LOW LEVELS OF SERUM CYANOCOBALAMIN IN A METFORMIN-TREATED PATIENT. CASE REPORT AND COMPARISON WITH LITERATURE DATA

Anca-Monica Strugaru1*, Gina Botnariu3, Cristina Tuchiluş2, Ecaterina Anisie4, Luminiţa Agoroaei1, Ioana-Cezara Grigoriu1, Elena Butnaru1

University of Medicine and Pharmacy “Grigore T. Popă”-Iași
Faculty of Pharmacy
1. Department of Toxicology
2. Department of Microbiology
Faculty of Medicine
3. Department of Medical Sciences (I)
“Sf. Spiridon” County Clinical Emergency Hospital Iasi
4. Medical Analysis Laboratory

* Corresponding author. E-mail: anca-monica.strugaru@umfiasi.ro

LOW LEVELS OF SERUM CYANOCOBALAMIN IN A METFORMIN-TREATED PATIENT. CASE REPORT AND COMPARISON WITH DATA FROM LITERATURE (Abstract): Metformin is a widely used oral antidiabetic biguanide compound. According to the literature, metformin may lower the serum cyanocobalamin levels. We present the case of a 71-old-male treated with metformin for 15 years. When presenting to a periodic checkup, low serum cyanocobalamin levels were found. Laboratory tests showed levels below normal range for hemoglobin (12.7 g/dL) and hematocrit (37.8 %). After patient reevaluation, a change in antidiabetic treatment will be considered if metformin will be found the cause of low serum cyanocobalamin levels. Other cases reported in the literature support this hypothesis, justifying the study of the influence of metformin therapy on serum vitamin B₁₂ levels in patients diagnosed with diabetes. The influence of patient age, metformin dosage, duration of treatment and time since diabetes diagnosis on serum levels of vitamin B₁₂ also need to be determined. Keywords: METFORMIN, CYANOCOBALAMIN, DIABETES.

Cobalamin or vitamin B₁₂ refers to a group of cobalt-containing compounds that have biological activity in humans. Vitamin B₁₂ is required for two essential enzyme reactions: (a) homocysteine methylation to methionine, and (b) isomerization of methylmalonyl coenzyme A (CoA), which is produced by degradation of amino acids and fatty acids with odd number of carbon atoms (1). These processes are affected when vitamin B₁₂ levels drop in the body. There are summarized the main causes of vitamin B₁₂ deficiency (tab. I).

An important indicator for vitamin B₁₂ status in the body is serum vitamin B₁₂ level, expressed as pmol/L or pg/mL. According to Mazokopakis and Starakis (2), serum vitamin B₁₂ levels can be interpreted as follows:

• >300 pg/mL (>221 pmol/L): normal; B₁₂ deficiency is unlikely (1-5%);

• 200–300 pg/mL (148–221 pmol/L): borderline; B₁₂ deficiency is possible;

• <200 pg/mL (<148 pmol/L): low; con-
sistent with vitamin B$_{12}$ deficiency (specificity of 95-100%).

Metformin (1,1-dimethylbiguanide hydrochloride) belongs to the biguanide class of antidiabetic drugs. Metformin has been used in Europe and Canada for over 50 years (since 1957). The recommendations of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) suggest that metformin therapy should be initiated (unless contraindicated) together with lifestyle changes at the time of diabetes mellitus diagnosis (2,4).

### TABLE I

**Causes of cyanocobalamin deficiency (2,3)**

<table>
<thead>
<tr>
<th>The causes of cyanocobalamin deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastric abnormalities</strong></td>
</tr>
<tr>
<td>Pernicious anemia, malabsorption of vitamin B$_{12}$, bariatric surgery, gastritis, metaplastic autoimmune gastric atrophy, infection with <em>Helicobacter pylori</em></td>
</tr>
<tr>
<td><strong>Diseases of the small bowel</strong></td>
</tr>
<tr>
<td>Malabsorption syndrome, ileal bypass, Crohn's disease</td>
</tr>
<tr>
<td><strong>Pancreatic insufficiency</strong></td>
</tr>
<tr>
<td>Strict vegetarian diet, vegetarian diet in pregnancy</td>
</tr>
<tr>
<td><strong>Agents that prevent absorption</strong></td>
</tr>
<tr>
<td>Neomycin, metformin, proton pump inhibitors, H$_2$ receptor antagonists, colchicine, p-amino salicylic acid, N$_2$O anesthetic</td>
</tr>
<tr>
<td><strong>Misuse</strong></td>
</tr>
<tr>
<td>Congenital transcobalamin II deficiency</td>
</tr>
<tr>
<td><strong>Biological competition for vitamin B$_{12}$ in the diet</strong></td>
</tr>
<tr>
<td>Bacterial overgrowth syndromes, tapeworm infestation</td>
</tr>
</tbody>
</table>

However, long-term treatment with metformin is a known cause of cyanocobalamin deficiency, as evidenced within the first 10-12 years after it started to be used, and is also associated with decreased serum folate concentration (not deficiency). Decreased levels of vitamin B$_{12}$ and folate can cause megaloblastic anemia, and increased serum total homocysteine levels, an independent risk factor for cardiovascular diseases particularly in patients with type 2 diabetes. Also, metformin may cause exacerbation of peripheral neuropathy in patients with type 2 diabetes mellitus, which have low vitamin B$_{12}$ levels and elevated fasting total homocysteine and methylmalonic acid levels. Moreover, no reference ranges for the screening for metformin-induced vitamin B$_{12}$ deficiency based on serum vitamin B$_{12}$ level have been established.

