

# Metformin Use and Vitamin B<sub>12</sub> Deficiency in Patients with Type-2 Diabetes Mellitus

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## Abstract

Metformin is commonly used oral hypoglycaemic agent in the treatment of type-2 Diabetes Mellitus (DM). One of the important side effect of long term metformin therapy is malabsorption of vitamin B<sub>12</sub> which could lead to megaloblastic anemia and peripheral neuropathy. Therefore annual screening of serum vitamin B<sub>12</sub> level or serum methylmalonic acid (MMA)/serum homocysteine level should be done in cases taking metformin for more than four to five years with average dose of >1g per day, even in the absence of haematological or neurological abnormalities. However, as the incidence of type-2 DM is increasing, cost of annual measurement of vitamin B<sub>12</sub> level also increases. Considering cost factor for annual screening, vitamin B<sub>12</sub> supplementation appears to be more cost effective approach rather than annual screening for routine prophylaxis. Routine vitamin preparations available in the market may contain less amount of B<sub>12</sub> and hence are not of much therapeutic use in treatment of B<sub>12</sub> deficiency due to Metformin. Hence there is a need to look for higher doses of approximately 500-2000µg/day.

**Keywords:** Metformin, Type-2 Diabetes Mellitus, Vitamin B<sub>12</sub> Deficiency

## 1. Introduction

Metformin, a biguanide, is one of the commonly used oral hypoglycaemic agent<sup>1</sup>. Metformin is the preferred drug among type 2 diabetes patients, particularly those with overweight and having normal kidney function<sup>2</sup>. Various guidelines propose that in the absence of contraindications for metformin, it should be preferred drug with concurrent lifestyle modifications while initiating the therapy for type-2 DM<sup>2-4</sup>.

One of the risky side effect of biguanides is lactic acidosis which can be overcome with judicious use of metformin. Other side effects like abdominal distress and diarrhoea<sup>5</sup> appear within first few days' of initiation of metformin but disappear after discontinuation of metformin therapy. However, malabsorption of vitamin B<sub>12</sub> may not be easily diagnosed without close attention. Various studies have reported that an average of 10-30 %

of patients taking metformin for longer duration and at higher dosage have shown vitamin B<sub>12</sub> deficiency<sup>6-9</sup>.

Vitamin B<sub>12</sub> level should be done among patients with type 2 diabetes, especially those taking metformin therapy for longer duration<sup>7</sup>. Clinical manifestations of vitamin B<sub>12</sub> deficiency include alteration in mental status, megaloblastic anemia and neurological damage<sup>7,10,11</sup>. However, diabetic neuropathy can also present with symptoms such as paresthesias, numbness and tingling in hands and feet etc<sup>12</sup>. These symptoms could give rise to confusion between diagnosis of peripheral neuropathy due to vitamin B<sub>12</sub> deficiency and diabetic peripheral neuropathy<sup>10,11</sup>. The progression of neurological damage could be managed by early detection of vitamin B<sub>12</sub> deficiency and with appropriate B<sub>12</sub> supplementation<sup>13</sup>. However, this vitamin B<sub>12</sub> deficiency may lead to permanent neurological damage if it is misdiagnosed as diabetic neuropathy<sup>11</sup>.

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## 2. Absorption and Deficiency of Vitamin B<sub>12</sub>

The principal source of vitamin B<sub>12</sub> includes liver, egg yolk, meat, cheese etc. About 2/3 to 4/5 of body's content of vitamin B<sub>12</sub> is stored in liver<sup>14,15</sup>. Vitamin B<sub>12</sub> is absorbed mainly in terminal ileum with the help of intrinsic factor secreted from parietal cells of stomach. Vitamin B<sub>12</sub> can also be absorbed by the process of passive diffusion in the small intestine which doesn't require intrinsic factor. However only about 1% of the vitamin B<sub>12</sub> dose is absorbed by passive diffusion. In other words, when 100µg of vitamin B<sub>12</sub> is administered, approximately 1µg is likely to be absorbed.

The various causes of vitamin B<sub>12</sub> deficiency includes nutritional deficiency, gastric mucosal damage, pernicious anaemia, drugs like metformin and Proton Pump Inhibitors (PPIs) etc.

## 3. Physiological Role of Vitamin B<sub>12</sub>

Vitamin B<sub>12</sub> is important in methylation of homocysteine to methionine and the conversion of methylmalonyl coenzyme A (CoA) to succinyl-CoA. Methionine is then converted into S-adenosyl-methionine which acts as donor of methyl group to myelin, membrane phospholipids and to various neurotransmitters.

