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Review Article

Review for the management of vitamin B12 deficiency in diabetic patients on metformin

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ABSTRACT

Long-term usage of Metformin is associated with lower serum vitamin B12 levels. The lower than normal levels could worsen neurological complications of diabetes, including diabetic neuropathy and poor cognition. Guidelines advise periodic monitoring of vitamin B12 but do not specify frequency, treatment targets or treatment modality. This commentary aims to review the prevalence and the severity of the presentation and to provide evidence-based answers to those clinical questions not answered by current guidelines.

Keywords: Diabetes mellitus, Diabetic neuropathies, Metformin, Prevalence, Vitamin B12 deficiency

INTRODUCTION

Metformin in type 2 diabetes patients

Metformin is used for the treatment of type 2 diabetes for more than 60 years, and reports date starting of usage since 1957.[1] The medication has the most reliable evidence base for long-term safety. Diabetes Canada (DC), American Diabetes Association (ADA), National Institute for Health and Care Excellence (NICE) and Scottish Intercollegiate Guidelines Network (SIGN) guidelines recommend the consideration of Metformin as a first-line oral treatment for all type 2 diabetes patients.[2-5] It is also recommended for type 2 diabetes prevention; it should be especially considered in those with BMI ≥35 kg/m^2, those aged <60 years, and women with prior gestational diabetes mellitus. Treatment is also recommended as a dual and triple therapy combined with other types of type 2 diabetes medication to achieve individually agreed targets. There is extensive research evidence that supports the usage of metformin-based combinations, and the progressive nature of type 2 diabetes puts a large cohort of patients on long-term usage of Metformin. It is estimated that nearly 120 million patients are using Metformin for the treatment of diabetes-related condition worldwide.[4-7] Once initiated, Metformin should continue if it is well-tolerated and not contraindicated. 15% of type 2 diabetic patients do not tolerate Metformin or have a contraindication for usage.

Vitamin B12

Vitamin B12 is a water-soluble vitamin which functions as a co-factor for different intracellular enzymatic reactions. It is crucial for DNA synthesis and amino-acids and fatty acid metabolism. The reactions impact mainly the functions of the nervous system and erythropoiesis.

Animals form the primary source of vitamin B12 in the human diet. Absorption and transport of Vitamin B12 are somewhat complicated. B12 is stored mainly in the liver and to a lesser extent in the kidney. Stomach hydrochloric

acid (HCL), Intrinsic factor and calcium are few of many factors that could affect the multifaceted absorption process.

Vegans, vegetarians and older adults are believed to be at risk of vitamin B12 deficiency due to low intake or poor absorption. Patients with stomach related conditions including decreased gastric acid secretions, pernicious anaemia or those patients with gastric surgery or chronic h pylori infection are also at high risk. Pancreatitis, Crohn's disease and ileal resection may also lead to B12 deficiency. Metformin, proton pump inhibitors and H2 antagonists are associated with Vitamin B12 deficiency.

Metformin and vitamin B12 deficiency mechanism

Vitamin B12 deficiency secondary to long term metformin usage was described in 1971, where 30% of 71 patients had B12 malabsorption. B12 malabsorption was measured using a double isotope technique and was deemed to be statistically significant. The test is dependent on binding to the intrinsic factor of human gastric juice. Of interest, B12 malabsorption reversed on stoppage of Metformin for 28 days. Besides, Calcium supplementation seems to reverse the impact.[1,8] The impact is dose dependant that tends to occur as early as six weeks to 3 months period. Studies suggested that Metformin at a dose higher than 1500 mg could be a significant factor in vitamin B12 deficiency.

Prevalence and strength of association

Prevalence of B12 deficiency among patients using Metformin treated patients varied from 5.8% to 52% in different reports.[11] Diabetic patients using long term Metformin have an approximately 2-fold increased incidence of Vitamin B12 deficiency.[10,12,13] Receiving Metformin for a few months can significantly lower B12 levels to borderline, and deficiency levels.

Table 1: Summary of associations.

