УДК 577.164.16:616.379-008.64

VITAMIN B12 DEFICIT IN PATIENTS WITH TYPE 1 DIABETES MELLITUS

(Review)

Alieva A.V., Khaydarova F.A., Kendjaeva K.Sh.

Republican Specialized Scientific-and-Practical Medical Centre of Endocrinology named after Academician Ya.Kh.Yurakulov under the Ministry of Health of the Republic of Uzbekistan

✓ ***Resume***

The review explains the main possible mechanisms for the development of vitamin B12 deficiency in type 1 diabetes mellitus, as well as issues of active screening and treatment of this vitamin deficiency.

Keywords: vitamin B12, type 1 diabetes mellitus, polyneuropathy, replacement therapy

ДЕФИЦИТ ВИТАМИНА В12 У ПАЦИЕНТОВ С САХАРНЫМ ДИАБЕТОМ I ТИПА

(обзор литератур)

Алиева А.В., Хайдарова Ф.А., Кенджаева К.Ш.

Республиканский специализированный научно-практический медицинский центр эндокринологии имени академика Я.Х.Юракулова при Министерстве здравоохранения Республики Узбекистан

✓ ***Резюме***

В обзоре приведены основные возможные механизмы развития дефицита витамина В12 при сахарном диабете 1 типа, а также вопросы активного скрининга и лечения дефицита данного витамина.

Ключевые слова: витамин В12, сахарный диабет 1 типа, полинейропатия, заместительная терапия

I-ТУР ҚАНДЛИ ДИАБЕТ БЕМОРЛАРДА ВИТАМИН В12 ЕТИШМОВЧИЛЛИГИ

(адабиётлар шарҳи)

Алиева А.В., Хайдарова Ф.А., Кенджаева К.Ш.

Ўзбекистон Республикаси Соғлиқни сақлаш вазирлиги ҳузуридаги Академик Я.Х.Тўрақулов номидаги Республика ихтисослаштирилган Эндокринология Илмий-Амалий Тиббиёт Маркази

✓ ***Резюме***

Адабиётлар шарҳида I-тур қандли диабетда В12 витамини етишмовчилигини ривожланишнинг асосий механизмлари, шунингдек, ушбу витамин етишмовчилигини фаол текшириш ва даволаш масалалари келтирилган.

Калит сўзлар: В12 витамини, I-тур қандли диабет, полинейропатия, алмаштириш терапияси

Relevance

Vitamin B12 is a co-enzyme of two important reactions: 1) the formation of succinic acid from fatty acids and amino acids; 2) the formation of homocysteine and methionine, which are necessary for the synthesis of choline, phosphatidylcholine, as well as adrenaline, creatine and carnitine. In addition, during the second reaction, folic acid is retained in the cell and thus adequate nucleic acid synthesis is ensured.

Vitamin B12 deficiency is biochemically accompanied by an increase in the level of methylmalonic acid (MMK) and homocysteine, and a decrease in the level of methionine and folic acid. Clinical-

ly, vitamin B12 deficiency is manifested by megaloblastic anemia, funicular myelosis, distal paresthesias, increased tendon reflexes, the appearance of ataxia, disorientation, hallucinations and memory impairment [16].

In a cross-sectional study in South India among 90 patients with type 1 diabetes, low levels of vitamin B12 were found in 54% of patients, regardless of gender, age, duration of diabetes and glycemic control [15]. However, the data of Indian authors should be regarded with caution, taking into account the peculiarities of nutrition: vegetarianism is one of the factors contributing to the development of vitamin B12 deficiency, since animal proteins are the main source of this vitamin.

On the other hand, in a study that analyzed the data of the laboratory that determines the level of vitamin B12 from all examined individuals, deficiency was detected in 28% of cases (from referrals to the laboratory), of which only 2% were patients with type 1 diabetes [25].

The increased risk of vitamin B12 deficiency in type 1 diabetes can be explained by the following factors.

