Review Article

Prevalence of vitamin B-12 deficiency among patients with thyroid dysfunction

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Due to the non-specificity of symptoms and possibly severe consequences of untreated vitamin B-12 deficiency, screening is important for at-risk patients to ensure the prompt delivery of treatment. In this review, studies assessing the prevalence of vitamin B-12 deficiency in thyroid dysfunction are evaluated to determine whether regular vitamin B-12 screening is necessary. A literature search was conducted using multiple electronic databases. Only original studies assessing the prevalence of vitamin B-12 deficiency in thyroid dysfunction that reported their findings as percentages of the sample were eligible for inclusion. From a total of 7091 manuscripts generated, 6 were included in this review. The prevalence of vitamin B-12 deficiency in hypothyroidism was reported as 10, 18.6, and 40.5% in three separate studies. The prevalence of deficiency in autoimmune thyroid disease was reported as 6.3, 28, and 55.5% in three studies. The prevalence of vitamin B-12 deficiency in hypothyroidism and autoimmune thyroid disease are reflective of the nutrition status of the population. Autoimmune thyroid disease is also associated with the autoimmune disorders pernicious anemia and atrophic gastritis which may lead to malabsorption of vitamin B-12. Vitamin B-12 screening is recommended upon initial diagnosis with autoimmune thyroid disease and then periodically thereafter. There is not enough evidence to recommend regular screening for patients with hypothyroidism unless the underlying cause is autoimmune thyroid disease.

Key Words: vitamin B-12, vitamin B-12 deficiency, thyroid, autoimmune thyroid disease (AITD), hypothyroidism

INTRODUCTION

Vitamin B-12 (B-12) has the largest and most chemically complex structure of all of the vitamins. Also called cobalamin, B-12 is the only active substance in the body containing an atom of cobalt.[1] B-12 is synthesized by anaerobic microorganisms in the gut of animals, and as a result, is found naturally in foods of animal sources, including meat, fish, poultry, eggs, and dairy. It is also available in the crystalline form in supplements and fortified foods.[2]

Forms of the vitamin include cyanocobalamin and hydroxocobalamin, which may convert to either of the two cofactor forms of B-12: methylcobalamin, the cofactor of methionine synthase, or adenosylcobalamin, the cofactor of L-methymalonyl-CoA.[1] These reactions are essential for the synthesis of nucleic acids, myelination of the central nervous system, and effective erythropoiesis in bone marrow. An adequate B-12 supply is required to maintain these reactions.[3]

B-12 deficiency is associated with a wide range of hematological and neurological, as well as psychiatric and cardiovascular symptoms.[4,5] The classic manifestations of deficiency include glossitis, megaloblastic anemia, and myelin deterioration.[4] Neurological and psychiatric manifestations, which may include myelopathy, neuropathy, impaired memory, depression, and dementia, are particularly serious, as they can occur even with subclinical deficiency and may become irreversible if left untreated. In addition, the increased concentration of homocysteine associated with B-12 deficiency indicates a risk factor for atherosclerotic and thrombotic events.[6]

B-12 has a complicated mechanism of absorption beginning with the vitamin being split from its protein-bound form by pepsin and gastric acid. The free vitamin then binds to R-proteins, or haptocorrins, secreted by the salivary glands for transport from the stomach to the intestinal lumen, where B-12 is released to bind with intrinsic factor. Intrinsic factor, which is secreted by gastric parietal cells, forms a complex with B-12 for transport into the small intestine where it is absorbed at a specific site in the terminal ileum. B-12 then enters the enterocyte and is released to bind with plasma binding proteins transcobalamin I, II, or III for circulation in the blood, delivery to the tissues, or storage in the liver. This process of absorption is complex and is likely to be adversely affected by disorders of the gastrointestinal system.[3,7]

Inadequate dietary intake and malabsorption are the most common causes of B-12 deficiency. Inadequate dietary intake is less likely to occur in developed countries, where foods of animal sources compose a major portion of the diet. Strict vegetarians and the elderly, especially those who are malnourished, are more likely to be defi-

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cient due to inadequate intake.[8]

Conditions such as atrophic gastritis, Helicobacter pylori infection, and long term antacid therapy adversely affect pepsin and/or gastric acid secretion and may lead to malabsorption by impairing the ability to release B-12 from its protein-bound form. Conditions such as atrophic gastritis, partial gastrectomy, and gastric bypass reduce the availability of functional gastric mucosa and the ability to secrete intrinsic factor. Pernicious anemia is an autoimmune disorder that causes atrophy of gastric parietal cells resulting in lack of intrinsic factor and impaired hydrochloric acid secretion. Antibodies, such as anti-gastric parietal cell antibodies and anti-intrinsic factor antibodies, are also present in pernicious anemia.[9]