Metformin dose	Higher than 1500mg daily
Time to vitamin B12 reduction	6 weeks to 3 months
Percentage of reduction	6% to 27%
Mean difference	-53.9, 95% CI -81.4 to -26.4 pmol/l, p <0.01[9] -65.8, 95% CI -78.1 to -53.6 pmol/l, p <0.01[10]
Incidence	OR = 2.45, 95% CI 1.74-3.44, p <0.01
Prevalence	5.8% to 52%

Percentage of reduction varies from 6% to nearly 27%. The effect seems to be progressive and to levels that may require substitution, and the effect could be noticed in up to half of the patients.[14]

Different systematic reviews examined the effect of Metformin on vitamin B12 levels. Reviews concluded a statistically significant overall mean reduction and increasing incidence. Results were dose dependant and happened less in patients who took multivitamins.[9,15] (Table 1).

Vitamin B12 serology level for diagnosis of vitamin B12 deficiency

Serum B12 levels are considered an acceptable test for diagnosis but levels <148 pmol/l (<200 pg/mL) miss around 3-5% of deficient cases and <200 pmol/l (<271 pg/mL) diagnose all deficient cases but results in higher false-positive results. Ranges between 150 and 220 pmol/l with no symptoms may suggest a subclinical form for Vitamin B12 deficiency. Vitamin B12 level ≥148 pmol/l is suggested to have the sensitivity of 95-97%, but specificity is not clear.[16] In a literature review, 37% of authors agreed on using values between 148 pmol/l and 150 pmol/l for prevalence studies.[17,18,11]

Pregnancy is associated with lower levels and false-negative results. On the other hand, leukaemia, some cancers, and impaired renal functions may result in higher values (Table 2).

Table 2: Serum vitamin B12 levels for diagnosis of deficiency.

Serum vitamin B12 levels	Sensitivity	Impact
<148 pmol/l (<200 pg/mL)	95-97%	Misses out on 3-5% of B12 defciency
<200 pmol/l (<271 pg/mL)	100%	Increase number of false positive

Pregnancy is associated with lower levels
Leukaemia, cancer, impaired renal functions are associated with others.

Vitamin B12 toxicity has not established, and there are no scientific reports of vitamin B12 overdose. The diabetic population is at a higher risk of deficiency and is more prone to neurological complications. Clinicians may safely elect to diagnose and treat to higher thresholds in view of the absence of reported harm.

Limitations of B12 levels as a serological marker for B12 deficiency

In many cases, symptoms, and signs of Vitamin B12 deficiency do not correlate with serum vitamin B12 serum levels. It is not clear if the serological values genuinely reflect the real B12 metabolic status and the real impact of the malabsorption on the patient's physiological condition. While there is a near consensus on the cut-off levels for diagnosis of Vitamin B12 deficiency, less than 20% of patients with low vitamin B12 level have macrocytic anaemia and many patients are asymptomatic despite pathologically low vitamin B12

serum levels. However, different reports suggested improvement of neurological symptoms with Vitamin B12 supplements despite normal baseline B12 levels.[19,20]

While testing for more specific serum biomarkers like methylmalonic acid and total homocysteine levels may provide more concrete answers, mostly those are not available to primary care providers. A practical approach might be to suspect Vitamin B12 deficiency in patients with anaemia, raised MCV and / or characteristic symptoms (e.g. diabetic neuropathy, or poor cognition). Physicians may consider testing in all patients who have either risk factors or symptoms.

Because of the mismatch between clinical presentation and serological values, few researchers suggested age and gender-specific cut-off diagnostic value.

CLINICAL IMPACT IN DIABETIC POPULATION

Vitamin B12 deficiency causes anaemia related symptoms, psychiatric and neurological symptoms. Anaemia symptoms may include fatigue, palpitations, pallor, while neurologic symptoms include paraesthesia in hands and feet, muscle cramps, dizziness, cognitive disturbances, ataxia, and erectile dysfunction. Anaemia presentation may lag behind serum B12 levels and are not specific to the diabetic population.