1. Autoimmune atrophic gastritis. Patients with type 1 diabetes have 3 times higher prevalence of chronic autoimmune gastritis comparing to the general population (2%). In this disease, production of antibodies to the parietal cells of the stomach and to the Castle internal factor result in block of binding of vitamin B12 to IFC, which disrupts the absorption of vitamin B12. Therefore, pernicious anemia is diagnosed 5-10 times more often among patients with type 1 diabetes comparing to the general population [8].

2. Autoimmune thyroiditis in the stage of hypothyroidism. Vitamin B12 deficiency in patients with autoimmune thyroiditis can be explained by the presence of the same antibodies to the parietal cells of the stomach and Castle factor, a decrease in vitamin intake from food, impaired erythropoiesis due to hypothyroidism, and impaired absorption due to decreased gastrointestinal motility, swelling of the gastrointestinal wall and excessive growth of bacterial flora [14].

3. Celiac disease is a common autoimmune gastrointestinal disease occuring in 1-16% of patients with type 1 diabetes compared to 0.3-1% in the general population. The ingestion of cereal gluten and a number of other proteins is a trigger for this condition in individuals with genetic predisposition. Due to enteropathy, patients often experience physical retardation, chronic diarrhea, and anemia due to malabsorption of folic acid and vitamin B12 [21].

It is important to remember that a variety of neuropathies and the presence of glossitis can be manifestations of vitamin B12 deficiency while the hemoglobin level is within a normal range [25].

So, the question arises, when and how one should screen for vitamin B12 deficiency in patients with type 1 diabetes. Despite the high frequency and potential severity of B12-deficient conditions, there are still no uniform international recommendations regarding the methods of diagnosis and treatment, as well as screening for vitamin B12 deficiency in patients with diabetes. The fact is that the amount of vitamin B12 in the liver is sufficient to ensure the enzymatic reactions in which it participates for 3-5 years. Therefore, the clinical manifestations of vitamin B12 deficiency may be delayed for a specified period of time. A manifestation of the biochemical deficiency of the vitamin itself will be preceded by an increase of homocysteine and methylmalonic acid in the blood – these are the substrates of biochemical reactions with vitamin B12 as a coenzyme.

However, M.J. Rose and N. Berliner (2000) showed that, in the presence of obvious clinical manifestations, vitamin B12 deficiency was also confirmed by laboratory, and only in about 5% of patients with clinical manifestations of vitamin B12 deficiency its blood level was within the lower reference range. In these patients, for the diagnosis of B12 deficiency, the authors recommend additionally testing for homocysteine and methylmalonic acid metabolites in blood serum.

De-Block C. et al. [8] consider that due to the high prevalence of pernicious anemia and subsequent deficiency of vitamin B12 among patients with type 1 diabetes, screening for vitamin B12 deficiency should be performed upon diagnosis, and then annually for the first 3 years, and then every 5 years or more often if there are any clinical indications, since vitamin B12 deficiency can develop at any time. Screening should include an assessment of serum vitamin B12 levels and markers of autoimmune gastric diseases, such as antibodies to parietal cells of the stomach and autoantibodies to Castle's intrinsic factor, especially in patients with type 1 diabetes with antibodies to glutamate decarboxylase (GAD-65) and antibodies to thyroperoxidase (Ab-TPO). The presence of these autoantibodies increases the likelihood of vitamin B12 deficiency [8].

The level of vitamin B12 <200 pg/ml corresponds to a deficit (97% sensitivity) [7], the level of > 400 pg/ml confirms the absence of vitamin B12 deficiency. Measurement of homocysteine and methylmalonic acid (MMA) levels in blood serum is a more sensitive and specific screening approach, especially for patients with borderline vitamin B12 values from 200 to 400 pg/dl and mild hematological signs [12; 24].

So why not start screening for vitamin B12 deficiency by determining homocysteine and MMA? The answer to this question is in the absence of the unified reference values and methods for testing for these substances. The reference value of homocysteine is 5-15 μmol/L. In addition, it is very important to comply with the requirements for collection and storage of blood samples. The blood sample should be stored in the refrigerator, and centrifugated within 2 hours after sampling [24].

