Prevalence of vitamin B12 deficiency in Indian type 2 diabetes subjects on metformin therapy

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Abstract

Background: To find out the prevalence of vitamin B12 deficiency in Indian type 2 diabetes subjects on metformin therapy.

Material & Methods: 161 type 2 diabetes subjects were studied over a period of 6 months at Karnataka institute of endocrinology Bangalore. All subjects gave written informed consent. BMI, Waist circumference, FPG, PPPG and HBA1c were estimated. Vitamin B12 levels were estimated by electrochemiluminescence. We have excluded patients taking alcohol, vitamin B12 supplements, pregnant woman, and type 1 diabetics. Subjects whose vitamin B12 less than 200 picogram/ml were considered to be deficient in vitamin B12. Subjects who were on metformin treatment for more than 6 months were included in the study.

Results: 118 diabetes subjects were males. They were in the age group of 30 to 80 years. Duration of diabetes was 1 to <5 years in 20.5%, 5 to <10 years in 28.5% and 10 years and more in 51% of diabetes subjects studied respectively. 55.9% of subjects had positive family history of type 2 diabetes. 112 subjects were on 1000 mg metformin for one year or more and 49 were on 2000 mg metformin for one year or more. Prevalence of vitamin B12 deficiency was 27.33%.

Conclusions: The prevalence of vitamin B12 deficiency is 27.33% in type 2 diabetes subjects on metformin therapy. The percentage of deficiency increased with increase in dosage of metformin but there was no correlation to duration of metformin therapy.

Keywords: vitamin B12, Metformin, Type 2 diabetes

Introduction

Vitamin B12 or cobalamin is a water-soluble vitamin that plays a very fundamental role in DNA synthesis, optimal haemopoiesis and neurological function. The clinical picture of vitamin B12 deficiency hence, is predominantly of features of haematological and neuro-cognitive dysfunction [1].

The proposed mechanisms to explain metformin induced vitamin B12 deficiency among patients with T2DM include: alterations in small bowel motility which stimulates bacterial overgrowth and consequential vitamin B12 deficiency, competitive inhibition or inactivation of vitamin B12 absorption, alterations in intrinsic factor (IF) levels and interaction with the cubulin endocytic receptor[2]. Metformin has also been shown to inhibit the calcium dependent absorption of the vitamin B12-IF complex at the terminal ileum. This inhibitory effect is reversed with calcium supplementation [3]. Decrease in vitamin B12 absorption and levels following metformin use typically starts as early as the 4th month [4]. There is a large storage of vitamin B12 in the liver so overt clinical features manifest by 5 to 10 years [2].

Screening approach for vitamin B12 deficiency among patients with T2DM- Currently, there are no published guidelines advocating for routine screening for vitamin B12 deficiency among patients with T2DM.
However, among type 2 diabetic patients, it is clinically plausible to screen for vitamin B12 deficiency prior to initiation of metformin and later annually among elderly patients with history of long term use of metformin ≥3-4 years, use of high doses of metformin (≥2 g/day), clinically worsening diabetic distal polyneuropathy in the presence or absence of the haematological abnormalities [5].

The screening approach for vitamin B12 deficiency among diabetic patients and the general population is similar. Measurement of the serum vitamin B12 concentrations should be the preliminary screening step for vitamin B12 deficiency among patients with T2DM. Concentrations <200 pg/ml are usually diagnostic of vitamin B12 deficiency while concentrations >400 pg/ml confirm absence of vitamin B12 deficiency [6].

Measurement of serum MMA or homocysteine concentrations is a more sensitive and specific approach for screening especially among type 2 diabetic patients with borderline serum vitamin B12 concentrations of 200-400 pg/ml and subtle haematological manifestations.

Serum homocysteine and methylmalonic acid concentrations of 5-15 μmol/l and <0.28 μmol/l are considered within the normal range respectively[5,7].

Reinstatler et al. in the National Health and Nutrition Examination Survey of 1999–2006 in the USA defined Biochemical B12 deficiency as serum levels ≤148 pmol/L, borderline deficiency as serum B12 >148 to ≤221 pmol/L, and normal as >221 pmol/L(400 Pmol/L=550pg/ml [8].