Diabetic neuropathy

Diabetic neuropathy is a common and well-recognised microvascular complication of diabetes mellitus that associated with a higher mortality rate and poor prognosis. It could be asymptomatic, and Vitamin B12 deficiency might worsen the recognised complications, including foot ulcer and amputation.[21]

Multiple cross-sectional studies suggested that Metformin usage has a linear correlation with diabetic neuropathy.[22-25] Conversely, many reported no association with metformin usage and diabetic neuropathy despite the confirmed association with low serum vitamin B12.[26-28]

Most studies had a low number of participants and used different methods to diagnose diabetic neuropathy. The diagnosis of diabetic neuropathy faces its challenge as the symptoms and signs of diabetic neuropathy are subjective and non-specific most of the time. Moreover, the validated measures of small nerve fibre neuropathy are not readily available in most of the community and clinical settings.[21]

A systematic review in 2005 concluded that B12 supplements improved somatic symptoms in diabetic patients with diabetic neuropathy, including pain and paraphasia. The improvement was noted to a lesser extent with respect to vibration perception and electrophysiological studies.[19]

However, another systematic review in 2016 concluded that vitamin B12 supplementation resulted in no improvement of clinical symptoms in patients with diabetes. It is worth mentioning that both have noted the small number of participants and poor quality for some studies.[29] Screening for diabetic neuropathy is part of routine biannual diabetes care, and physicians should consider screening for vitamin B12 in those patients with symptoms to treat and prevent irreversible damage.

Given the above, more high-quality research with larger samples is required to conclude the clinical impact of low vitamin B12 level and to examine the impact of supplementation on patients' symptoms in this vulnerable population especially in those with Vitamin B12 deficiency or symptomatic patients with a normal vitamin B12 level. The practice of Vitamin B12 prophylaxis in the absence of B12 deficiency or symptoms seems to be lacking any evidence to support it.

Cognitive impairment

The diabetic population is at higher risk of cognitive decline, and the rate of decline seems to be higher compared to non-diabetic population.[30] Besides, patients with diabetes are at higher risk of developing Alzheimer's and vascular dementia.[31]

The association of Vitamin B12 deficiency with cognitive decline was always debatable because of the considerable variation in the results of clinical studies. Of note, the usage of biomarkers with adequate specificity for Vitamin B12 deficiency such as holoTC and/or methylmalonic acid had consistent results.[32] Similarly, higher homocysteine (Hcy) levels have been identified as a modifiable risk factor associated with cognition and dementia. Higher homocysteine is noted in patients with Vitamin B12 deficiency status.[33]

Early systematic review for Vitamin B12 supplementation in elderly and demented people concluded insufficient evidence to justify its use.[34] While there was an improvement noted, it was not statistically significant. It is worth mentioning that the follow-up period in the studies included was as short as three months, and the intervention was not targeted at a population with low vitamin B12 levels.

Another systematic review noted no obvious evidence of a difference between placebo and vitamin B12 supplements in adults with mild cognitive impairment. Of note, the systematic review included only one RCT with 75 participants.[35] Also, the review was not specific to diabetic patients and has not targeted patients with vitamin B12 deficiency.

On subgroup analysis of patients with higher than the median of the serum homocysteine levels and possible vitamin B12 deficiency, it was noted that vitamin B12 supplementation reduced brain atrophy and had a

beneficial impact on episodic memory in elderly people.[36] Similarly, long-term use of a combination of folic acid and vitamin B12 appeared to improve the cognitive function of healthy older people with high homocysteine levels.[37] Both imply the benefit of treatment in case of Vitamin B12 deficiency, but not in population with normal Vitamin B12 status.

TREATMENT

Two systematic reviews compared oral vitamin B12 replacement regimes to the parenteral form and reported similar results. The later was specific to patients with malabsorption conditions, including patients with pernicious anaemia, gastrectomy, inflammatory bowel disease and others. Both reviews concluded that oral vitamin B12 is an effective alternative to the parenteral form with favourable side effects profile.

A daily dose of 1mg was adequate to normalise vitamin B12 serum levels and cure clinical manifestation related to the deficiency in the healthy population as well as in patients with GI disorders.[38] Also, the Oral form of treatment fewer contraindications, as well as lower, cost.[39] Both systematic reviews noted that the quality of evidence available is of low quality, and many trials have focused on serum levels rather than outcomes.