The reference values of MMA range from 0.27 to 0.75 μmol/L, depending on the laboratory. An increase in MMA per se is not strictly specific for vitamin B12 deficiency. The level of MMA may increase in patients with chronic kidney disease, hemoconcentration and the syndrome of excessive bacterial growth in the small intestine. Despite these limitations, a pronounced increase in MMA (> 0.75 μmol/L) is typical precisely for vitamin B12 deficiency. Price is also of no less importance: MMA is tested for by the expensive method of gas chromatography or mass spectrometry, which limits its widespread use [24].

Treatment for vitamin B12 deficiency does not depend on its etiology. Although there are no unite recommendations for treatment yet. De-Block C. et al. note that in young patients with type 1 diabetes and vitamin B12 deficiency, replacement therapy with intramuscular injection or oral administration of vitamin B12 at a dose of 100 μg for a week, then 1 time per month, is sufficient. In severe cases, parenteral or oral administration of vitamin B12 in dose of 1000 μg/day is recommended for a week, followed by the same dose weekly for 1 month, and then monthly [8].

Concomitant folate deficiency should be treated with oral replacement at a dose of 5 mg per day for 1-4 months. Folate should not precede the correction of vitamin B12 deficiency, as this can lead to the progression or worsening of neurological manifestations [10].

Vitamin B12 replacement therapy leads to symptom relief in patients with severe diabetic neuropathy. A meta-analysis showed a significant improvement of somatic symptoms such as pain and paresthesia when taking vitamin B12 as monotherapy or in combination with a complex of B vitamins. It also showed an improvement in autonomic symptoms when using vitamin B12 as monotherapy [2]. An increase in cobalamin levels for every 25 pmol/L was associated with a 6% reduction in the risk of neuropathy (RR 0.94, 95% CI 0.88–1.00, p = 0.034) [11].

An Iranian randomized blinded clinical study performed among 100 patients with diabetic neuropathy showed a decrease in pain and paresthesia score when using vitamin B12 compared to nortriptyline [23].

Conclusion

Is it necessary to take vitamin B12 supplementation in type 1 diabetes before the development of clinical manifestations of its deficiency? There are currently no clinical recommendations for the prophylactic use of vitamin B12. There is also no data on the optimal prophylactic dose.

This emphasizes the need for further studies to determine the optimal dose and frequency of prophylactic intake of vitamin B12 in patients with diabetes.

Thus, clinical and biochemical deficiency of vitamin B12 is widespread among patients with type 1 diabetes. Further extensive well-planned studies are required to screen for vitamin B12 deficiency, to reveal the optimal regimen and dose of its supplementation among patients with type 1 diabetes to create uniform clinical recommendations for practitioners. In patients with diabetes who have specific risk factors for vitamin B12 deficiency, and these are patients with type 1 diabetes with concomitant autoimmune thyroiditis, atrophic gastritis and celiac disease, it may be advisable to screen for vitamin B12 deficiency annually using more sensitive methods such as testing for homocysteine and methylmalonic acid levels in blood serum.

LIST OF REFERENCES:

1. Al-Ameri G., Alkadasi M., E. Ali Hassan Al-shuga, Sallam A. et al. Association of Chronic H. pylori infection with Pernicious Anemia in Ibb. //The Journal of Medical Research. 2018; 4 (2): 93–97.

