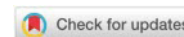


VITAMIN B12 DEFICIENCY IN CONTINUOUS METFORMIN TREATMENT

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Abstract: As we know type 2 diabetes is a global disease with many complications. The long-term treatment with metformin as a first line of therapy has been proven to cause low levels of cobalamin /vit. B12/. The main purpose of this analysis is to show the frequency of vitamin B12 deficiency among patients treated with biguanides. The RSNC/regional non-profit association/ "Diabetes Care" in Burgas conducted the study. Patients on metformin treatment for 5 to 10 years were included in it. From January to September 2022 was the period when all the data was collected. Information on the duration of metformin treatment was collected through an anamnesis. All patients were tested for vitamin B12 levels and the average value was found to be < 145 pmol/L - according to certified laboratory reference values - from 145 to 569 pmol/l. All participants in this study had laboratory evidence of anemia and were deficient in this vitamin. Vitamin B12 deficiency is preventable and these data show us the need of regular screening in patients on long-term treatment with metformin. This will allow the identification of patients with vitamin deficiency and the addition of treatment with it or/and discontinuation of metformin treatment.

Keywords: Vitamin B12, deficiency, diabetes mellitus type 2, metformin

Field: Medical Sciences and Health

INTRODUCTION

Vitamin B 12/cyanocobalamin/is a complex organic molecule consisting of a centrally activated cobalt atom connected by a covalent nitrogen bond to a tetrapyrrole ring and to a cyanide group. Vit. B12 has two active coenzymes: methylcobalamin/with an important role for DNA synthesis/ and 5-deoxy-adenosylcobalamin, responsible for myelinization. Microorganisms/bacteria and fungi/ are the main sources of Vit.B12 in nature. For plants and animals, vitamin B12 is only of exogenous origin. The following products are relatively richer in content: meat, eggs, milk, raw liver, as well as fermenting plant products such as beer, brewer's yeast, pickles. The human body contains only 5 mg. the liver appears to be the largest depot of vitamin B12.(Grudeva P, 2020)

Vitamin B12 ingested with food in the acidic environment of the stomach is released from the proteins and binds to two specific ligands - 1/c intrinsic factor/IF/- glycoprotein produced by the parietal cells of the fundus and 2/c proteins R, called cobaltophilins. which are contained in the gastric juice. The IF-vitamin B12 complex is absorbed in the distal ileum. After passing through the enterocyte, vitamin B12 enters the blood, bound to a protein - transcobalamin, synthesized by the endothelial cells of the vessels. This complex reaches the bone marrow, where it enters the cells by endocytosis. Vit. B12 accumulates as a reserve mainly in the liver/about 2-3 g./- quantities sufficient for 3-4 years. Daily needs are 1-2 mg.(Kerticova S.,2000).

Vitamin B12 is a key micronutrient responsible for DNA methylation and has diverse metabolic roles ranging from lipid metabolism to endothelial dysfunction (McNulty H, Pentieva K, Hoey L, Ward M, 2008). Metformin treatment is the first-line treatment in patients with type 2 diabetes in combination with lifestyle modification according to the current recommendations of the American Diabetes Association (ADA), European Association for the Study of Diabetes (EASD), and the American Association of Clinical Endocrinologists/American College of Endocrinology. These recommendations are based mainly on its glucose-lowering effects, its relatively low cost, and few side effects. Furthermore, unlike other antidiabetic medications, metformin appears to be neutral with respect to body weight. Metformin is a safe treatment for type 2 DM in the over 60 age group(Stanchev P. et al.,2021).

Metformin is suitable as initial therapy in newly diagnosed type 2 diabetes mellitus, in the absence of contraindications.

Positive effects:

- suppresses endogenous hepatic glucose production
- weight neutral with chronic use, with potential for some weight reduction

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- does not increase the risk of hypoglycemia;
- beneficial effects on lipid indicators; -there is evidence of cardiovascular benefits;
- effects regarding protection from carcinogenesis have been established.