Vitamin B-12 and thyroid dysfunction

Autoimmune thyroid disease (AITD) encompasses a group of disorders characterized by the immune system's production of antibodies that attack the thyroid gland. AITD is much more common in women than men, and in people between 40 and 60 years of age. Grave's disease and Hashimoto's thyroiditis are common examples. Diagnosis of these disorders is confirmed by the presence of thyroid autoantibodies in serum, which are typically directed against three main thyroid autoantigens: thyroglobulin, thyroperoxidase (TPO), and the thyroid stimulating hormone receptor (TSH).[10,11] Although AITD is the underlying cause in many cases of hypothyroidism, patients with AITD may also present as hyperthyroid or even euthyroid.[10,12]

AITD and autoimmune disorders in general are often associated with the presence of other coexisting autoimmune disorders. The association between AITD and B-12 deficiency is likely related to the presence of the autoimmune disorders atrophic gastritis and/or pernicious anemia, both of which lead to impaired absorption of B-12.[12] Atrophic gastritis has been found to be as prevalent as 35% and 40%, in separate studies, of patients with AITD, the former of which also found a 16% occurrence of pernicious anemia within these same patients.[13,14] The presence of B-12 deficiency was not determined in either of these studies.

Hypothyroidism is a relatively common yet potentially serious hormone disorder that is particularly prevalent in older women. While iodine deficiency is an important cause of hypothyroidism worldwide, the most common cause in the US, where iodine fortification is widespread, is AITD. Other causes include congenital thyroid disorders, previous thyroid surgery, irradiation, use of drugs such as lithium carbonate and amiodarone, and pituitary and hypothalamic disorders.[15] The association between hypothyroidism and B-12 deficiency in the absence of AITD has not been evaluated in detail and may vary according to dietary habits across population groups.[16]

The symptoms of B-12 deficiency in patients with thyroid disorders have not been evaluated in detail. Jabbar et al[16] noted that hypothyroid patients reported symptoms of weakness, numbness, diarrhea, abdominal pain, impairment of memory, parasthesia, dysphagia, dizziness and depression. Numbness, parasthesia, and dysphagia, in particular, were reported most often by hypothyroid patients with B-12 deficiency compared to those with sufficient B-12.[16] Wang et al noted that among 190 patients with thyroid antibodies attending an oral mucosal disease clinic, the most commonly reported symptoms were burning sensation of the tongue, dry mouth, lingual varicosity, and numbness of the tongue.[17]

The goal of this review is to describe the prevalence of B-12 deficiency among patients with thyroid dysfunction, including hypothyroidism and AITD.

METHODS

A literature search was carried out from August to September 2014 using electronic databases including Ebscohost, PubMed, Medline, CINAHL plus, ERIC, Health Source, Nursing and Allied Health Collection, and Nursing/Academic Edition. Combinations of the following search terms were used to identify relevant manuscripts: 'B-12 deficiency', 'cobalamin deficiency', 'thyroid', 'hypothyroidism', and 'hyperthyroidism'. No specific key words were required as inclusion criteria. The titles and abstracts of the resulting publications were then screened to identify manuscripts which report B-12 status among patients with thyroid disorders. The reference lists of relevant manuscripts were also screened to search for additional manuscripts that may not have been identified in the initial database search. Relevant manuscript titles and abstracts were then screened for their eligibility for inclusion.

Only original studies assessing the prevalence of vitamin B-12 deficiency in thyroid dysfunction that reported their findings as percentages of the sample were included in this review. 'Cobalamin deficiency' and 'hypothyroidism' generated 436 manuscripts, 'cobalamin deficiency' and 'hyperthyroidism' generated 117 manuscripts, and 'cobalamin deficiency' and 'thyroid' generated 737 manuscripts. 'B-12 deficiency' and 'hypothyroidism' generated 1641 manuscripts, 'B-12 deficiency' and 'hyperthyroidism' generated 596 manuscripts, and 'B-12 deficiency' and 'thyroid' generated 3564 manuscripts. Altogether, the search terms generated 7091 manuscripts. Titles and abstracts were reviewed for eligibility and 7076 were excluded because they were not specific to the prevalence of vitamin B-12 deficiency in thyroid disorders. Following review of the articles, 15 additional manuscripts were excluded. Two more manuscripts were excluded because they were case studies and 13 studies were excluded for reporting only means or medians without percentages of the sample with deficiency. A total of six studies were eligible for inclusion in this review.

