Mini Review

Open Access

CrossMark

Long term Metformin use association with vitamin b_{12} deficiency and anemia

Keywords: metformin, anemia, t2dm patients, megaloblastic, gastrectomy, EGFR, glycemic control, EASD, ADA, vitamin b_{12}

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

Volume 4 Issue 1 - 2017

Petros Thomakos,[1] Kyriakoula Marinou[2]
[1]Diabetes Center & Clinic, Hygeia Hospital, Greece
[2]University School of Medicine, Greece

Correspondence: Kyriakoula Marinou, University School of Medicine, Greece, Email kikimarinou@yahoo.gr

Received: August 16, 2016 | **Published:** March 07, 2017

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 diarrhoea 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^2 and treatment discontinued if the eGFR drops below 30ml/min/1.73m^2.[11]

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

Some studies[15–17] have shown a reducing effect of metformin on the overall mean B_{12} 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_{12} 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_{12} deficiency has not been fully identified. It has been suggested that metformin impedes the absorption of B_{12} from the terminal ileum. A relevant study has demonstrated that the malabsorption of B_{12} 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_{12} deficiency would be very common among such a large population. However, in accordance with the studies regarding metformin treatment and vitamin B_{12} 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_{12} 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_{12} 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_{12} 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_{12} deficiency. For example, vegetarians (independent of the type) tend to have a higher prevalence of B_{12} deficiency compared to that of non-vegetarian.[28] To clarify the cause of the B_{12} 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_{12} deficiency.[29] It has been demonstrated that T2DM patients with symptomatic peripheral neuropathy using metformin, can exhibit lower vitamin B_{12} levels

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 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.[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, Zirlik 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. Wulffelé 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, Vamvini 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, Ferrannini 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. Scarpello 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.
12. Aroda VR, Edelstein SL, Goldberg RB, et al. Long-term Metformin Use and Vitamin B12 Deficiency in the Diabetes Prevention Program Outcomes Study. Diabetes Prevention Program Research Group. *J Clin Endocrinol Metab*. 2016;101:1754–1761.
13. Oh R, Brown DL. Vitamin B12 deficiency. *Am Fam Physician*. 2003;67(5):979–986.
14. Nygard O, Nordrehaug JE, Refsum H, et al. Plasma homocysteine levels and mortality in patients with coronary artery disease. *N Engl J Med.* 1997;337(4):230–236.
15. Liu Q, Li S, Quan H, et al. Vitamin B12 Status in Metformin Treated Patients: Systematic Review. *PLoS One*. 2014;9(6):e100379.
16. Chapman LE, Darling AL, Brown JE. Association between metformin and vitamin B12 deficiency in patients with type 2 diabetes: A systematic review and meta-analysis. *Diabetes Metab*. 2016;42(5):316–327.
17. Niafar M, Hai F, Porhomayon J, et al. The role of metformin on vitamin B12 deficiency: a meta-analysis review. *Intern Emerg Med*. 2015;10(1):93–102.
18. Ting RZ, Szeto CC, Chan MH, et al. Risk factors of vitamin B(12) deficiency in patients receiving metformin. *Arch Intern Med*. 2006;166(18):1975–1979.
19. Bauman WA, Shaw S, Jayatilleke E, et al. Increased intake of calcium reverses vitamin B12 malabsorption induced by metformin. *Diabetes Care*. 2000;23(9):1227–1231.
20. He L, Meng S, Germain Lee EL, et al. Potential biomarker of metformin action. *J Endocrinol* 2014;221(3):363–369.
21. Angelousi A, Larger E. Anaemia, a common but often unrecognized risk in diabetic patients: a review. *Diabetes Metab*. 2015;41(1):18–27.
22. Filioussi K, Bonvoas S, Katsaros T. Should we screen diabetes patients using biguanides for megaloblastic anaemia? *Aust Fam Physician*. 2003;32(5):383–384.
23. Callaghan TS, Hadden DR, Tomkin GH. Megaloblastic anaemia due to vitamin B12 malabsorption associated with long-term metformin treatment. *Br Med J.* 1980;280(6225):1214–1215.
24. Liu KW, Dai LK, Jean W. Metformin-related vitamin B12 deficiency. *Age Ageing.* 2006;35(2):200–201.
25. Fujita H, Narita T, Yoshioka N, et al. A case of megaloblastic anemia due to vitamin B12 deficiency precipitated in a totally gastrectomized type II diabetic patient following the introduction of metformin therapy. *Endocr J.* 2003;50(4):483–484.
26. Price EA, Mehra R, Holmes TH, et al. Anemia in older persons: etiology and evaluation. *Blood Cells Mol Dis*. 2011;46(2):159–165.
27. Adams JF, Clark JS, Ireland JT, et al. Malabsorption of vitamin B12 and intrinsic factor secretion during biguanide therapy. *Diabetologia.* 1983;24(1):16–18.
28. Pawlak R, Parrott SJ, Raj S, et al. How prevalent is vitamin B(12) deficiency among vegetarians? *Nutr Rev*. 2013;71(2):110–117.
29. Saperstein DS, Barohn RJ. Peripheral Neuropathy Due to Cobalamin Deficiency. *Curr Treat Options Neurol.* 2002;4(3):197–201.
30. Wile DJ, Toth C. Association of metformin, elevated homocysteine, and methylmalonic acid levels and clinically worsened diabetic peripheral neuropathy. *Diabetes Care*. 2010;33(1):156–161.
31. Kibirige D, Mwebaze R. Vitamin B12 deficiency among patients with diabetes mellitus: is routine screening and supplementation justified? *J Diabetes Metab Disord*. 2013;12(1):17.