**Research methods**-Study design-161 type 2 diabetes subjects were studied over a period of 6 months at Karnataka institute of endocrinology and research Bangalore.All subjects gave written informed consent. BMI, Waist circumference, FPG, PPPG and HBA1c were estimated. Vitamin B12 levels were estimated by electrochemiluiminescence.

Inclusion criteria-Patients with type 2 diabetes, aged 30 to 80 yr, who had taken metformin for at least six months were recruited at Karnataka institute of endocrinology.

Exclusion criteria included patients with newly diagnosed type 2 diabetes, patients who had pernicious anemia, pregnant women, type 1 diabetes, decreased renal function (serum creatinine levels > 1.5 mg/dL for men and > 1.4 mg/dL for women), gastrectomy, colectomy, inflammatory bowel disease, Patients were also excluded if they had any severe medical illness, such as sepsis, severe infection, malignancy, liver cirrhosis, heart failure, or renal failure patients taking alcohol, vitamin B12 supplements.

Statistical methods- Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5% level of significance.

The following assumptions on data is made, **Assumptions:**

1. Dependent variables should be normally distributed.

2. Samples drawn from the population should be random, Cases of the samples should be independent Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups.

In this study we have used values of

<200 pg/m/ml for definite vitamin B12 deficiency

>200 to 300 pg/ml for borderline vitamin B12 deficiency.

>300 pg/ml for normal vitamin B12 levels

**Results**-118 diabetes subjects were males. They were in the age group of 30 to 80 years. Table 1
Table- 1: Age distribution of patients studied.

| Age in years | Gender | Total |
|--------------|--------|-------|
|              | Female | Male  |
| <40          | 1(2.3%) | 3(2.5%) | 4(2.5%) |
| 40-50        | 9(20.9%) | 27(22.9%) | 36(22.4%) |
| 51-60        | 21(48.8%) | 37(31.4%) | 58(36%) |
| 61-70        | 12(27.9%) | 39(33.1%) | 51(31.7%) |
| 71-80        | 0(0%) | 12(10.2%) | 12(7.5%) |
| Total        | 43(100%) | 118(100%) | 161(100%) |

BMI was less than 25 in 41% of patients, 25 to 30 in 44.7% and more than 30 in 14.3% of diabetes patients. Table 2

Table- 2: BMI (kg/m^2) distribution of patients studied.

| BMI (kg/m^2) | Gender | Total |
|--------------|--------|-------|
|              | Female | Male  |
| <18.5        | 0(0%) | 0(0%) | 0(0%) |
| 18.5-25      | 7(16.3%) | 59(50%) | 66(41%) |
| 25-30        | 23(53.5%) | 49(41.5%) | 72(44.7%) |
| >30          | 13(30.2%) | 10(8.5%) | 23(14.3%) |
| Total        | 43(100%) | 118(100%) | 161(100%) |

Duration of diabetes was 1 to <5 years in 26.1%, 5 to <10 years in 34.8% and 10 years and more in 39.1% of diabetes subjects studied respectively. 55.9% of subjects had positive family history of type 2 diabetes.

Table- 3: Vitamin B12 of patients studied.

| Vitamin B12 | Gender | Total |
|-------------|--------|-------|
|              | Female | Male  |
| <200        | 9(20.9%) | 35(29.7%) | 44(27.3%) |
| 200-300     | 9(20.9%) | 34(28.8%) | 43(26.7%) |
| >300        | 25(58.1%) | 49(41.5%) | 74(46%) |
| Total       | 43(100%) | 118(100%) | 161(100%) |

Table- 4: Metformin dose of patients studied.

| Metformin dose | Gender | Total |
|----------------|--------|-------|
|                | Female | Male  |
| 1000           | 34(79.1%) | 78(66.1%) | 112(69.6%) |
| 2000           | 9(20.9%) | 40(33.9%) | 49(30.4%) |
| Total          | 43(100%) | 118(100%) | 161(100%) |

Table- 5: Vitamin B12 in relation to Metformin duration.

