequences.

Vitamin B12 deficiency can cause peripheral neuropathy (Table 19.1) and combined system diseases including demyelination of the dorsal columns and the corticospinal tract. An extensive assortment of neuropsychological symptoms and signs has been found, such as spasticity, muscle weakness, reduced or hyperactive reflexes, urinary or fecal incontinence, ataxia, orthostatic hypotension, loss of vision, dementia, psychoses, and disturbances of mood. Several neurological syndromes or symptoms

are often seen in a single patient. The severity of pathology before treatment is undoubtedly related to the duration of symptoms prior to diagnosis [19].

Multiple sclerosis (MS) and vitamin B12 deficiency have common inflammatory and neurodegenerative pathophysiological characteristics. As a result of these similarities in the clinical appearance and MRI findings, the differential diagnosis between vitamin B12 deficiency and MS may be not easy. Moreover, low or decreased levels of vitamin B12 have been demonstrated in MS patients. In addition, current studies suggest that vitamin B12, in addition to its known role as a cofactor in myelin formation, has significant immunomodulatory and neurotrophic effects. These findings raise the questions of the potential causal association between the two disorders and merit further studies into the need to routinely determine vitamin B12 levels in MS patients [20] or more routinely in the hospital or clinical setting.

The role of vitamin B12 deficiency in psychiatric illness has been studied and discussed since the 1940s. Vitamin B12 has essential roles in brain functioning as well as cognitive processing. The broad psychiatric appearances of vitamin B12 deficiency are mood disorders, depression [21], psychotic status [22], mania, and obsessive compulsive disorders. The severity of disease and the therapeutic efficacy of treatment depend on the duration of the pathology. Consequently, the testing for serum vitamin B12 levels and consideration of vitamin B12 deficiency are recommended in patients with atypical psychiatric symptoms and the spectrum of organic brain syndromes.

There is a well-characterized association between levels of vitamin B12 and homocysteine which has been implicated as a risk factor for cardiovascular diseases, as well as brain atrophy. Some data supports the finding that increased circulating homocysteine is a risk factor for cognitive impairment in dementia (e.g., Alzheimer's disease) through vascular involvement as well as direct neurotoxic influence [23–25]. This may be due to the reason that in some research, increased plasma total homocysteine levels have been associated with ischemic stroke risk [26–28]. Several retrospective and prospective studies have revealed a consistent, independent relationship between hyperhomocysteinemia and cardiovascular disease, as well as all-cause mortality.

According to some guidelines the treatment of hyperhomocysteinemia is recommended for the apparently healthy general population [29]. Some large studies confirm that a supplementation with group B vitamins do not reduce the risk of major cardiovascular events or all-cause mortality in patients with vascular disease [30, 31]. It is possible that the outcomes of these and similar trials could be different if the studies had addressed the following points:

1. Using vitamin B12 or B complex as secondary prevention (i.e., curative aspects) of cardiovascular events for patients with irreversible changes of blood vessels has limited efficacy. Rather, vitamin B12 or B complex should be used within the context of primary prevention (i.e., preventative aspects).
2. Using high doses of vitamin B12 to reduce cardiovascular risk factors will probably be more effective than using cocktails of group B vitamins. Furthermore, using folic acid alone for prevention of cardiovascular diseases has been proven to be ineffective [32], while very high doses of vitamin B12 (60 mg every day for 6 months) has been used effectively, without any toxic side effects, for the treatment of other diseases [33].

The vitamin B12 carrier proteins, the transcobalamins (TC), are elevated during trauma, chronic infections, and inflammatory diseases. The scientific basis of this is not fully known, but it is possible that such elevations in transcobalamins could signal a compensatory reaction that primes the potential delivery of vitamin B12 to counteract inflammation via a multitude of processes such as the regulation of NFkappaB [34] There is clinical data to suggest that high doses of vitamin B12 ameliorate sepsis, traumatic shock, and systemic inflammatory response syndrome [34]. For example, septic shock has a high mortality rate. In the United States approximately 200,000 people die annually from this disease. The high mortality results in part from severe hypotension secondary to high serum nitric oxide (NO) concentrations [34]. In relation to current clinical data, cobinamide, a precursor of vitamin B12, has been proposed as a scavenger and cytoprotective agent to bind and inactivate NO [35].