Parenteral Vitamin B12 may be considered in patients who are symptomatic or show an inadequate response to oral treatment. Most guidance recommends an initial dose of 1 mg intramuscularly on alternate days for two weeks and then once every other month.[16]

CURRENT GUIDANCE ON B12 MEASUREMENTS IN TYPE 2 DIABETIC PATIENTS ON METFORMIN

Diabetes Canada and ADA guidelines highlighted that the long-term use of Metformin might be associated with low B12 biochemical levels. They advise periodic measurement in those who are using Metformin. The guidance highlighted those who suffer from anaemia and diabetic neuropathy as a high-risk group. There is no clear definition of the cut-off levels, the frequency of testing or modality of treatment.[24] NICE and SIGN have not addressed the issue in their guidance for the treatment of diabetes.[3,5]

KNOWLEDGE AND INSIGHTS

The incidence of vitamin B12 deficiency increase to a near two folds and the prevalence could be as high as 50% among the diabetic population on long term metformin. The association is a dose and duration dependant and, in many cases, reversible which suggest a causality. In most of the cases, the impact is a drop to low normal levels. However, it could cause a deficiency.

The diabetic population are more prone to many of the neurological complications, including diabetic neuropathy and poor cognition. Vitamin B12 is implied in both, and deficiency may worsen the presentations or at least hinders recovery. Periodic testing, preferably once to twice annually, is recommended in this high-risk population.

Vitamin B12 supplements seem to help with signs and symptoms of diabetic neuropathy and may delay the cognitive decline in patients with B12 deficiency. Thus, identifying patients with Vitamin B12 deficiency, along with early interventions, is crucial.

Normal levels of vitamin B12 <148 pmol/l (<200 pg per mL) could miss up to 5% of Vitamin B12 deficiency. It could be argued to treat up to levels of B12 >200 pmol/l (<271 pg/mL) in the diabetic population. The population is at higher risk of deficiency and more prone to neurologic symptoms, including diabetic neuropathy and cognitive decline. Recurrence may justify treatment with Vitamin B12 supplements if the patient continues Metformin.

Oral vitamin B12 tablets at a dose of 1 mg / daily seem to be as effective as intramuscular treatment and have better safety and economic profile. Parenteral vitamin B12 injections should be reserved for patients who are symptomatic or with poor compliance. Patients on long term metformin with recurrent low vitamin B12 levels might benefit from lifelong prophylaxis.

The quality of evidence for treating Vitamin B12 deficiency in diabetic patients on long-term Metformin population is of low quality, and many trials have focused only on serum levels. Future research trials should focus on the quality of the design as well as measuring clinical outcomes, quality of life and adverse events. Primary care seems to be the most appropriate settings to conduct such trials.

CONCLUSION

Metformin dose of >1500 mg daily for 6 weeks or longer might be associated with lower vitamin B12 levels. The decline happens in up to 50% of patients and could be as high as 25% decline. In view of the above, Diabetic patients on long term metformin should have vitamin B12 checked at least annually. Diabetic patients might benefit from high diagnostic and treatment targets of levels of B12>200 pmol/l (<271 pg/mL) with no to little harm. Treatment with vitamin B12 tablets at a dose of 1mg/daily is as effective as a parenteral form. The quality of evidence is low, and future trials should focus on measuring clinical outcomes.

