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Review Article

The epidemiology and importance of vitamin B12 screening in diabetic patients

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ABSTRACT

Peripheral neuropathy is a commonly reported chronic adverse event among diabetes mellitus (DM) patients secondary to poor glycemic control. It might also result secondary to deficiency of vitamin B12, reportedly common among diabetic patients. Deficiency of vitamin B12 might result from prolonged metformin administration in patients with type II DM (T2DM). It might also result from reduced absorption and impaired metabolism-related events in type I DM (T1DM) patients. This occurs secondary to the presence of associated autoimmune disorders. Vitamin B12 deficiency is a commonly encountered condition among diabetic patients, both T1DM and T2DM, with variable etiologies. Our current study discussed the epidemiology and importance of screening of vitamin B12 in these patients. However, our findings show that screening is not commonly practiced in different settings. Therefore, awareness is low about the benefits and complications of this practice. Therefore, further research is encouraged to alleviate the quality of care in diabetic patients. Screening for vitamin B12 deficiency might intervene against any potential complications, including irreversible, painful, and potentially disabling nerve injury. Accordingly, it is recommended that screening should be initiated since the start of metformin administration and every year or when relevant clinical manifestations were reported.

Keywords: Anemia, Vitamin B12 deficiency, Diabetes mellitus, Epidemiology, Management, Screening

INTRODUCTION

Diabetes mellitus (DM) is a common endocrine disorder that is highly prevalent across different global countries. The disease is correlated with a high mortality and morbidity rate that significantly reduce the quality of life of the impacted patients.[1] Controlling blood glucose levels is challenging for many patients because of reduced compliance with the proposed restricting management approaches. Furthermore, management of the disease requires integrating other approaches to managing various associated complications with the condition.[2,3]

Evidence shows that many complications can develop among diabetic patients, probably due to poor glycemic control and medication administration. Some of the reported complications include cardiovascular-related complications and other events as peripheral neuropathy.[4,5] Peripheral neuropathy might also result secondary to deficiency of vitamin B12, reportedly common among diabetic patients. Deficiency vitamin B12 might result from prolonged metformin administration in patients with type II DM (T2DM). It might also result from reduced absorption and impaired metabolism-related events in type I DM (T1DM) patients. This occurs secondary to the presence of associated autoimmune disorders.[6] Previous studies have reported that screening vitamin B12 among diabetic patients would be vital to achieving early intervention against vitamin B12 deficiency and subsequent complications.[7-9] The present literature review aims to shed more light on The epidemiology and importance of vitamin B12 screening in patients with diabetes.

METHODS

This literature review is based on an extensive literature search in Medline, Cochrane, and EMBASE databases which was performed on 27 November 2021 using the medical subject headings (MeSH) or a combination of all possible related terms, according to the database. To avoid missing potential studies, a further manual search for papers was done through Google Scholar while the reference lists of the initially included papers. Papers discussing the epidemiology and importance of vitamin B12 screening in diabetic patients were screened for useful information. No limitations were posed on date, language, age of participants, or publication type.

DISCUSSION

Many previous studies have indicated that T1DM and T2DM patients are at increased risk of having a deficiency of vitamin B12.[10-14] Among the different investigations of T2DM, it has been shown that frequently using metformin is the major etiology of developing deficiency of vitamin B12.[15,16] The studies that reported that metformin is the major reason for developing deficiency of vitamin B12 among diabetic patients estimated that the frequency of this event ranges between 5.8-33%.[13-15] The reported different prevalence rates might be attributed to the different measurements of deficiency of vitamin B12 across the relevant investigations. Furthermore, evidence shows that comparing the public and patients with diabetes is complex because definitions of deficiency of vitamin B12 are hugely variable, and the different demographics and behavioral and cultural beliefs. For example, a previous population-based study in Finnland demonstrated that the frequency of deficiency of vitamin B12 was 12.1% between elderly diabetics (65-100 years old). Moreover, it has been demonstrated that deficiency of vitamin B12 was previously diagnosed in 2.6% of the included patients. The exact rate was also estimated for having vitamin B12 replacement therapy.[17] Religious and cultural beliefs are also important to consider when assessing and evaluating the dificiency of vitamin B12. For instance, previous research from India, where a big part of the population is vegetarian because of their religious beliefs, demonstrated that around two-thirds (67%) of the included participants had been diagnosed with a deficiency of vitamin B12. This was furtherly evidenced that reduced frequency of deficiency of vitamin B12 was remarkably associated with a vegetarian diet when multivariate analysis.[18] However, it should be noted that other investigations in India also demonstrated lower prevalence rates among their populations. For instance, Shobha et al. reported that the estimated frequency of deficiency of vitamin B12 in their study was 16% among <60-year-old participants. However, it has been shown that the frequency significantly increased to 55% when the authors used serum methylmalonic acid to assess vitamin B12 deficiency, being a more sensitive tool.[19]