2. Alvarez M., Sierra O., Saavedra G., Moreno S. Vitamin B12 deficiency and diabetic neuropathy in patients taking metformin: a cross-sectional study. //Endocr Connect. 2019; 8(10): 1324-1329.
3. Andres E., Serraj K. Optimal management of pernicious anemia. //Journal of Blood Medicine. 2012; 3: 97–103.
4. Aslinia F., Mazza J., Yale S. Megaloblastic Anemia and Other Causes of Macrocytosis. //Clinical Medicine & Research. 2006; 4: 236–241.
5. Bell D. Metformin-induced vitamin B_{12} deficiency presenting as a peripheral neuropathy. //South Med J. 2010; 103: 265–267.
6. Ben Ahmed H., Bouzid K., Hassine M. et al. Prevalence of non-conventional cardiovascular risk factors in Tunisian diabetics. //Presse. Med. 2014; 43(1): e9-e16.
7. Carmel R., Sarrai M. Diagnosis and management of clinical and subclinical cobalamin deficiency: advances and controversies. //Curr Hematol Rep 2006;5(1):23–33.
8. De-Block C., De-Leeuw H., Van-Gaal L. Autoimmune Gastritis in Type 1 Diabetes: A Clinically Oriented Review. //J Clin Endocrinol Metab. 2008; 93: 363–371.
9. Devalia V., Hamilton M., Molloy A., British Committee for Standards in Haematology. Guidelines for the diagnosis and treatment of cobalamin and folate disorders. //Br J Haematol. 2014; 166(4): 496–513.
10. Fedosov S., Brito A., Miller J. et al. Combined indicator of vitamin B12 status: modification for missing biomarkers and folate status and recommendations for revised cut-points. //Clin Chem Lab Med 2015; 53(8): 1215–1225.
11. Hansen CS, Jensen JS, Ridderstrale M et al. Vitamin B12 deficiency is associated with cardiovascular autonomic neuropathy in patients with type 2 diabetes. //J Diabetes Complications 2017; 31 (1): 202–8.
12. Harrington D. Laboratory assessment of vitamin B12 status. J Clin Pathol. 2017; 70(2): 168-173.
13. Hunt A., Harrington D., Robinson S. Vitamin B_{12} deficiency. //BMJ. 2014; 349: g5226.
14. Joffe B., Distiller L., Landau S. et al. Spectrum of Autoimmune Disorders in Type 1 Diabetes – A Cross-Sectional Clinical Audit. //J Diabetes Metab. 2010; 1: 112.
15. Koshy A., Kumari J., Ayyar V., Kumar P. Evaluation of serum vitamin B_{12} levels in type 1 diabetics attending a tertiary care hospital: a preliminary cross sectional study. //Indian Journal of Endocrinology and Metabolism. 2012;16:S79–82.
16. Langan R., Goodbred A. Vitamin B12 Deficiency: Recognition and Management. //Am Fam Physician. 2017; 96(6): 384-389.
17. Loikas S., Koskinen P., Irjala K. Vitamin B12 deficiency in the aged: a population-based study. Age and Ageing. 2007; 36: 177–183.
18. Mahajan R., Gupta K. Revisiting metformin: annual vitamin B12 supplementation may become mandatory with longterm metformin use. //J Young Pharm. 2010; 2: 428–429
19. Marwan A. Metformin and Vitamin B12 Deficiency: Where Do We Stand? //J Pharm Pharm Sci. 2016; 19 (3): 382–398.
20. Mazokopakis E., Starakis I. Recommendations for diagnosis and management of metformin-induced vitamin B_{12} (Cbl) deficiency. Diabetes research and clinical practice. 2012; 97: 359–367.
21. Selimoglu M., Karabiber H. Celiac Disease- Prevention and Treatment. //J Clin Gastroenterol. 2010; 44: 4–8.
22. Shobhaa V., Tareya S., Singh R. Vitamin B12 deficiency and levels of metabolites in an apparently normal urban south Indian elderly population. //Indian J Med Res. 2011; 134: 432–439.
23. Talaei A., Siavash M., Majidi H., Chehrei A. Vitamin B12 may be more effective than nortriptyline in improving painful diabetic neuropathy. //Int J Food Sci Nutr. 2009; 60: 71–76.
24. Красновский А.Л., Григорьев С.П., Алёхина Р.М., Ежова И.С., Золкина И.В., Лошкарева Е.О. Современные возможности диагностики и лечения дефицита витамина В12. //Ж.Клиницист 3-2016 том 10. - С.15-25 DOI: 10.17 650 / 1818-8338-2016-10-3-15-25
25. Перекатова Т.Н., Остроумова М.Н. Еще раз о дефиците витамина В12. //Ж. Клиническая онкогематология. Том 2. Номер 1. 2009. С.185-195.

Entered 09.04.2022