Vitamin B12 has a fundamental role in hematopoiesis, i.e., red cell production (Table 19.2). Usually, low vitamin B12 produces the classic picture of macrocytic anemia, with a mean corpuscular volume (MCV) greater than 100 fL. The MCV correlates extremely well with vitamin B12 deficiency: an MCV of 80–100 fL indicates less than 25 % probability of vitamin B12 deficiency, MCV of 115–129 fL indicates a 50 % probability, and MCV greater 130 indicates 100 % probability [36]. This is a classic *textbook* picture of vitamin B12 deficiency. However, hematological abnormalities, such as anemia or macrocytosis, may be absent at the time of neurological presentation [37]. It is well known now that vitamin B12 deficiency may be accompanied by iron deficiency, and this association could mask macrocytosis [38, 39].

There are no generally accepted guidelines for the definition, diagnosis, treatment, and follow-up of vitamin B12 deficiency. Total serum vitamin B12 may not reliably indicate vitamin B12 status. The probability of "functional" vitamin B12 deficiency decreases upon increasing the blood level of vitamin B12. To increase the specificity and sensitivity of diagnosing vitamin B12 deficiency, it has been proposed that homocysteine, MMA, and holotranscobalamin II (holoTC), a subfraction of biologically active vitamin B12, should be measured [40].

Observations on Recurrent Aphthous Stomatitis

Recurrent aphthous stomatitis (RAS), the most common oral mucosa lesions seen in primary care, is seen in up to 25 % of the general population. Most treatments given to patients suffering from RAS achieve short-term therapeutic goals, such as alleviation of pain, reduction of ulcer duration, and recovery of normal oral function. A few treatment regimens have achieved long-term therapeutic goals, such as a reduction in the frequency and severity of RAS and maintenance of remission. With 10-year clinical experience of this disease, the lead author of this Chapter IV has shown that vitamin B12 treatment achieves long-term therapeutic goals and can be effective for patients suffering from RAS, regardless of their serum vitamin B12 level (Fig. 19.1).

A randomized, double-blind placebo-controlled trial has been carried out to confirm this observation [41]. The results of this study, conducted in the primary care setting, indicated that vitamin B12 treatment

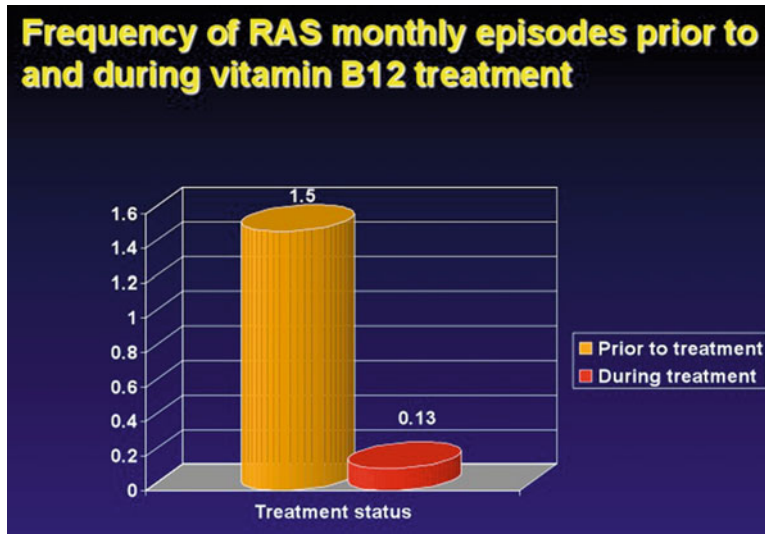

Fig. 19.1 Frequency of RAS episodes prior to and during vitamin B12 treatment (episodes per month)

can achieve long-term therapeutic goals in the management of RAS, in terms of various disease parameters such as pain, the number of ulcers, and duration of outbreak. This outcome did not depend on initial level of vitamin B12. Although a statistical significance was found between the interventional and control groups, the results need to be carefully interpreted due to the small sample size (58 people in the study) even though a prospective double-blind study design was used. The results nonetheless confirm previous clinical observations from our group. More than 74 % of patients in the interventional group were free from aphthous ulcers at the end of the treatment period, in comparison to 32 % in the control group. No adverse events were associated with vitamin B12 treatment in our study, and it is worth pointing out that this is the most comprehensive study on this disease to date.

Fertility

A potential association between vitamin B12 and problems of fertility and early recurrent abortions has been under discussion for long time [42–44]. In a meta-analysis of five studies, a significant correlation between serum vitamin B12 and early recurrent abortions was found [45]. No difference was noticed between early recurrent abortions and controls for folate [45].