| Vitamin B12 | Metformin duration | Total |
|-------------|--------------------|-------|
|              | <5                 | 5-10  | >10   |
| <200        | 27(33.3%)          | 10(21.3%) | 7(21.2%) | 44(27.3%) |
| 200-300     | 20(24.7%)          | 13(27.7%) | 10(30.3%) | 43(26.7%) |
| >300        | 34(42%)            | 24(51.1%) | 16(48.5%) | 74(46%) |
| Total       | 81(100%)           | 47(100%) | 33(100%) | 161(100%) |
112 subjects were on 1000 mg metformin for one year or more and 49 were on 2000 mg metformin for one year or more. Prevalence of vitamin B12 deficiency was 27.33%. Subgroup analysis showed that 23.2% on 1000 mg metformin and 36.73% on 2000 mg metformin were deficient in vitamin B12 respectively. There was no correlation between vitamin B12 deficiency and duration of metformin therapy. Table 3,4,5.

Discussion

According to ADA-EASD consensus, AACE, IDF and NICE guidelines metformin is the first drug of choice in type 2 diabetes unless contraindicated or not tolerated. Several cross-sectional studies [9,10] and case reports [11,12] have documented an increased frequency of vitamin B12 deficiency among type 2 DM patients. Metformin use has been unequivocally demonstrated as the prime factor associated with vitamin B12 deficiency among patients with T2DM [13]. Studies assessing type 2 diabetic patients on metformin have reported the prevalence of vitamin B12 deficiency to range from 5.8% to 33% [8,13,14].

This wide variation in the reported prevalence could probably be explained by the varied study definitions of vitamin B12 deficiency. In the cross sectional study by Pflipsen et al. on 203 outpatient type 2 diabetic patients at a large military primary care clinic in USA, definite vitamin B12 deficiency was defined as serum vitamin B12 concentrations of <100 pg/ml or elevated serum methylmalonic acid of >243 nmol/L or homocysteine concentrations of >11.9 nmol/L if serum vitamin B12 concentrations were between 100 to 350 pg/mL [8]. In one cross sectional study that documented a high prevalence of vitamin B12 deficiency of 33% among adult patients with T2DM by Qureshi et al., vitamin B12 deficiency was defined as serum vitamin B12 concentrations <150 pmol/L. However, patients enrolled in this study were those who were on high dose (>2 g/day) and long-term (4 years) metformin treatment, both clinical factors known to be associated with vitamin B12 deficiency.

Due to the diverse definitions of vitamin B12 deficiency used in most studies and the cultural and religious beliefs in different regions of the world, comparison of the prevalence of vitamin B12 deficiency among T2DM patients and healthy general populations is difficult.

In India, a country with a large proportion of vegetarians due to cultural and religious beliefs, very high prevalence of vitamin B12 deficiency among the general population has been reported. In one study by Yajnik et al. to determine the frequency of vitamin B12 deficiency and hyper homocysteinemia among 441 healthy middle aged Indian men, vitamin B12 deficiency as defined by vitamin B12 concentrations <150 pmol/L was reported among 67% of the study participants [15]. In another cross sectional study among 175 healthy elderly Indian subjects aged >60 years, vitamin B12 deficiency also defined as vitamin B12 concentrations <150 pmol/L was reported among 16% of the study participants [16]. In one early randomized controlled trial by DeFronzo et al., metformin decreased the serum vitamin B12 levels by 22% and 29% compared to placebo and glyburide respectively [17]. A recent, randomized control trial designed to examine the temporal relationship between metformin and serum B12 found a 19% reduction in serum B12 levels compared with placebo after 4 years [18]. Although classical B12 deficiency presents with clinical symptoms such as anaemia, peripheral neuropathy, depression, and cognitive impairment, these symptoms are usually absent in those with biochemical B12 deficiency[19].

Vitamin B12 deficiency is clinically important because it is a reversible cause of bone marrow failure and demyelinating nerve disease. Neurologic damage, a possible consequence of metformin-induced vitamin B12 deficiency, can present as peripheral neuropathy and may be mistaken for diabetic neuropathy in patients on metformin treatment [20].