## 4. Clinical Studies of Vitamin B<sub>12</sub> Deficiency in Indian Population

In an Indian study conducted among 441 healthy middle aged men to assess the frequency of vitamin B<sub>12</sub> deficiency, defined by vitamin B<sub>12</sub> concentrations <150 pmol/L was observed among 67% of the study participants<sup>16</sup>. Vegetarian diet was a significant factor associated with low vitamin B<sub>12</sub> levels in this study on multivariate analysis.

In another cross sectional study among 175 healthy elderly Indian subjects aged >60 years, vitamin B<sub>12</sub> deficiency was observed among 16% of the study participants<sup>17</sup>.

## 5. Metformin Induced Vitamin B<sub>12</sub> Deficiency among Patients with Type-2 DM

Despite being efficacious oral hypoglycaemic agent,

metformin decreases vitamin B<sub>12</sub> levels after prolonged use of four to five years. Study conducted by DeFronzo et al; has shown that metformin decreased the serum vitamin B<sub>12</sub> levels by 22% and 29% in comparison to placebo and glyburide respectively<sup>18</sup>.

Vitamin B<sub>12</sub> malabsorption was observed in 30% of patients taking long-term metformin therapy and low serum levels of vitamin B<sub>12</sub> were observed in about 20% of cases having vitamin B<sub>12</sub> malabsorption<sup>19</sup>. Vitamin B<sub>12</sub> malabsorption and its levels may start declining as early as the 4th month after initiating metformin therapy<sup>20</sup>. However due to storage in liver, clinical symptoms of vitamin B<sub>12</sub> deficiency may manifest after 5–10 years<sup>21</sup>.

Various mechanisms have been proposed to explain vitamin B<sub>12</sub> deficiency observed among patients with type-2 DM taking metformin therapy which include: changes in small intestinal motility which stimulates bacterial overgrowth and consumption of B<sub>12</sub> by bacteria, changes in Intrinsic Factor (IF) levels which could adversely affect vitamin B<sub>12</sub> absorption etc<sup>21</sup>. Metformin may also inhibit the calcium dependent absorption of the vitamin B<sub>12</sub> and intrinsic factor complex at the terminal ileum. This inhibitory effect could be reversed with calcium supplementation<sup>22</sup>.

Increase in metformin dose by 1g /day increases risk of vitamin B<sub>12</sub> deficiency by greater than two fold. Subjects consuming metformin for more than ten to twelve year and daily dosage ≥ 2g showed about a fourfold higher risk of vitamin B<sub>12</sub> deficiency compared to those with metformin use of less than four yr and daily dosage of ≤1g<sup>23</sup>.

## 6. Screening for Metformin Induced Vitamin B<sub>12</sub> Deficiency

Till date no published guidelines are there which recommends routine screening of vitamin B<sub>12</sub> deficiency in DM patients. However type 2 diabetic patients should be screened for vitamin B<sub>12</sub> deficiency prior to initiation of metformin and later annually among elderly patients especially those taking metformin for more than 4-5 years and at higher doses of more than 2g/day<sup>24</sup>.

Serum vitamin B<sub>12</sub> level should be the preliminary screening step for diagnosis of vitamin B<sub>12</sub> deficiency among patients with type-2 DM. Concentrations <200 pg/ml are usually indicative of vitamin B<sub>12</sub> deficiency while concentrations >400 pg/ml substantiate absence of vitamin B<sub>12</sub> deficiency<sup>25</sup>.

Measurement of serum MMA or homocysteine level should be considered among type-2 diabetic patients having borderline serum vitamin B<sub>12</sub> level of 200- 400 pg/ml and subtle haematological manifestations. Serum homocysteine and MMA concentrations of 5-15 µmol/l and <0.28 µmol/l are considered within the normal range respectively<sup>24,26</sup>.

## 7. Diagnosis of Metformin Induced Vitamin B<sub>12</sub> Deficiency

As metformin induced vitamin 12 deficiency produces neuropathy which can be confused with diabetic neuropathy, careful history should be elicited for metformin dose and duration of therapy. Further as suggested in screening, serum vitamin B<sub>12</sub> level or serum MMA/serum homocysteine level should be done to establish proper diagnosis of metformin induced vitamin B<sub>12</sub> deficiency.