RESULTS

Hypothyroidism

Three of the reviewed studies reported on the prevalence of B-12 deficiency in hypothyroidism. One study reported on the prevalence of deficiency among 116 hypothyroid patients attending an endocrine clinic in Pakistan. The authors determined that B-12 deficiency, defined as <200 pg/mL, was present in 40.5% of the participants. The mean age of participants was 44±13.7 years. The average duration of thyroid disease was not reported.[16] Another study, conducted in Turkey, reported deficiency as 25.6% among 100 patients with subclinical hypothyroidism and 18.6% among 100 patients with overt hypothyroidism.

Deficiency in this study was defined as <189 pg/mL. The average age of participants and duration of thyroid disorder were not reported.[18] In the third study, the prevalence B-12 deficiency in hypothyroid patients in India was reported as 10%.[19] The authors failed to report a criterion for deficiency or the average duration of thyroid disorder. The average age of the sample was 36.5 years.[19]

Autoimmune thyroid disease

Three studies assessed the prevalence of B-12 deficiency among patients with anti-thyroid antibodies and/or diagnosed autoimmune thyroid disease. One study, conducted in Israel, found a 28% prevalence of deficiency among 115 patients with diagnosed AITD. Deficiency in this study was defined as <180 pg/mL. The sample consisted mainly of patients with hypothyroidism and Graves disease, whose duration of disease were not reported. These patients had a mean age of 47±15 years.[20] The second study reported a 55.5% prevalence of deficiency, defined as <200 pg/mL, among 350 patients diagnosed with AITD and attending a hospital in South India. These patients had an average age of 32.2 years and average 2.4 year duration of thyroid disease.[10] A study conducted in Taiwan reported a 6.3% prevalence of B-12 deficiency, defined as <200 pg/mL, among 190 patients with anti-thyroid antibodies.[17] The mean age of the participants was 60.5±11.7 years and the average duration of thyroid disease was not reported.[17]

DISCUSSION

In this review, the prevalence of B-12 deficiency in thyroid disorders was assessed through an evaluation of published studies. One of the main findings is that the prevalence is highly variable among populations. Depending on the criterion used, the prevalence of B-12 deficiency in thyroid disorders ranged from about 6.3 to 55.5%. The range was 9 to 40.5% in hypothyroidism and 6.3 to 55.5% in AITD.[16,18,19]

Hypothyroidism

The prevalence of B-12 deficiency in hypothyroidism was reported as 10, 18.6, and 40.5% in three separate studies conducted in India, Turkey, and Pakistan, respectively.[16,18,19] There was no significant variation in the reported cutoffs of deficiency used or in the factors utilized to include or exclude participants from the study. The authors that reported 10 and 18.6% deficiency noted that this prevalence was similar to that of the general population. For example, Mehmet et al reported that although 18.6% of the overt hypothyroid patients were deficient in B-12, 19.2% of the healthy control group was also B-12 deficient.[16,18] Similar findings were reported by Caplan et al who found that B-12 levels did not differ greatly between patients with hypothyroidism and in control subjects.[21] This study did not report the percent of deficiency.[21]

On the other hand, Jabbar et al reported a 40.5% prevalence of deficiency.[16] This study did not include a control group for comparison. The authors reported that intrinsic factor and gastric parietal cell antibody assays were unavailable, therefore the underlying etiology of the deficiency and possible association with pernicious anemia or atrophic gastritis was unable to be determined. The authors of this study recommended screening for B-12 following diagnosis and then periodically thereafter.[16] The differences noted in these studies may be due to differences in the nutrition status of the populations studies as well differences in the duration of thyroid disorder in the individual participants.

AITD

The prevalence of B-12 deficiency in AITD was reported as 6.3, 28, and 55.5% in the three reviewed studies.[10,17,20] Although the populations and reported percent of prevalence were different, authors of each study concluded that the association between AITD and B-12 deficiency was significant. In these cases, the differences in the prevalence of deficiency may also be due to the differences in diet and nutrition status in the populations studied. Ness-Abramoff et al recommended screening for vitamin B-12 deficiency following initial diagnosis of AITD and then periodically every 3 to 5 years, independent of thyroid status.[20] It was also recommended that serum gastrin be assessed if low B-12 is found, although it is debatable whether or not deficient patients with high serum gastrin levels should undergo gastroscopy to confirm the diagnosis of pernicious anemia or other gastric disorders.[20]

The reviewed studies utilized the serum vitamin B-12 assay to assess B-12 status. Methods of administering and interpreting the assay differ between laboratories. Also, multiple cutoff values for B-12 deficiency were used in different studies included in this review.[23] The sensitivity of serum B-12 as an indicator of B-12 status is also debatable as it does not adequately reflect levels of the vitamin in the tissues, which may be depleted as serum levels are maintained.[13] Due to these constraints, measures such serum methylmalonic acid (MMA) and holotranscobalamin II (holo-TCII), which are recognized as more sensitive indicators of B-12 status, are often used in the place of or alongside serum assays. Since these markers are not readily available in all laboratories, the serum vitamin B-12 assay continues to be utilized.[10]

