Chapter 7

Epidemiology of Vitamin B_{12} Deficiency

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Abstract

Vitamin B_{12} is only synthesized by microorganisms in nature and thus, is obtained by human beings through their diet. Since the most important source of vitamin B_{12} is animal proteins, vegetarians may lack sufficient quantities of this vitamin in their diets. Vitamin B_{12} deficiency may stem from a lower dietary intake, an autoimmune issue related to intrinsic factors or gastrointestinal system diseases resulting in vitamin B_{12} malabsorption. The most important symptoms and findings of severe vitamin B_{12} 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 B_{12} 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 B_{12} 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 B_{12} deficiency and to point out the importance of identifying and treating it.

Keywords: epidemiology, vitamin B_{12}, anemia, deficiency, nutrition

1. Introduction

Vitamin B_{12} 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 B_{12} is animal proteins, vegetarians may lack sufficient quantities of this vitamin in their diets.

Vitamin B_{12} 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 B_{12} malabsorption [2]. The most important symptoms and findings of severe vitamin B_{12} deficiency are anemia and neurological problems. Vitamin B_{12} 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 B_{12} 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 B_{12} deficiency and to point out the importance of identifying and treating it.

2. The metabolism of vitamin B_{12}

The major metabolic pathway of vitamin B_{12} formation is shown in **Figure 1**.

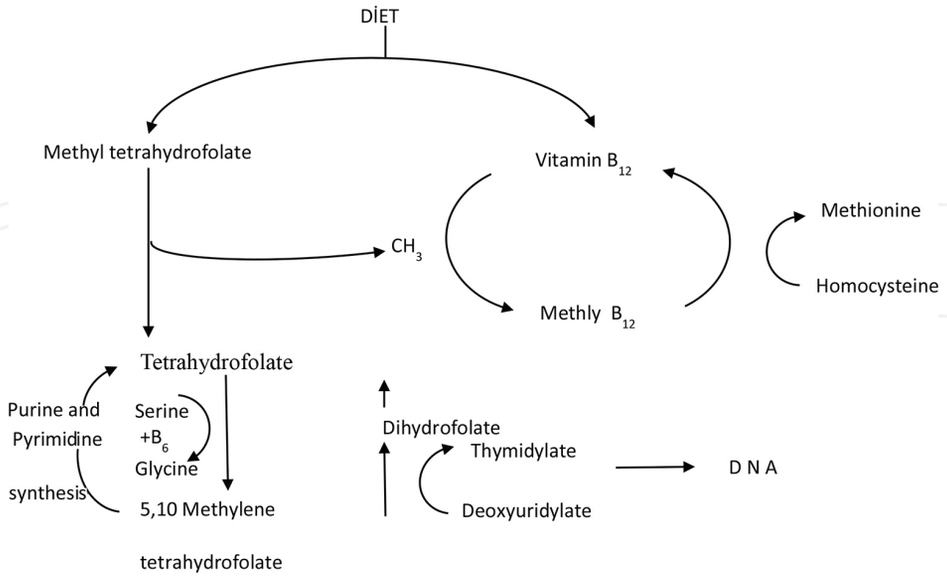

Figure 1. The mechanism of vitamin B_{12}.

Vitamin B_{12} is essential for DNA synthesis in cells. It has two different forms in cells.

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Deoxyadenosyl B_{12} 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 B_{12}, 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 B_{12}

The absorption of vitamin B_{12} is a multiple staged process. Vitamin B_{12} 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 B_{12} is absorbed efficiently when it combines with such intrinsic factors. In fact, very little uncombined free vitamin B_{12} is absorbed. The vitamin B_{12} 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 B_{12} is bound with transcobalamin proteins in circulation. The most important transcobalamin protein is transcobalamin II that is the main transporter protein in distributing vitamin B_{12} to the tissues and liver [5].

Tissues rich in vitamin B_{12} 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 B_{12} 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 B_{12} deficiency because they only consume 0.25–0.5 mcg/day vitamin B_{12} from their diet [6]. Vitamin B_{12} is stored well in tissues; for adults, vitamin B_{12} levels are 2–5 mg and this is mostly located in the liver (approximately 1 mg). Daily loss of vitamin B_{12} level is 0.1%. When someone no longer obtains vitamin B_{12} through their diet, depletion of the stored vitamin may take as long as 3–4 years [6].

4. The clinical spectrum of vitamin B_{12} deficiency

Both vitamin B_{12} deficiency and folate deficiency cause megaloblastic anemia. In fact, only vitamin B_{12} deficiency causes neuorological change. Additionally, the difference between these two anemia types is the duration between the start of deficiency and symptoms being apparent. The symptoms of B_{12} deficiency appear within years after the removal of vitamin B_{12} from the diet whereas the symptoms of folate deficiency are seen within 4–6 weeks.

Vitamin B_{12} 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 B_{12} deficiency, which have used different methods and evaluated different disorders accompanying it [8, 9].

5. The epidemiology of vitamin B_{12} deficiency

Although vitamin B_{12} 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 B_{12} 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 B_{12} deficiency was 61% [11].

The data extracted from this study have shown that vitamin B_{12} deficiency is still a public health problem in these regions. The main reasons for vitamin B_{12} 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 B_{12} 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 B_{12} 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 B_{12} deficiency that involve to identify the inadequate vitamin level and to receive supplements containing B_{12} 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 B_{12} deficiency and vegetarianism [13].

The effects of vitamin B_{12} on the central nervous system are well known. Lifelong optimal vitamin B_{12} levels are very important for cognitive function. Vitamin B_{12} deficiency that is caused by suboptimal vitamin B_{12} intake and/or changes in absorption due to aging, directly causes neurocognitive deficiencies by neurotoxic effect [35, 36]. Several epidemiological studies about vitamin B_{12} and the effects of aging on cognitive function have found a correlation between vitamin B_{12} and cognitive function among middle-aged and elderly cases in Central and Eastern Europe [37].

Another study which researched vitamin B_{12} prevalence among the middle-aged and elderly in Europe reported vitamin B_{12} deficiency to be between 5 and 46% [38–40].

Vitamin B_{12} 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 B_{12} absorption by affecting the calcium-dependent ileal absorption of intrinsic factor-vitamin B_{12} 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 B_{12} 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 B_{12} and the use of metformin in treatment doses in 2006 [16, 44].

Vitamin B_{12} 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 B_{12} deficiency and there was a correlation between the metformin dosage and level of vitamin B_{12} deficiency [46].

Levodopa is another drug which is used for parkinsonism and believed to cause vitamin B_{12} deficiency. Levodopa has an effect on vitamin B_{12} levels by affecting the catechol-*O*-methyl transferase pathway and carbidopa metabolism [47–49]. According to these studies, vitamin B_{12} levels should be checked before planning to use metformin and levodopa for a long-term period.

The prevalence of vitamin B_{12} 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 B_{12} deficiency has been found to be very common in specific groups of the population, and there is a high risk of vitamin B_{12} 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 B_{12} deficiency among such cases.

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