## 8. Treatment of Vitamin B<sub>12</sub> Deficiency among Diabetic Patients

Dosing pattern of vitamin B<sub>12</sub> depends on cause of the deficiency and the severity of the disease. Vitamin B<sub>12</sub> should be given either by oral or parenteral route in case of deficiency.<sup>27</sup> Both oral and parenteral formulations can produce comparable improvements in symptoms of vitamin B<sub>12</sub> deficiency regardless of its aetiology<sup>28</sup>.

Vitamin B<sub>12</sub> can be supplemented in various forms like hydroxycobalamin, methylcobalamin and cyanocobalamin. However studies have shown that methylcobalamin is better retained in the body in comparison to its cyanide containing sibling, cyanocobalamin. Data from available studies recommends doses of >100 µg/day of vitamin B<sub>12</sub> in alimentary causes and doses of 500–2000 µg/day in disorders resulting from malabsorption of vitamin B<sub>12</sub> for treatment and prophylaxis of vitamin B<sub>12</sub> deficiency. According to Cochrane Group review the efficacy of orally administered vitamin B<sub>12</sub> to treat deficiency with initial doses of 1-2mg daily, then weekly, is confirmed and is just as effective as parenteral administration. However, in severe neurological disorders parenteral administration of vitamin B<sub>12</sub> should be done for immediate effect<sup>29</sup>.

Coexisting deficiency of folic acid should be treated with oral folic acid supplementation in doses of 5 mg daily for 1–4 months. Folic acid should be administered

after vitamin B<sub>12</sub> supplementation only; otherwise it may results into progression of the associated neurological manifestations<sup>27</sup>.

## 9. Conclusion

It appears that vitamin B<sub>12</sub> deficiency occurs commonly among patients with type-2 diabetes taking metformin therapy for longer duration and at higher dosage. This emphasises routine screening of vitamin B<sub>12</sub> level among type-2 DM, especially those consuming metformin for more than four to five years with average dose of more than 1g/day, even in the absence of haematological and neurological abnormalities.

However, considering increasing prevalence of diabetes and cost of laboratory investigation, it is uncertain that such monitoring will be possible in all diabetic patients. The amount of B<sub>12</sub> available in general multi-vitamins preparations seen in the market may not be enough to correct metformin induced vitamin B<sub>12</sub> deficiency among those with diabetes. Hence vitamin B<sub>12</sub> supplementation might be done in doses of >100 µg/day in alimentary causes and doses of 500–2000 µg/day in disorders resulting from malabsorption for the treatment and prophylaxis of vitamin B<sub>12</sub> deficiency. Thus routine supplementation of vitamin B<sub>12</sub> given to patients on long-term high dose metformin therapy seems to be clinically more prudent and a cost-effective approach.

## 10. References

1. Mazokopakis EE, Starakis IK. Recommendations for diagnosis and management of metformin-induced vitamin B<sub>12</sub> (Cbl) deficiency. *Diabetes Res Clin Pract.* 2012; 97:359–67.
2. American Diabetes Association. Standards of medical care in diabetes: 2013. *Diabetes Care.* 2013; 36:S11–66.
3. Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, Zinman B. American Diabetes Association; European Association for Study of Diabetes. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care.* 2009; 32:193–203.
4. Committee of Clinical Practice Guideline. Treatment guideline for diabetes. 4th ed. Seoul: Korean Diabetes Association, 2011.

