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Epidemiology of Vitamin B₁₂ Deficiency

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Abstract

Vitamin B₁₂ is only synthesized by microorganisms in nature and thus, is obtained by human beings through their diet. Since the most important source of vitamin B₁₂ is animal proteins, vegetarians may lack sufficient quantities of this vitamin in their diets. Vitamin B₁₂ deficiency may stem from a lower dietary intake, an autoimmune issue related to intrinsic factors or gastrointestinal system diseases resulting in vitamin B₁₂ malabsorption. The most important symptoms and findings of severe vitamin B₁₂ deficiency are anemia and neurological problems. If it is not treated, anemia symptoms and neurological disturbances resulting in spinal cord and cerebral cortex demyelination may emerge. Vitamin B₁₂ deficiency is one of the most frequent vitamin deficiencies worldwide. This deficiency is a highly important public health issue because of its serious complications if it is not detected and treated appropriately, although its treatment is very simple. Epidemiological studies in this field are, therefore, of great value. Most of the studies on this subject have been examined vitamin status of the general population. The research generally contains to the national or provincial populations data. Nevertheless, the few data are not fully representative in the general population. Determining risk factors and at-risk groups, and educating them about vitamin B₁₂ deficiency and proper diet would prevent the irreversible complications of this type of deficiency. The goal of this study is to review epidemiological studies related to vitamin B₁₂ deficiency and to point out the importance of identifying and treating it.

Keywords: epidemiology, vitamin B₁₂, anemia, deficiency, nutrition

1. Introduction

Vitamin B₁₂ is only synthesized by microorganisms in nature and thus, is obtained by human beings through their diet [1]. Since the most important source of vitamin B₁₂ is animal proteins, vegetarians may lack sufficient quantities of this vitamin in their diets.

Vitamin B₁₂ deficiency may be caused by a lower dietary intake (impaired absorption or decreased intake), an autoimmune issue related to intrinsic factors or gastrointestinal system diseases resulting in vitamin B₁₂ malabsorption [2]. The most important symptoms and findings of severe vitamin B₁₂ deficiency are anemia and neurological problems. Vitamin B₁₂ deficiency is one of the most common causes of macrocytic anemia [3, 4]. If it is not treated, anemia symptoms and neurological disturbances resulting in spinal cord and cerebral cortex demyelination may emerge [5].

Epidemiology concerns health and disorders, etiological agents, the symptoms of disorders, diagnoses and the benefits of clinical care, and its discontinuation. Determining risk factors and at-risk groups as well as educating them about vitamin B₁₂ deficiency, proper diet, and replacement would prevent any irreversible complications of this type of deficiency. The goal of this study is to review epidemiological studies related to vitamin B₁₂ deficiency and to point out the importance of identifying and treating it.

2. The metabolism of vitamin B₁₂

The major metabolic pathway of vitamin B₁₂ formation is shown in **Figure 1**.

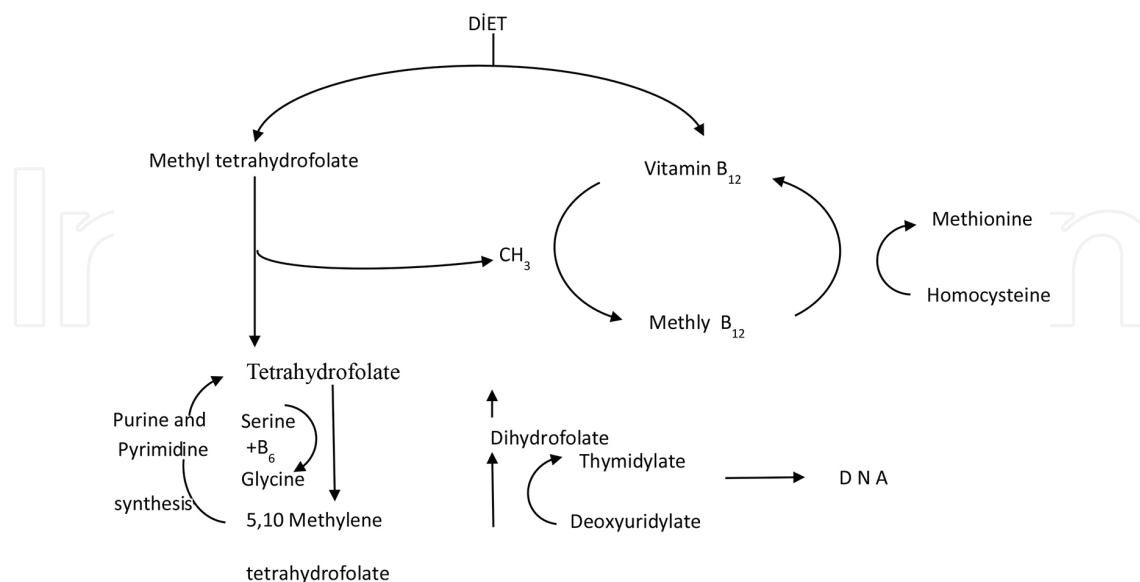


Figure 1. The mechanism of vitamin B₁₂.