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REFERENCES

1. Tomkin GH, Hadden DR, Weaver JA, Montgomery DAD. Vitamin-B12 Status of Patients on Long-term Metformin Therapy. Br Med J. 1971;2(5763):685.
2. Houlden RL. Diabetes Canada 2018 Clinical Practice Guidelines. Can J Diabetes. 2018;28z;42:S1-5.
3. National Insitute of Clinical and Health Excellence. Overview. Type 2 diabetes in adults: management. Guidance. NICE. 2015 Dec. Available at: https://www.nice.org.uk/guidance/ng28%0Ahttps://www.nice.org.uk/guidance/ng28/resources/type-2-diabetes-in-adults-management-pdf-1837338615493. Accessed on 28 March 2020.
4. Johnson EL, Feldman H, Butts A, Billy CDR, Dugan J, Leal S, et al. Standards of medical care in diabetes-2019 abridged for primary care providers. Clin Diabetes. 2019 Jan 1;37(1):11-34.
5. Scottish Intercollegiate Guidelines Network (SIGN). SIGN 154. Pharmacological management of glycaemic control in people with type 2 diabetes. 2017 November):1-57. Available at: www.nice.org.uk/. Accessed on 23 December 2019.
6. Kirpichnikov D, McFarlane SI, Sowers JR. Metformin: an update. Annals Inter Med. 2002;137(1):25-33.
7. Ahmed MA. Metformin and Vitamin B12 deficiency: Where do we stand? J Pharm Pharm Sci. 2016 Oct 25;19(3):382-98.
8. Bauman WA, Shaw S, Jayatilleke E, Spungen AM, Herbert V. Increased intake of calcium reverses vitamin B12 malabsorption induced by Metformin. Diabetes Care. 2000;23(9):1227-31.
9. Liu Q, Li S, Quan H, Li J. Vitamin B12 status in Metformin treated patients: Systematic review. PLoS One. 2014 Jun 24;9(6).
10. Niafar M, Hai F, Porhomayon J, Nader ND. The role of Metformin on vitamin B12 deficiency: a meta-analysis review. Int Emerg Med. Springer-Verlag Italia s.r.l. 2014;10:93-102.
11. Aparicio-Ugarriza R, Palacios G, Alder M, González-Gross M. A review of the cut-off points for the diagnosis of vitamin B12 deficiency in the general population. Clinical Chemistry and Laboratory Medicine. Walter de Gruyter GmbH. 2015;53:1149-59.
12. Aroda VR, Edelstein SL, Goldberg RB, Knowler WC, Marcovina SM, Orchard TJ, et al. Long-term metformin use and vitamin B12 deficiency in the diabetes prevention program outcomes study. J Clin Endocrinol Metab. 2020;101(4):1754-61.
13. De Jager J, Kooy A, Lehert P, Wulffelé MG, Van der Kolk J, Bets D,, et al. Long term treatment with Metformin in patients with type 2 diabetes and risk of vitamin B-12 deficiency: Randomised placebo controlled trial. BMJ. 2010 May 29;340(7757):1177.
14. Wolffenbuttel BHR, Wouters HJCM, Heiner-Fokkema MR, van der Klauw MM. The Many Faces of Cobalamin (Vitamin B12) Deficiency. Mayo Clin Proc Innov Qual Outcomes. 2019 Jun;3(2):200-14.
15. Niafar M, Hai F, Porhomayon J, Nader ND. The role of Metformin on vitamin B12 deficiency: a meta-analysis review. Internal and Emergency Medicine. Springer-Verlag Italia s.r.l. 2014;10:93-102.
16. Langan RC, Goodbred AJ. Vitamin B12 Deficiency: Recognition and Management. Am Fam Physician. 2017;96(6):384-9.
17. Kim J, Ahn CW, Fang S, Lee HS, Park JS. Association between metformin dose and vitamin B12 deficiency in patients with type 2 diabetes. Medicine (Baltimore). 2019 Nov 1;98(46):e17918.
18. Devalia V, Hamilton MS, Molloy AM. Guidelines for the diagnosis and treatment of cobalamin and folate disorders. Br J Haematol. 2014;166(4):496-513.
19. Sun Y, Lai M-S, Lu C-J. Effectiveness of vitamin B12 on diabetic neuropathy: systematic review of clinical controlled trials. Acta Neurol Taiwan [Internet]. 2005;14(2):48-54.
20. Moore EM, Mander AG, Ames D, Kotowicz MA, Carne RP, Brodaty H, et al. Increased Risk of Cognitive Impairment in Patients With Diabetes Is Associated With Metformin. Diabetes Care 2013;36(10):2981-7.
21. Hamed E, Monem MA. A Review of Diabetic Peripheral Neuropathy Management given Recent Guidelines Updates. Arch Gen Intern Med. 2018;02(04).
22. Alvarez M, Sierra OR, Saavedra G, Moreno S. Vitamin B12 deficiency and diabetic neuropathy in patients taking Metformin: A cross-sectional study. Endocr Connect. 2019;8(10):1324-9.
23. Gupta K, Jain A, Rohatgi A. An observational study of vitamin b12 levels and peripheral neuropathy profile in patients of diabetes mellitus on metformin therapy. Diabetes Metab Syndr Clin Res Rev. 2018;12(1):51-8.
24. Kothiwale V, Chafekar ND, Babaliche P, Chougule NA. 576-P: Prevalence of Vitamin B12 Deficiency and Clinical Neuropathy with Metformin Use in Type 2 Diabetes Mellitus Patients. Diabetes. 2019;68(Suppl 1):576.
25. Singh AK, Kumar A, Karmakar D, Jha RK. Association of B12 deficiency and clinical neuropathy with metformin use in type 2 diabetes patients. J Postgrad Med. 2013 Oct;59(4):253-7.
26. Ahmed MA, Muntingh G, Rheeder P. Vitamin B12 deficiency in metformin-treated type-2 diabetes patients, prevalence and association with peripheral neuropathy. BMC Pharmacol Toxicol. 2016;17(1):44.
27. Elhadd T, Ponirakis G, Dabbous Z, Siddique M, Chinnaiyan S, Malik RA. Metformin use is not associated with B 12 deficiency or neuropathy in patients with type 2 diabetes Mellitus in Qatar. Front Endocrinol (Lausanne). 2018;9.