5. Nathan DM, Buse JB, Davidson MB, Heine RJ, Holman RR, Sherwin R, Zinman B. Professional Practice Committee, American Diabetes Association; European Association for the Study of Diabetes. Management of hyperglycaemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetologia*. 2006; 49:1711–21.
6. Tomkin GH, Hadden DR, Weaver JA, Montgomery DA. Vitamin-B<sub>12</sub> status of patients on long-term metformin therapy. *Br Med J*. 1971; 2:685–7.
7. De Jager J, Kooy A, Lehert P, Wulffelé MG, van der Kolk J, Bets D, Verburg J, Donker AJ, Stehouwer CD. Long term treatment with metformin in patients with type 2 diabetes and risk of vitamin B-12 deficiency: randomised placebo controlled trial. *BMJ*. 2010; 340:c2181.
8. Ting RZ, Szeto CC, Chan MH, Ma KK, Chow KM. Risk factors of vitamin B(12) deficiency in patients receiving metformin. *Arch Intern Med*. 2006; 166:1975–9.
9. Bauman WA, Shaw S, Jayatilleke E, Spungen AM, Herbert V. Increased intake of calcium reverses vitamin B<sub>12</sub> malabsorption induced by metformin. *Diabetes Care*. 2000; 23:1227–31.
10. Bell DS. Metformin-induced vitamin B<sub>12</sub> deficiency presenting as a peripheral neuropathy. *South Med J*. 2010; 103:265–7.
11. Pierce SA, Chung AH, Black KK. Evaluation of vitamin B<sub>12</sub> monitoring in a veteran population on long term, high-dose metformin therapy. *Ann Pharmacother*. 2012; 46:1470–6.
12. Pflipsen MC, Oh RC, Saguil A, Seehusen DA, Seaquist D, Topolski R. The prevalence of vitamin B(12) deficiency in patients with type 2 diabetes: a cross-sectional study. *J Am Board Fam Med*. 2009; 22:528–34.
13. Lindenbaum J, Healton EB, Savage DG, Brust JC, Garrett TJ, Podell ER, Marcell PD, Stabler SP, Allen RH. Neuropsychiatric disorders caused by cobalamin deficiency in the absence of anemia or macrocytosis. *N Engl J Med*. 1988; 318:1720–8.
14. Oh R, Brown D. Vitamin B<sub>12</sub> Deficiency. *Am Fam Physician*. 2003; 67:979–86.
15. Andres E, Loukili N, Noel E, et al. Vitamin B<sub>12</sub> (cobalamin) deficiency in elderly patients. *CMAJ*. 2004; 171:251–9.
16. Yajnik C, Deshpande S, Lubree H, et al. Vitamin B<sub>12</sub> Deficiency and Hyperhomocysteinemia in Rural and Urban Indians. *JAPI*. 2006; 54:775–82.
17. Shobhaa V, Tareya S, Singh R, et al. Vitamin B<sub>12</sub> deficiency and levels of metabolites in an apparently normal urban south Indian elderly population. *Indian J Med Res*. 2011; 134:432–9.
18. DeFronzo R, Goodman A. Efficacy of metformin in patients with noninsulin-dependent diabetes mellitus. The Multicenter Metformin Study Group. *N Engl J Med*. 1995; 333:541–9.
19. Tomkin GH, Hadden DR, Weaver JA, Montgomery DA. Vitamin-B<sub>12</sub> status of patients on long term metformin therapy. *Br Med J*. 1971; 2:685–7.
20. Wulffele M, Kooy A, Lehert P, et al. Effects of short-term treatment with metformin on serum concentrations of homocysteine, folate and vitamin B<sub>12</sub> in type 2 diabetes mellitus: a randomized, placebo-controlled trial. *J Intern Med*. 2003; 254:455–63.
21. Andres E, Noel E, Goichot B: Metformin-associated vitamin B<sub>12</sub> deficiency. *Arch Intern Med*. 2002; 162(Andres E, Noel E, Goichot B):2251–2.
22. Bauman W, Shaw S, Jayatilleke E, Spungen A, Herbert V. Increased intake of calcium reverses vitamin B<sub>12</sub> malabsorption induced by metformin. *Diabetes Care*. 2000; 23:1227–31.
23. Ko S-H, Ko S-H, Ahn Y-B, Song K-H, Han K-D, Park Y-M, Ko S-H, Kim H-S. Association of Vitamin B<sub>12</sub> Deficiency and Metformin Use in Patients with Type 2 Diabetes. *J Korean Med Sci*. 2014; 29:965–72.
24. Mazokopakis E, Starakis I: Recommendations for diagnosis and management of metformin-induced vitamin B<sub>12</sub> (Cbl) deficiency. *Diabetes Research and Clinical Practice*. 2012; 97:359–67.
25. Snow C. Laboratory Diagnosis of vitamin B<sub>12</sub> and folate deficiency. A guide for the primary care physician. *Arch Intern Med*. 1999; 159:1289–98.
26. Klee G. Cobalamin and folate evaluation: measurements of methylmalonic acid and homocystein vs vitamin B<sub>12</sub> and folate. *Clin Chem*. 2000; 46:1277–83.
27. Hvas A, Nexø E. Diagnosis and treatment of vitamin B<sub>12</sub> deficiency. An update. *Haematologica*. 2006; 91:1506–12
28. Butler C, Vidal-Alaball J, Cannings-John R, et al. Oral vitamin B<sub>12</sub> versus intramuscular vitamin B<sub>12</sub> for vitamin B<sub>12</sub> deficiency: a systematic review of randomized controlled trials. *Fam Pract*. 2006; 10:279–85.
29. Grober U, Kisters K, Schmidt J. Neuro enhancement with Vitamin B<sub>12</sub>-Underestimated Neurological Significance. *Nutrients*. 2013; 5:5031–45