Long term Metformin use association with vitamin B₁₂ deficiency and anemia

**Keywords:** metformin, anemia, T2DM patients, megaloblastic, gastrectomy, EGFR, glycemic control, EASD, ADA, vitamin B₁₂

**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.²³ 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.⁵⁶ It is widely approved that Metformin suppresses hepatic glucose production and improves insulin signaling mainly in muscle, hepatic and adipose tissue.⁷⁸

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 45 ml/min/1.73 m² and treatment discontinued if the eGFR drops below 30 ml/min/1.73 m².¹¹

Lately many studies have also linked long term metformin use with biochemical vitamin B₁₂ deficiency and anemia.¹² Vitamin B₁₂ plays an important role in red blood cell formation, nerve cell physiology, and in the metabolism of homocysteine.¹³ Vitamin B₁₂ 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 B₁₂ blood levels. This significant correlation is evident in current meta-analysis results which demonstrate a mean reduction of 57 pmol/L (95% CI: -35 to -79 pmol/L), 65.8 pmol/L (95% CI: -3.6 to -78.1 pmol/L) and 53.93 pmol/L (95% CI: -26.42 to -81.44 pmol/L) respectively.

Several studies have indicated that vitamin B₁₂ deficiency is associated with the dosage as well as the duration of metformin use.¹⁸ The exact mechanism by which metformin use may promote B₁₂ deficiency has not been fully identified. It has been suggested that metformin impedes the absorption of B₁₂ from the terminal ileum. A relevant study has demonstrated that the malabsorption of B₁₂ 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 B₁₂ deficiency would be very common among such a large population. However, in accordance with the studies regarding metformin treatment and vitamin B₁₂ deficiency, associated complications and symptoms are rarely seen clinically.²¹

A pertinent study done regarding megaloblastic anemia (during a mean screening duration of 11.8 years) 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 B₁₂ 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 B₁₂ 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 B₁₂ 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 B₁₂ deficiency. For example, vegetarians (independent of the type) tend to have a higher prevalence of B₁₂ deficiency compared to that of non-vegetarian.²⁸ To clarify the cause of the B₁₂ 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 B₁₂ deficiency.²⁹ It has been demonstrated that T2DM patients with symptomatic peripheral neuropathy using metformin, can exhibit lower vitamin B₁₂ levels.
and concurrently more severe symptoms compared with similar individuals with no metformin exposure.\textsuperscript{30}

Although there are no current published guidelines advocating for screening and monitoring of vitamin $B_12$ in T2DM may be particularly useful in subjects receiving long term metformin treatment, especially if other risk factors are present. Monitoring the $B_12$ levels would also be helpful in $B_12$ supplementation at least annually. Vitamin $B_12$ supplementation should most likely be considered in elderly T2DM individuals on long term high dose metformin treatment especially if they have other risk factors.\textsuperscript{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 $B_12$ 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 $B_12$ deficiency, as well as the necessity of supplementary vitamin $B_12$ in T2DM populations.

**Acknowledgements**

None.

**Conflict of interest**

Author declares that there is no conflict of interest.

**References**

1. American Diabetes Association Standards of Medical Care in Diabetes. Diabetes Care. 2016.
2. Isoda K, Young JL, Zirlk A, et al. Metformin inhibits proinflammatory responses and nuclear factor-kappaB in human vascular wall cells. *Arterioscler Thromb Vasc Biol*. 2006;26(3):611‒617.
3. Wulfffelé MG, Kooy A, de Zeeuw D, et al. The effect of metformin on blood pressure, plasma cholesterol and triglycerides in type 2 diabetes mellitus: a systematic review. *J Intern Med*. 2004;256(1):1‒14.
4. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998;352(9131):854‒865.
5. Evans JM, Donnelly LA, Emslie-Smith AM, et al. Metformin and reduced risk of cancer in diabetic patients. *BMJ*. 2005;330(7503):1304‒1305.
6. Thakkar B, Aronis KN, Vanvini MT, et al. Metformin and sulfonylureas in relation to cancer risk in type II diabetes patients: a meta-analysis using primary data of published studies. *Metabolism*. 2013;62(7):922‒934.
7. Natali A, Ferramini E. Effects of metformin and thiazolidinediones on suppression of hepatic glucose production and stimulation of glucose uptake in type 2 diabetes: a systematic review. *Diabetologia*. 2006;49(3):434‒441.
8. Stumvoll M, Nurjhan N, Perriello G, et al. Metabolic effects of metformin in non-insulin-dependent diabetes-mellitus. *N Engl J Med*. 1995;333(9):550‒554.
9. Scarpey JHB. Optimal dosing strategies for maximising the clinical response to metformin in type 2 diabetes. *Br J Diabetes Vasc Dis*. 2001;1(1):28‒36.
10. Misbin RI, Green L, Stadel BV, et al. Lactic acidosis in patients with diabetes treated with metformin. *N Engl J Med*. 1998;338(4):265‒266.
11. National Institute for Health and Clinical Excellence. The Management of Type 2 Diabetes: 2010 NICE Guidelines. London, UK: National Institute for Health and Clinical Excellence. 2010.