The relationship between metformin and reduced vitamin B$_{12}$ absorption was described in 1969, but the first case of megaloblastic anemia induced by vitamin B$_{12}$ deficiency induced by the long-term treatment with metformin (8 years) was reported in 1980 (2).

Subsequently, other cases of low vitamin B$_{12}$ levels in patients treated with metformin (5-9) have been reported, and studies analyzing the influence of metformin on serum cyanocobalamin levels have been conducted (10).

### CASE REPORT

A 71-year-old patient was referred in May 2015 for a routine check to the Day Care Unit for Diabetes, Nutrition and Metabolic Diseases of the Iasi County "St. Spiridon" Emergency Hospital. The patient
was known with type 2 diabetes since 1991, and was on antidiabetic medication (fig. 1). On admission day, the main diagnosis was complicated, unbalanced insulin-treated type 2 diabetes and secondary diagnoses were diabetic peripheral sensorimotor polyneuropathy, moderate non-proliferative diabetic retinopathy in right eye, operated (panretinal photocoagulation) proliferative diabetic retinopathy in the left eye (vitrectomized eye), grade 3 essential hypertensions with very high cardiovascular risk, grade 1 abdominal obesity, chronic leg venous insufficiency.

Oral medication at discharge is metformin 1000 mg x 3/day, nebivolol 5 mg ½ tablet/day, rilmenidine 1 mg/day, nifedipine 30 mg/day, diosmin 500 mg x 2/day, clopidogrel 75 mg/day, spironolactone 50 mg + furosemide 20 mg/day, vinpocetine 10 mg x 2/day, desloratadine 5 mg/day.

For this patient the serum vitamin B₁₂ level was below the detection limit of the apparatus (<150 pg/mL). This test was performed on a Immulite 2000 Vitamin B12, with a solid phase competitive enzyme immunoassay based on chemiluminescence. Normal range for serum vitamin B₁₂ was 193-982 pg/mL. According to case history, the patient has been on metformin treatment for 15.5 years.

In addition, the test results show levels below the normal range for hemoglobin (12.7 g/dL) (normal range 13.0-17.3 g/dL) and hematocrit (37.8%) (normal range 39-51%). The patient will be evaluated again and a change in antidiabetic treatment will be considered in case metformin is confirmed as the cause of low serum vitamin B₁₂ levels.
DISCUSSION

This may be a case of metformin-induced vitamin B₁₂ deficiency. In support of this hypothesis come the secondary diagnoses, which can be triggered and developed by vitamin B₁₂ deficiency-induced neuropathy (diabetic peripheral sensorimotor polynoepathy, chronic venous insufficiency).

In the literature (5,6,8) different side effects associated with metformin therapy are described. Besides lactic acidosis, a serious but rare adverse effect, metformin therapy may also cause deep vein thrombosis, vitamin B₁₂ deficiency, abnormal bowel transit. Melgar et al. (5) reported the case of a 65-year-old male, diagnosed with type 2 diabetes mellitus, dyslipidemia, hypertension and benign prostatic hyperplasia. The patient presented in the last 6 months’ changes in bowel movements, alternating episodes of diarrhea and constipation. The patient was complaining of abdominal pain, asthenia, diarrhea, and weight loss. The test results showed a vitamin B₁₂ level of 166 pg/mL (normal range 197-866 pg/mL). Hemoglobin and folic acid were within normal ranges and tumor markers and intrinsic anti-factor antibody were negative. A month after discontinuation of metformin repeat analyzes showed vitamin B₁₂ level within normal ranges.

Liu et al. (8) described the case of an 82-year-old female with type 2 diabetes for 20 years. On admission she was on metformin 1 g/day and famotidine. Tests showed a blood hemoglobin level of 10.3 g/dL, vitamin B₁₂ 131 pg/mL, normal folate levels and negative intrinsic anti-factor antibody. The discontinuation of metformin and vitamin B₁₂ supplementation led to improvements in her general status and hematologic abnormalities.

In none of these reported cases a relationship between the daily metformin dose and the intensity of adverse effects could be established. Sato et al. (11) tried to find a correlation between metformin concentration and vitamin B₁₂ serum levels, but the results were limited by the relatively small number of patients enrolled in the study.

Stargrove et al. (12) noted that metformin therapy reduces serum vitamin B₁₂ absorption and vitamin B₁₂ levels through the inhibition of intrinsic factor (IF). He also found that the B₁₂-intrinsic factor complex uptake by ileal cell membrane receptors is known to be calcium-dependent, and metformin affects calcium-dependent membrane action. The results of different studies confirmed the decrease in vitamin B₁₂ and folic acid levels following treatment with metformin (10-30 % of cases). These effects are reversible upon discontinuation of biguanide therapy and calcium supplementation.

CONCLUSIONS

From our point of view, the reported case illustrates that vitamin B₁₂ deficiency can be a side effect of metformin therapy, although it has many limitations, such as the presence of other causes of vitamin B₁₂ deficiency in the pathology of the patient.

We will further study the effect of metformin therapy on serum vitamin B₁₂ levels in patients diagnosed with diabetes. In addition, we will examine the influence of patient age, metformin dose, duration of treatment and time since diabetes diagnosis on vitamin B₁₂ serum levels.

ACKNOWLEDGEMENTS

This paper was published under the
frame of European Social Found, Human Resources Development Operational Pro-
gramme 2007-2013, project no. POSDRU/159/1.5/136893.

REFERENCES