Vitamin B₁₂ is essential for DNA synthesis in cells. It has two different forms in cells.

Deoxyadenosyl B₁₂ converts methylmalonyl CoA to succinyl CoA. It also transfers methyl groups from methyltetrafolate to synthesized methionine. Transferring a methyl group from methyltetrafolate forms tetrahydrofolate. If there is a lack of vitamin B₁₂, there is no receptor to transfer a methyl group from methyltetrafolate. Then the methylfolate is trapped and tetrahydrofolate that is needed to support DNA synthesis is decreased [2].

3. The absorption and distribution of vitamin B₁₂

The absorption of vitamin B₁₂ is a multiple staged process. Vitamin B₁₂ intake through dietary sources initially combines with binding proteins (R-protein) in the saliva. Then it reaches the intestine where pancreatic protease is extracted and it combines with intrinsic factors which contain glycoprotein. Vitamin B₁₂ is absorbed efficiently when it combines with such intrinsic factors. In fact, very little uncombined free vitamin B₁₂ is absorbed. The vitamin B₁₂ and intrinsic factor binds with a specific receptor on the mucosa cells of the terminal ileum and is extracted to the circulation system from the intestine wall. Vitamin B₁₂ is bound with transcobalamin proteins in circulation. The most important transcobalamin protein is transcobalamin II that is the main transporter protein in distributing vitamin B₁₂ to the tissues and liver [5].

Tissues rich in vitamin B₁₂ include parenchymal tissues (above 100 mcg/100 g), fish, muscular organs, dairy products, and egg yolks (1–10 mcg/100 g) [5]. In the West, daily vitamin B₁₂ intake by nonvegetarians is approximately 5–7 mcg/day, which is sufficient for normal homeostasis of body functions [6]. However, vegetarians are at risk of vitamin B₁₂ deficiency because they only consume 0.25–0.5 mcg/day vitamin B₁₂ from their diet [6]. Vitamin B₁₂ is stored well in tissues; for adults, vitamin B₁₂ levels are 2–5 mg and this is mostly located in the liver (approximately 1 mg). Daily loss of vitamin B₁₂ level is 0.1%. When someone no longer obtains vitamin B₁₂ through their diet, depletion of the stored vitamin may take as long as 3–4 years [6].

4. The clinical spectrum of vitamin B₁₂ deficiency

Both vitamin B₁₂ deficiency and folate deficiency cause megaloblastic anemia. In fact, only vitamin B₁₂ deficiency causes neurological change. Additionally, the difference between these two anemia types is the duration between the start of deficiency and symptoms being apparent. The symptoms of B₁₂ deficiency appear within years after the removal of vitamin B₁₂ from the diet whereas the symptoms of folate deficiency are seen within 4–6 weeks.

Vitamin B₁₂ deficiency is one of the most frequent vitamin deficiencies worldwide [7]. So, this deficiency is an extremely important public health issue owing to its serious complications if it is not detected and treated appropriately. Epidemiological studies in this field are, therefore, of great value. There are many epidemiological studies related to vitamin B₁₂ deficiency, which have used different methods and evaluated different disorders accompanying it [8, 9].

5. The epidemiology of vitamin B₁₂ deficiency

Although vitamin B₁₂ deficiency is considered to be a public health problem, its incidence and prevalence are not exactly known. The reasons for this condition are the ethnic and sociocultural differences between societies and their varying dietary habits. The most comprehensive knowledge about vitamin B₁₂ deficiency has been extracted from a review, which was conducted through studies in Africa, America, South-East Asia, Europe, Eastern Mediterranean, and Western Pacific in 2008 [10]. Another review evaluated 41 studies in Latin America and the Caribbean and found that the prevalence of vitamin B₁₂ deficiency was 61% [11].

The data extracted from this study have shown that vitamin B₁₂ deficiency is still a public health problem in these regions. The main reasons for vitamin B₁₂ deficiency are nutritional deficiencies that affect large sectors of the population including vegetarians and their children who are affected during and after pregnancy, the elderly, frequent drug users as well as nutritional deficiency linked to low socioeconomic level [12].

Vitamin B₁₂ deficiency among vegetarians was found to be between 21 and 85% regardless of age, address, type of vegetarianism, and demographics of the individuals concerned (Table 1) [13].

Although it is thought that vitamin B₁₂ deficiency is rarely seen except in strict vegetarians, it is, in fact, commonly seen in all vegetarian groups (lacto-vegetarians, ovo-vegetarians, lacto-ovo-vegetarians, and vegans), as well as among the elderly and for reasons related to medicine and drug use [13–16]. Particularly, vegetarians should take care of protective measures for vitamin B₁₂ deficiency that involve to identify the inadequate vitamin level and to receive supplements containing B₁₂ in necessary condition [13].

