Long term Metformin use association with vitamin b<sub>12</sub> deficiency and anemia

**Keywords:** metformin, anemia, t2dm patients, megaloblastic, gastrectomy, EGFR, glycemic control, EASD, ADA, vitamin b<sub>12</sub>

**Abbreviations:** EASD, european association for the study of diabetes; T2DM, type 2 diabetes mellitus; ADA, American diabetes association

**Mini review**

Since its introduction in the mid-1950s in Europe and in 1995 in USA, metformin is considered the most frequently prescribed medication for the treatment of Type 2 Diabetes Mellitus (T2DM). All guidelines, including the European Association for the Study of Diabetes (EASD) and the American Diabetes Association (ADA), focus on metformin as the first-line treatment option along with lifestyle intervention for hyperglycemic management in T2DM patients.1

Beyond glycemic control, metformin has a beneficial effect on lipid metabolism, inflammation and oxidative stress.2,3 Moreover, metformin can promote weight loss and has been proven to reduce the risk of myocardial infarction and all-cause mortality in overweight newly diagnosed T2DM patients.4 Several studies have also linked metformin use with a reduced cancer risk in T2DM individuals.5,6 It is widely approved that Metformin suppresses hepatic glucose production and improves insulin signaling mainly in muscle, hepatic and adipose tissue.7,8

The main side effects of metformin include gastrointestinal disturbances, such as diarrhea and vomiting.9 Individuals with renal, hepatic insufficiency and/or congestive heart failure, have an increased risk of lactic acidosis while on Metformin treatment.10 It can be used with caution in patients with renal impairment but the dose should be reviewed if the patient’s eGFR drops below 45ml/min/1.73m<sup>2</sup> and treatment discontinued if the eGFR drops below 30ml/min/1.73m<sup>2</sup>.11

Lately many studies have also linked long term metformin use with biochemical vitamin B<sub>12</sub> deficiency and anemia.12 Vitamin B<sub>12</sub> plays an important role in red blood cell formation, nerve cell physiology, and in the metabolism of homocysteine.13 Vitamin B<sub>12</sub> deficiency has been associated with megaloblastic anemia, peripheral neuropathy and cardiovascular disease.14

Some studies15-17 have shown a reducing effect of metformin on the overall mean B<sub>12</sub> blood levels. This significant correlation is evident in current meta-analysis results which demonstrate a mean reduction of 57pmol/L (95% CI: -35 to -79pmol/L), 65.8pmol/L (95% CI: -53.6 to -78.1pmol/L) and 53.93pmol/L (95% CI: -26.42 to -81.44pmol/L) respectively.

Several studies have indicated that vitamin B<sub>12</sub> deficiency is associated with the dosage as well as the duration of metformin use.18 The exact mechanism by which metformin use may promote B<sub>12</sub> deficiency has not been fully identified. It has been suggested that metformin impedes the absorption of B<sub>12</sub> from the terminal ileum. A relevant study has demonstrated that the malabsorption of B<sub>12</sub> induced by metformin is calcium dependent and can be reversed with increased intake of calcium.19

It is estimated that metformin is taken by more than 150 million individuals with T2DM worldwide.20 Therefore one would expect that symptoms related to vitamin B<sub>12</sub> deficiency would be very common among such a large population. However, in accordance with the studies regarding metformin treatment and vitamin B<sub>12</sub> deficiency, associated complications and symptoms are rarely seen clinically.21

A pertinent study done regarding megaloblastic anemia (during a mean screening duration of 11.8years) has shown that 9% of the patients on metformin therapy developed symptoms of the disease.22 In literature there are very few described cases of megaloblastic anemia due to metformin-associated B<sub>12</sub> deficiency. Since the early 1980s, Callaghan et al.,23 although they couldn’t prove the cause and effect relationship, reported the first case of megaloblastic anemia due to long-term metformin use. In this case, treatment with cyanocobalamin resulted in the increase of hemoglobin levels and fall of the mean corpuscular volume of red blood cells (MCV). Liu et al.24 presented two analogous cases that developed anemia, cognitive impairment, peripheral neuropathy and subacute combined degeneration of the spinal cord. Fujita et al.25 presented a case of megaloblastic anemia due to vitamin B<sub>12</sub> deficiency resulting in a total gastrectomy of a T2DM patient following the introduction of metformin therapy.

It must be underlined that older individuals have a greater risk of developing vitamin B<sub>12</sub> deficiency.26 Also, other potential causes of megaloblastic anemia like failure of Intrinsic Factor production, atrophic gastritis, or use of H2 antagonists should always be taken into account.27 The daily diet should also be considered as a possible cause of B<sub>12</sub> deficiency. For example, vegetarians (independent of the type) tend to have a higher prevalence of B<sub>12</sub> deficiency compared to that of non-vegetarian.28 To clarify the cause of the B<sub>12</sub> deficiency, comprehensive testing and complete history must be done on an individual basis to rule in or rule out all the possible causes of megaloblastic anemia.

It is noteworthy to mention that symptoms of peripheral neuropathy are often attributed to long term uncontrolled diabetes in T2DM and are rarely considered as a result of vitamin B<sub>12</sub> deficiency.29 It has been demonstrated that T2DM patients with symptomatic peripheral neuropathy using metformin, can exhibit lower vitamin B<sub>12</sub> levels in their blood.30

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and concurrently more severe symptoms compared with similar individuals with no metformin exposure.30

Although there are no current published guidelines advocating for screening and monitoring of vitamin B12 in T2DM may be particularly useful in subjects receiving long term metformin treatment, especially if other risk factors are present. Monitoring the B12 levels would also be helpful in B12 supplementation at least annually. Vitamin B12 supplementation should most likely be considered in elderly T2DM individuals on long term high dose metformin treatment especially if they have other risk factors.31

Conclusion

Metformin therapy is associated with increased risk of biochemical B12 deficiency and megaloblastic anemia. People with T2DM on metformin treatment should have their vitamin B12 levels tested at least once a year. More clinical studies are needed in order to understand the mechanisms involved in the relationship between metformin therapy and vitamin B12 deficiency, as well as the necessity of supplementary vitamin B12 in T2DM populations.

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Conflict of interest

Author declares that there is no conflict of interest.

References