Early initiation of treatment will prevent the long-term consequences of deficiency, such as cognitive impairment. B-12 deficiency is often treated with parenteral cobalamin administration in the form of cyanocobalamin or hydroxocobalamin. Tissue stores can be quickly replenished through the use of doses of 1000 μg injected intramuscularly, daily for one week, weekly for the following month, and then monthly thereafter.[23] Injections may continue to ensure adequate B-12 status is maintain for life. Oral B-12 therapy at daily doses of 2000 μg has also been reported to be an effective treatment for patients with B-12 deficiency, including those with pernicious anemia and atrophic gastritis. Compliance is an important consideration in determining whether parenteral or oral therapy is the most appropriate the method of treatment.[24]

The non-specificity of the symptoms of B-12 deficiency underscores the need for routine B-12 screening for at-risk patients. Authors of one of the reviewed studies noted that hypothyroid and B-12 deficient patients often have common symptoms. Thus, hypothyroidism may potentially mask B-12 deficiency. These symptoms, which include weakness, lethargy, impaired memory, numbness, and tingling, continued following thyroid

hormone replacement therapy.[10] In addition, neurologic and psychiatric manifestations of deficiency, such as motor disturbances and memory loss, may be mistaken for normal symptoms of aging.[22]

Limitations

The review included studies which assessed B-12 status using only the serum B-12 assay, the accuracy of which has been debated. Other markers, such as MMA, holo-TCII, and tHcy were not utilized. The studies reviewed did not report performing a complete dietary evaluation of participants prior to beginning the study, so the factor of diet in B-12 deficiency and thyroid dysfunction cannot be completely ruled out. Many of the studies of B-12 deficiency in hypothyroidism failed to report the underlying etiology of their participants' hypothyroidism diagnosis. The unreported prevalence of thyroid antibodies or AITD diagnosis may have influenced results in regards to the prevalence and etiology of vitamin B-12 deficiency in specific thyroid disorders. Ambiguity exists regarding whether B-12 deficiency occurs as a result of AITD rather than concomitant hypothyroidism. Lastly, many parameters are increased in hypothyroidism. It is possible that the criteria used to diagnose vitamin B-12 deficiency in euthyroid patients may not apply to hypothyroid patients.

Conclusion

This study assessed the prevalence of B-12 deficiency in thyroid dysfunction, including hypothyroidism and AITD. The reported prevalence of B-12 deficiency in both hypothyroidism and AITD are likely reflective of the nutrition status of the population studied. AITD is also independently associated with the autoimmune disorders pernicious anemia and atrophic gastritis which may lead to B-12 malabsorption. B-12 screening is recommended for patients with AITD at diagnosis and then periodically thereafter. Overall, there is not enough evidence to recommend regular screening for patients with hypothyroidism unless the underlying cause is AITD.

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甲状腺功能紊乱患者中维生素 B-12 缺乏症的患病率

由于维生素 B-12 缺乏症状没有特异性以及不治疗可能引起严重的后果，筛选出有风险的患者以确保及时治疗非常重要。本综述评估了甲状腺功能紊乱患者中维生素 B-12 缺乏症的患病率，以确定定期筛查维生素 B-12 是否必要。在多个电子数据库中进行文献检索。只有在甲状腺功能紊乱患者中评估维生素缺乏症的患病率、并报告了患病率的原始研究才纳入分析。全部查到的 7091 篇文献中，有 6 篇纳入本综述。三个独立的研究报告甲状腺机能减退患者中维生素 B-12 缺乏的发生率分别为 10%、18.6%和 40.5%。三个研究报告自身免疫性甲状腺疾病维生素 B-12 的缺乏率分别为 6.3%、28%和 55.5%。甲状腺功能减退和自身免疫性甲状腺疾病患者中维生素 B-12 的缺乏反映了该人群的营养状况。自身免疫性甲状腺疾病也与自身免疫性疾病恶性贫血和萎缩性胃炎有关，而恶性贫血和萎缩性胃炎又可能导致维生素 B-12 吸收不良。建议在初次诊断自身免疫性甲状腺疾病时筛查维生素 B-12，之后定期检查维生素 B-12。没有足够的证据建议在甲状腺功能减退患者中需定期筛查维生素 B-12，除非甲状腺功能减退的根本原因是自身免疫性疾病。

关键词：维生素 B-12、维生素 B-12 缺乏、甲状腺、自身免疫性疾病、甲状腺功能减退