Together with lifestyle modifications, metformin has been suggested as the primary line of therapy for T2DM due to its favorable effects on reducing blood glucose levels. Moreover, it has been reported to have lower hepatic and renal complications.[20,21] However, despite all of the reported favorable events, it has been indicated that vitamin B12 deficiency has been associated with the long-term administration of metformin. Therefore, DeFronzo et al conducted a previous randomized controlled trial.[22] They found that vitamin B12 reduction was significantly reported among patients with metformin administration by 29% and 22% more than patients with glyburide and placebo administration. Similar findings were also reported among various investigations in the literature, including randomized controlled trials, cross-sectional studies, and single case reports.[10-13,16,23]

It should be noted that different factors usually contribute to the effect of metformin on vitamin B12 deficiency. Some of these factors include the duration of administration, dose of metformin, and patient age.[23-26] This has been furtherly indicated in a previous case-control study in China. The authors found that an odds ratio of 2.9 for vitamin B12 deficiency was associated with one g/day increase in the dose of metformin administration. It has been further estimated that an odds ratio of 2.4 for developing vitamin B12 deficiency for patients using metformin for ≥3 years compared to other patients who administered the drug for a shorter duration.[24] A previous investigation also reported that the negative effect of metformin over reducing vitamin B12 absorption usually takes place since the 4th month after administration.[27] However, another study reported that the clinical manifestation is not usually exhibited until 5-10 years after administration because of the high liver stores of vitamin B12.[28] In addition, different actions were reported for metformin, which reduces the serum levels of vitamin B12. Some of these factors include interacting with the cubulin endocytic receptor, altering levels of intrinsic factor, and inactivation and competitive inhibition of vitamin B12

absorption. Other factors include vitamin B12 secondary to bacterial overgrowth and inhibition of calcium dependant vitamin B12-intrinsic factor absorption at the distal ileum.[28-30]

The epidemiology of vitamin B12 screening and deficiency was also reported among patients with T1DM. However, the main reason for developing these events is probably the development of related autoimmune disorders, common among patients with T1DM. For instance, evidence shows that pernicious anemia is a potential factor for vitamin B12 deficiency. Thus, the disease is an autoimmune disorder that is more prevalent among patients with T1DM than in the general population.[31,32] A previous study in India reported that the prevalence of vitamin B12 deficiency among patients with T1DM ranged between 45.5% and 54% based on the definition of vitamin B12 deficiency. However, it should be noted that the authors reported that vitamin B12 deficiency was not significantly correlated with the level of glycemic control, duration of DM, age, and gender.[33] In addition, many previous studies have reported the presence of specific antibodies that might contribute to the pathology of vitamin B12 deficiency among patients with T1DM. Some of the reported antibodies include parietal cell antibodies, autoantibodies against intrinsic factor types I and II. This is particularly common among patients with HLA-DQA1*0501-B1*0301 haplotype and glutamate decarboxylase-65 antibodies. These antibodies contribute to the development of pernicious anemia among patients with T1DM more than the general population. This significantly leads to reduced vitamin B12 and secondary deficiency.[31,34-36] It has been furtherly demonstrated that the metabolism of vitamin B12 is also impacted by celiac disease and primary autoimmune hypothyroidism. These conditions are reportedly common among patients with T1DM.[37-40] For instance, a previous cross-sectional investigation estimated that primary autoimmune hypothyroidism and celiac disease prevalence was 0.6% and 20.2% among patients with T1DM.[41] Bacterial overgrowth, bowel wall edema, decreased bowel motility, and reduced absorption is all factors that contribute to vitamin B12 deficiency secondary to autoimmune thyroiditis. Other factors also include dyserythropoietic, reduced oral intake, and the presence of autoantibodies against intrinsic factors and parietal cells secondary to reduced thyroid hormones.[37] The epidemiology of vitamin B12 deficiency was also reported among other investigations. It has been demonstrated that celiac disease is prevalent among 16% of T1DM patients.[38] Associated malabsorption is the main factor contributing to developing vitamin B12 deficiency among these patients.[42]