Side effects - from the gastrointestinal tract - metallic taste, nausea, vomiting, diarrhea, bloating, flatulence; may lead to low vitamin B12 levels, necessitating periodic monitoring and replacement at low levels, especially in patients with anemia and neuropathy. Contraindications: all conditions associated with severe tissue hypoxia and ischemia - severe heart failure, acute stage of myocardial infarction, liver failure, CKD IV degree (Borisova AM, 2019). It is used as monotherapy or in combination with other drugs (Hirst J.A, Farmer A.J, Ali R, Roberts N.W, Stevens R.J, 2012). However, one of its side effects is a decrease in vitamin B12 levels. There are several pathophysiological theories about how metformin decreases the absorption of vitamin B12. According to one of them, it changes the distribution in the tissues and the metabolism of B12. Also, the liver accumulates B12, as a result of which its circulating levels in the serum decrease (Aroda et al, 2016). Another theory is that metformin slows down the absorption of glucose, which slows down gut motility and allows bacterial overgrowth, which interferes with the complex of intrinsic factors and reduces the absorption of B12 (Beulens et al., 2015). However, the most plausible and generally accepted cause of vitamin B12 deficiency due to metformin-induced malabsorption is interference with calcium-dependent binding of the inducing factor-vitamin B12 complex to the receptor in the terminal ileum (Bauman, W.A., Shaw, S., Jayatilake, E., Spungen, A.M., Herbert, V., 2000). Another mechanism by which B12 deficiency can be reached is by displacement of calcium from the ileal mucosa by metformin. As a trace element, calcium is required for the B12-intrinsic factor complex. (William, A. and all, 2000). Different cut-off values invariably result in underestimation or overestimation of cases of vitamin B12 deficiency. Vitamin B12 deficiency is defined as serum levels < 148 pmol/L. Levels between 148 and 221 pmol/L are considered borderline and suggest marginal deficiency. (Green R et al, 2017). Metformin reduces circulating B12 levels by about 25% (Beulens JW et al, 2014) Another study in Africa showed that the prevalence of vitamin B12 deficiency, defined by levels <150 pmol/L, in metformin-treated T2DM patients was 28.1%. The authors recommend regular screening for vitamin B12 deficiency in patients on long-term metformin therapy (Ahmed, M.A., Muntingh, G., and Rheeder, P. 2016). In a study conducted in Ghana, the prevalence of vit. B12 deficiency was reported to be 32.1%. The authors reported the negative impact of long-term metformin therapy, its higher daily dose and high body fat content, which increase the possibility of manifestation of cyanocobalamin deficiency. In diabetics taking metformin in a total daily dose of ≥ 1500 mg, for a period of ≥ 6 years, the research team recommends regular and systematic monitoring of vitamin B12 levels (Laing, E.F. et al, 2019). Other authors estimate the deficiency of vitamin B12 at 14.1%. Compared to diabetics without metformin in therapy, the prevalence of its deficiency is significantly higher in the group of patients treated with it. After 4.9 years of metformin use, the authors report, that the chances of developing neuropathy or anemia cannot be predicted (Groot-Kamphuis, D.M. et al, 2013). Among the Bulgarian population of patients with type 2 diabetes mellitus, the status of vitamin B12 was investigated. In the studied population of 308 diabetics, deficiency was found in 34%, low-normal levels in 28%. 37.7% of the group of patients treated with metformin were deficient in vitamin B12. 18% of diabetics on non-metformin therapy were also found to be B12 deficient. The mean level of vit. B12 in the group receiving metformin was 178 pmol/l, and in the group without metformin 235 pmol/l. It turns out that the level of vit. B12 correlates with the average dose of metformin, and not with the duration of therapy. Each increase in the dose of metformin by 250 mg. increases the risk of vitamin B12 deficiency by 15% (Chakarova N. et al., 2019). The influence after a 6-month treatment with metformin on the serum levels of vitamin B12 in type 2 diabetics was also investigated by another Bulgarian group. 18 patients were studied - 9 women and 9 men, with an average age of 47.6 years with an average duration of diabetes of 6.1 years. Plasma vitamin B12 levels were measured at baseline and after 6 months of treatment with an average daily dose of 1500 mg metformin. Regarding vit B12, a certain decrease was registered, which, however, could not reach statistical significance/ from 233.3 to 207.4 pmol/l. Changes in erythrocytes and serum iron were observed. (Boyanov, M., Boneva, Zh., Tsoncheva, A., Protich, M., 2003)

Considering the consequences of possible vitamin B12 deficiency, such as megaloblastic anemia and polyneuropathy, screening among patients treated with metformin is appropriate. Follow-up testing is also appropriate. This would identify patients with insufficient serum levels of vitamin B12 and allow for prompt correction of the deficiency. With this in mind, a group of scientists developed a list of criteria that aims to cover the high-risk group of patients treated with metformin - their screening and periodic follow-up. The proposed criteria include:

- guiding clinical signs for vit. B12 deficiency
- patients with type 2 DM with available comorbidities - diabetic peripheral neuropathy, autonomic

neuropathy, or both

- metformin treatment lasting more than 5 years
 - the patient over 65 years old
 - minimum six months of metformin treatment at a daily dose ≥ 1500 mg and high total cumulative exposure
 - antacid medications administered together with metformin for a period of ≥ 12 months
 - presence of other diseases and risk factors leading to an increased risk of vitamin B12 deficiency.
- (Infante, M., et al. 2021).

MATERIAL AND METHODS

The main purpose of this study was to evaluate the vitamin B12 deficiency and the presence of anemic syndrome in all tested patients. The medical records and laboratory tests were conducted on sixty-one participants who were on treatment with metformin for a period between 5-10 years. All the 61 participants were Caucasian- 41 women and 20 men, respectively.

Regardless of gender, the average age of the participants was 78.73 years/ from 48 years. to 93 years/. For women it is 80.26 years/ from 48 years to 92 years/, and for men it is 75.6 years/ from 50 years to 93 years/.

RESULTS

After processing the data, it was found that the average level of vit.B12 in the studied group of patients was 112.99 pmol/L

DISCUSSION

Vitamin B12 deficiency is less well known and can be a reason for health consequences, such as megaloblastic anemia and peripheral neuropathy. Considering the above data, we are obliged to focus on the necessity of early screening, routine examination, identification and timely correction of the deficiency of this vitamin in diabetics with metformin treatment. Low levels of vitamin B12 is a highly prevalent, yet easily correctable factor that would lead to improved patient care.

CONCLUSION

The present analysis also has some serious limitations, such as the small number of examined patients, the majority of whom fall into the age range over 75 years. Larger studies with more patients are needed to determine whether the deficiency of vit. B12 is a chance finding, whether it is the result of long-term metformin use or it is result of dietary factors.

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