Observations on Bone Disease

Osteoporosis is a common problem, which frequently has destructive health outcomes because of its association with fragility fractures and functional disabilities. The total number of fractures, and hence the cost to society, will increase dramatically over the next 30–50 years as a result of demographic changes in the amount of elderly people. Thus, prevention of osteoporosis by identifying risk factors or risk indicators, as well as the development of new treatment strategies, is a major health issue. Some data suggest that vitamin B12 status affects bone metabolism, bone quality, and fracture risk in humans [46]. A preventive regimen of vitamin B12 supplementation for healthy people with risk factors for osteoporosis or treatment of patients suffering from osteoporosis with vitamin B12 is advocated. Controlled clinical trials should thus be conducted to confirm the safety and effectiveness of vitamin B12 therapy and prophylaxis for osteoporosis.

Observations on the Aged and Aging

As mentioned above there is a changing demographic profile in most countries in which the proportion and number of elderly will rise in the foreseeable future. For example, recent data shows a world population of 7.0 billion [47]. This will increase to 9.3 billion by 2050. In Europe one third of the population will be over 60 years of age by 2050, and worldwide the proportion of people over 60 years of age will increase from 11 % in 2011 to 22 % in 2050. The relevance of this pertains to the incidence of vitamin B12 deficiency in the elderly. The prevalence varies but it is not uncommon to see figures of over 50 % being reported in some vulnerable groups though the general figure is probably about 10–20 % of elderly patients [9]. Vitamin B12 deficiency may arise as a consequence of poor intakes, food-cobalamin malabsorption syndrome, or pernicious anemia [48]. In pernicious anemia there is damage in the stomach with a consequential loss of intrinsic factor [49]. Intrinsic factor (also called gastric intrinsic factor) is needed for the binding of vitamin B12 and its subsequent absorption across the mucosa of the small intestinal ileum. The relevance of vitamin B12 deficiency

relates to the fact that cognitive decline as well as neuroelectricphysiological disturbances are associated with reduced plasma vitamin B12 which may occur independently of homocysteinemia [50]. Furthermore vitamin B12 supplementation in the elderly improves cognitive measures [51]. It is not unreasonable then to suggest more routine vitamin B12 supplementation in the elderly, preferably within the food matrices. However, the efficiency at which vitamin B12 is bioavailable varies depending on the food sources, i.e., less than 10 % from eggs and approx. 40–90 % from meats [52]. Obviously, the mode at which vitamin B12 is supplemented needs to be explored further [53], but the outcome of some studies has been negative [54].

Necessity of a New Approach to the Problem of Vitamin B12

Folic acid fortification of some foods has prevented the occurrence of neural tube defects in many countries. However, excessive folic acid fortification may be harmful to those with vitamin B12 deficiency. For example, among participants with vitamin B12 deficiency in the National Health and Nutrition Examination Survey, high serum folate (>59 nmol/L) was linked with a higher prevalence of anemia and cognitive impairment when compared with normal serum folate. Researchers also found a rise in serum levels of homocysteine and MMA, two useful indicators of low vitamin B12 status [55].

According common guideline (Recommended Dietary Allowances), the vitamin B12 intake is about 2.4 μg/day [56]. This contrasts with the some novel recommended daily intakes of between 2 and 6 μg [57]. Today there is a tendency in modern society to change habits, for example, cessation of smoking, "fighting" with overweight, accentuating physical exercise, and adopting correct eating habits. We have come to the conclusion that as a result of media information disseminating the relationship between meat, cholesterol, and cardiovascular diseases, consumption of meat, particularly beef, has decreased. We suppose that the decrease of level of vitamin B12 in the population with higher educational level is caused by a premeditated decrease in consumption of animal products. Also in modern society there is a tendency for ideological motives, particularly among the younger generation, to be vegans. To address the above, the issue of food fortification needs to be addressed. The advantage of vitamin B12 supplementation or fortification is that toxicity is rare, and at the same time it will address the needs of vulnerable groups.

Conclusion

Changes in lifestyle among segments of the population with a high socioeconomic level, on one hand, and the existence of poverty, on the other, are two main factors in the decreasing consumption of animal products (particularly red meat). This causes a decrease in the level of vitamin B12 in the general population, and as a consequence, this will increase pathology due to vitamin B12 deficiency (such as neurological and hematological disorders). As mentioned, vitamin B12 deficiency has various and serious health effects. In lieu of these possible developments and in order to prevent serious health problems, routine vitamin B12 fortification should be seriously considered and discussed.

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