Recent evidence shows that patients with metformin medication should have routine screening against vitamin B12 deficiency to intervene against the development of serious nerve damage. In addition, it has been shown that early detection of the condition might provide good prevention against the development of a potentially-disabling, painful, and irreversible nerve injury. However, previous studies demonstrated that many diabetic patients have vitamin B12 deficiency secondary to metformin use, and the association is dose and duration dependant. Therefore, healthcare authorities should exert more efforts in screening and early identification of diabetic patients with vitamin B12 deficiency to achieve optimal management and reduce adverse events.[43-45] In addition, healthcare authorities should also target increasing knowledge about patients to enhance attitudes and practice care towards administering metformin. However, according to relevant research, not many institutions perform routine screening. Therefore, not many healthcare professionals and patients are aware of the vitality of this step in managing vitamin B12 deficiency.[46]

Evidence shows no current guidelines about the favorable screening events for vitamin B12 deficiency among T1DM and T2DM patients. This is probably secondary to reducing adequate investigations in the literature elaborating the effectiveness of such screening approaches for the targeted population. However, it should be recommended that clinicians should advise their T2DM patients to perform routine screening of vitamin B12 before initiating metformin administration. In the same context, routine annual screening of vitamin B12 should also be indicated for elderly patients using metformin for T2DM, that have clinically worsening manifestations of polyneuropathy, that administer high doses of metformin (≥2 g/day), and that administer metformin for a prolonged period (≥3-4 years). It should be noted that the evidence suggests that routine screening should be specific for these criteria, irrespective of the presence of any other hematological abnormalities.[47] Evidence shows that screening of vitamin B12 deficiency is similar in the general population and when performed for patients with diabetes. For patients with T2DM, targeting serum levels of vitamin B12 should be considered the preliminary step in the screening approach for vitamin B12 deficiency in these patients. It has been shown that the diagnosis of vitamin B12 deficiency should be established at a level of <200 pg/ml. On the other hand, no diagnosis of vitamin B12 deficiency should be considered with a vitamin B12 of >400 pg/ml.[48] It is worth mentioning that measuring serum methylmalonic acid and homocysteine are more specific and sensitive for screening and detecting vitamin B12 deficiency. This approach is best recommended for T2DM patients with baseline serum levels of vitamin B12 of 200-400 pg/ml and abnormal hematological characteristics. The normal range, upon which deficiency of vitamin B12 should be based, includes <0.28 µmol/l and 5-15 µmol/l for serum methylmalonic acid and homocysteine, respectively.[47,49] Screening of vitamin B12 deficiency is also beneficial for patients with T1DM. However, no apparent guidelines were found in the literature about the best practice care and screening of vitamin B12 deficiency in these patients. On the other hand, a previous study recommended that routine screening be conducted at baseline since an annual routine screening follows diagnosis for three years. It has been further recommended that screening approaches be

conducted every five years or in the presence and development of clinical manifestations suggestive of vitamin B12 deficiency.[31] The recommended routine screening for patients with T1DM is probably due to the high prevalence of pernicious anemia and other autoimmune diseases in these patients and the subsequent development of vitamin B12 deficiency. Therefore, the screening in these settings should be conducted via assessing vitamin B12 levels in the high-risk population. Moreover, it is recommended to assess the presence of the antibodies above among patients with autoimmune disorders. Evidence shows that an increased risk of developing vitamin B12 deficiency is associated with these autoantibodies among T1DM patients.[31,50]

CONCLUSION

Vitamin B12 deficiency is a commonly encountered condition among diabetic patients, both T1DM and T2DM, with variable etiologies. Our current study discussed the epidemiology and importance of screening of vitamin B12 in these patients. However, our findings show that screening is not commonly practiced in different settings. Therefore, awareness is low about the benefits and complications of this practice. Therefore, further research is encouraged to alleviate the quality of care in diabetic patients. Screening for vitamin B12 deficiency might intervene against any potential complications, including irreversible, painful, and potentially disabling nerve injury. Accordingly, it is recommended that screening should be initiated since the start of metformin administration and every year or when relevant clinical manifestations were reported.

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