28. Chen S, Lansdown AJ, Moat SJ, Ellis R, Goringe A, Dunstan FDJ, et al. An observational study of the effect of Metformin on B12 status and peripheral neuropathy. Br J Diabetes Vasc Dis. 2012;12(4):189-93.
29. Jayabalan B, Low LL. Vitamin B supplementation for diabetic peripheral neuropathy. Singapore Med J. Singapore Medical Asso. 2016;57:55-9.
30. Cukierman T, Gerstein HC, Williamson JD. Cognitive decline and dementia in diabetes - Systematic overview of prospective observational studies. Vol. 48, Diabetologia. Springer. 2005;48:2460-9.
31. Biessels GJ, Staekenborg S, Brunner E, Brayne C, Scheltens P. Risk of dementia in diabetes mellitus: A systematic review. Vol. 5, Lancet Neurol. Elsevier. 2006;5:64-74.
32. O'Leary F, Allman-Farinelli M, Samman S. Vitamin B12 status, cognitive decline and dementia: A systematic review of prospective cohort studies. Vol. 108, Br J Nutrition. Cambridge University Press. 2012;108:1948-61.
33. Beydoun MA, Beydoun HA, Gamaldo AA, Teel A, Zonderman AB, Wang Y. Epidemiologic studies of modifiable factors associated with cognition and dementia: Systematic review and meta-analysis. BMC Public Health 2014;14(1):643.
34. Malouf R, Areosa Sastre A. Vitamin B12 for cognition. Cochrane Database Syst Rev. 2003;21:(3).
35. Davies SR. How do vitamin B supplements compare with placebo/no treatment for people with mild cognitive impairment? Cochrane Clin Answers. Available at: http://doi.wiley.com/10.1002/cca.2474.
36. Mccleery J, Abraham RP, Denton DA, Rutjes AWS, Chong LY, Al-Assaf AS, et al. vitamin and mineral supplementation for preventing dementia or delaying cognitive decline in people with mild cognitive impairment. Cochrane Database of Systematic Reviews. John Wiley and Sons Ltd; 2018:2018.
37. Malouf R, Evans JG. Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people. Cochrane Database of Systematic Reviews. John Wiley and Sons Ltd; 2008.
38. Andrès E, Zulfiqar A-A, Serraj K, Vogel T, Kaltenbach G. Systematic Review and Pragmatic Clinical Approach to Oral and Nasal Vitamin B12 (Cobalamin) Treatment in Patients with Vitamin B12 Deficiency Related to Gastrointestinal Disorders. J Clin Med. 2018 Sep 26;7(10):304.
39. Wang H, Li L, Qin LL, Song Y, Vidal-Alaball J, Liu TH. Oral vitamin B12 versus intramuscular vitamin B12 for vitamin B12 deficiency. Cochrane Database of Syst Rev. 2018;3(3):CD004655.

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