# Vitamin B12 Levels in Children After Metformin Treatment

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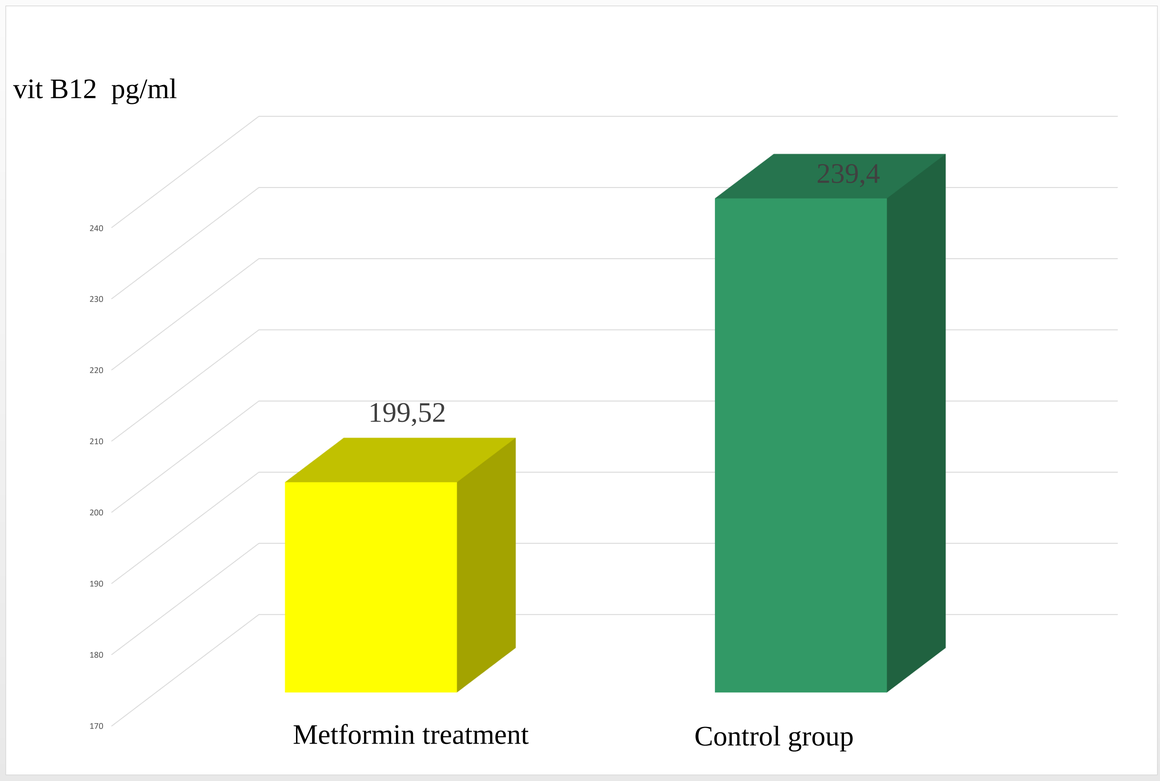
**Introductions and objectives**: Vitamin B12 is a water soluble vitamin that plays a fundamental role in DNA synthesis, optimal haemopoesis and neurological function. Vitamin B12 is an essential micronutrient that is required for optimal hemopoetic, cardiovascular and neuro-cognitive functions. Factors that reduce vit B12 levels include insufficient dietary intake, malabsorption due to chronic atrophic gastritis, pernicious anemia, celiac disease, chronic pancreatitis and drugs like Metformin and proton pump inhibitors (PPIs).
As first line therapy, Metformin is the most frequently prescribed medication in cases of hyperinsulinism and type 2 diabetes (1). It is one of a few antihyperglycaemic agents, associated with improvement in cardiovascular morbidity and mortality. Metformin acts by reducing the amount of glucose, produced by the liver, and increasing patient's sensitivity to insulin as well.
There are some literature data that Metformin induces vitamin B12 malabsorption, which may increase the risk of developing vitamin B12 deficiency and subsequently elevation of homocysteine levels (2, 3). High concentrations of homocysteine has been associated with higher risk of coronary artery disease, arterial hypertension, hip and other bone fractures, rheumatoid arthritis, diabetes, and other serious chronic diseases.
The proposed mechanisms to explain Metformin induced vitamin B12 deficiency include: alterations in small bowel motility which stimulates bacterial overgrowth and consequential vitamin B12 deficiency, competitive inhibition or inactivation of vitamin B12 absorption, alterations in intrinsic factor (IF) levels and interaction with the cubulin endocytic receptor (4). Metformin has also been shown to inhibit the calcium dependent absorption of the vitamin B12-IF complex at the terminal ileum. This inhibitory effect is reversed with calcium supplementation (5).

**Methods**: Twenty five children with obesity aged between 10 and 17 years were included in the study. Participants levels of B12 and homocysteine were measured. All of them had BMI>97$^{th}$ centile. Oral glucose tolerance test was performed and the children were diagnosed with hyperinsulinism. The patients were treated with Metformin 850 mg twice a day for a period of 1 to 3 years. The control group was 20 children with obesity and under no Metformin treatment.

**Results**: Ten patients, treated with metformin, had levels of B12 within the laboratory reference range and recommended homocysteine concentration <7.2 µmol/l. In 15 of the treated patients we found insufficient levels of vitamin B12 <200 pg/ml and elevated homocysteine levels, compared to the control group, with 6 patients with insufficient levels. The average level ot vit. B12 in the metformin group was 199.5 pg/ml, and the average level of vitamin B12 in the control group was 239.4 pg/ml. We found no statistically significant difference between vitamin B12 levels in the two groups.




**Conclusions**: Our results are consistent with literature data that Metformin is associated with low levels of vitamin B12. Nevertheless, we could not find statistically significant difference between vitamin B12 levels in the two groups. The most likely reason for this is the small number of patients. These are the first results of an ongoing study of our department. We recommend that vitamin B12 levels should be assessed regularly in patients treated with Metformin longer than a year.

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