Reference	Country	Participants	Rate of deficiency
Dhonukshe-Rutten et al. [17]	Netherlands	N = 73, age range : 9–15 years	41%
Donaldson [18]	USA	N = 49, mean age : 55 years	47%
Geisel et al. [19]	Germany	N = 71, mean age : 53–51 years	58%
Gibson et al. [20]	Ethiopia	N = 99, mean age : 27.8 years	62%
Gilsing et al. [21]	UK	N = 65, mean age : 42.8 years	40%
Hermann et al. [22]	Germany and Netherlands	N = 111, mean age : 46 years	55%

Reference	Country	Participants	Rate of deficiency
Hermann et al. [23]	Oman (German and Asian-Indian immigrants)	N = 96, mean age : 50 years	66% of German and 69% of Indians
Hermann et al. [24]	Germany	N = 34, mean age : 22 years	43%
Hermann et al. [25]	Germany and Netherland	N = 66, mean age : 48 years	73%
Hermann et al. [26]	Germany	N = 114, mean age : 50 years	74%
Kwok et al. [27]	China	N = 119, mean age : >55 years	42%
Kwok et al. [28]	Hong Kong	N = 113, mean age : >55 years	81%
Miller et al. [29]	USA	N = 110, adults (21–70 years) N = 42, children	30% 55%
Obeid et al. [30]	Germany and Netherland	N = 111	Unclear. Figure shows 58% but text reports 85%
Refsum et al. [31]	India	N = 78 (27–55 years)	75%
Rush et al. [32]	New Zealand	N = 6 (9–11 years)	50%
Schneede et al. [33]	Norway	N = 41, infants (11.4–21.9 months)	85.4%
van Dusseldorp et al. [34]	Netherlands	N = 73, adolescents (9–15 years)	21%

Table 1. Studies into vitamin B₁₂ deficiency and vegetarianism [13].

The effects of vitamin B₁₂ on the central nervous system are well known. Lifelong optimal vitamin B₁₂ levels are very important for cognitive function. Vitamin B₁₂ deficiency that is caused by suboptimal vitamin B₁₂ intake and/or changes in absorption due to aging, directly causes neurocognitive deficiencies by neurotoxic effect [35, 36]. Several epidemiological studies about vitamin B₁₂ and the effects of aging on cognitive function have found a correlation between vitamin B₁₂ and cognitive function among middle-aged and elderly cases in Central and Eastern Europe [37].

Another study which researched vitamin B₁₂ prevalence among the middle-aged and elderly in Europe reported vitamin B₁₂ deficiency to be between 5 and 46% [38–40].

Vitamin B₁₂ deficiency resulting from drug use has been shown in several previous studies and indeed is still being discussed. Especially, metformin, which is used to treat diabetes mellitus type-2 (DM), influences vitamin B₁₂ absorption by affecting the calcium-dependent ileal absorption of intrinsic factor-vitamin B₁₂ complex [41, 42].

However, there are studies which defend the contrary [42, 43]. Neither intestinal motility changes nor bacterial over reproduction could be shown in these studies. The relationship between vitamin B₁₂ absorption and metformin was first observed in 30% of type-2 diabetic patients in 1971, and Ting et al. also found a relationship between vitamin B₁₂ and the use of metformin in treatment doses in 2006 [16, 44].

Vitamin B₁₂ deficiency related with the use of metformin was observed among 30 patients, 90% of whom had minor hematological abnormalities, 30% had mild peripheral neuropathy, and two patients had symptomatic anemia and pancythopenia [45].

A meta-analysis, which evaluated six randomized controlled trials, found that using metformin in different doses caused vitamin B₁₂ deficiency and there was a correlation between the metformin dosage and level of vitamin B₁₂ deficiency [46].

Levodopa is another drug which is used for parkinsonism and believed to cause vitamin B₁₂ deficiency. Levodopa has an effect on vitamin B₁₂ levels by affecting the catechol-*O*-methyl transferase pathway and carbidopa metabolism [47–49]. According to these studies, vitamin B₁₂ levels should be checked before planning to use metformin and levodopa for a long-term period.

The prevalence of vitamin B₁₂ deficiency was reported to be very high over the last decade that is why national programs have been established to prevent it [50, 51].

Consequently, vitamin B₁₂ deficiency has been found to be very common in specific groups of the population, and there is a high risk of vitamin B₁₂ deficiency as far as vegetarians, infants, pregnant and breastfeeding mothers, and the elderly are concerned. There is clearly a need to establish both national and prophylaxis programs in order to prevent vitamin B₁₂ deficiency among such cases.

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