Low vitamin B12 levels have been reported to be associated with worse nerve conduction velocities and poorer responses to light touch by monofilament detection [21] This may lead to the unnecessary use of anticonvulsants or tricyclic antidepressants[20,22,23]. Another study explored the relationship between low serum vitamin B12 levels and cognitive impairment, depression and neuropathy. Low vitamin B12 states were more associated with symptoms of memory impairment with objective evidence of cognitive impairment
Prevalence of definite vitamin B12 deficiency in 27.3% and biochemical B12 deficiency in 26.3% is seen in the present study. Subgroup analysis showed that 23.2% on 1000 mg metformin and 36.73% on 2000 mg metformin were deficient in vitamin B12 respectively.

There was no correlation between vitamin B12 deficiency and duration of metformin therapy. As vitamin B12-associated neuropathy is a treatable and reversible condition, early detection and treatment of vitamin B12 deficiency is clinically important in patients with diabetes using metformin.

Conclusions

The prevalence of vitamin B12 deficiency is 27.33% in type 2 diabetes subjects on metformin therapy. The percentage of deficiency increased with increase in dosage of metformin but there was no correlation to duration of metformin therapy. Clinically if the physicians suspect vitamin B12 deficiency in type 2 diabetes subjects on metformin therapy he should do vitamin B12 assay and accordingly treat with oral or injection vitamin B12.

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Abbreviations

BMI- Body mass index. Type2 DM- Type 2 diabetes mellitus. ADA-American diabetes association. EASD-European association of study of Diabetes. AACE-American association of college of endocrinologyIDF-International diabetes federation

References

1. Oh R, Brown DL. Vitamin B12 deficiency. Am Fam Physician. 2003 Mar 1;67(5):979-86.

2. Andrès E, Loukili NH, Noel E, Kaltenbach G, Abdelgheni MB, Perrin AE, Noblet-Dick M, Maloisel F, Schlienger JL, Blicklé JF. Vitamin B12 (cobalamin) deficiency in elderly patients. Canadian Medical Association Journal. 2004 Aug 3;171(3):251-9.

3. Bauman WA, Shaw S, Jayatilleke E, Spungen AM, Herbert V. Increased intake of calcium reverses vitamin B12 malabsorption induced by metformin. Diabetes care. 2000 Sep 1;23(9):1227-31.

4. Wulffele MG, Kooy A, Lehert P, Bets D, Ogterop JC, Burg B, Donker AJ, Stenhouwer CD. Effects of short-term treatment with metformin on serum concentrations of homocysteine, folate and vitamin B12 in type 2 diabetes mellitus: a randomized, placebo-controlled trial. Journal of internal medicine. 2003 Nov 1;254(5):455-63.

5. Mazokopakis EE, Starakis IK. Recommendations for diagnosis and management of metformin-induced vitamin B12 (Cbl) deficiency. Diabetes research and clinical practice. 2012 Sep 30;97(3):359-67.

6. Snow CF. Laboratory diagnosis of vitamin B12 and folate deficiency: a guide for the primary care physician. Archives of internal medicine. 1999 Jun 28;159(12):1289-98.

7. Klee GG. Cobalamin and folate evaluation: measurement of methylmalonic acid and homocysteine vs vitamin B12 and folate. Clinical chemistry. 2000 Aug 1;46(8):1277-83.

8. Reinstatler L, Qi YP, Williamson RS, Garn JV, Oakley GP Jr. Association of biochemical B₁₂ deficiency with metformin therapy and vitamin B₁₂ supplements: the National Health and Nutrition Examination Survey, 1999-2006. Diabetes Care. 2012 Feb; 35 (2):327-33. doi: 10.2337/dc11-1582. Epub 2011 Dec 16.

9. 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 Sep-Oct; 22(5):528-34. doi: 10.3122/jabfm. 2009. 05. 090044.

10. Nervo M, Lubini A, Raimundo FV, Faulhaber GA, Leite C, Fischer LM, Furlanetto TW. Vitamin B12 in metformin-treated diabetic patients: a cross-
sectional study in Brazil. Rev Assoc Med Bras (1992). 2011 Jan-Feb;57(1):46-9.

11. Liu KW, Dai LK, Jean W. Metformin-related vitamin B12 deficiency. Age Ageing. 2006 Mar;35 (2): 200-1.

12. Kumthekar AA, Girwani HV, Kumthekar AB. Metformin-associated B12 deficiency. J Assoc Physicians India. 2012 Mar; 60:58-60.

13. Kos E, Liszek MJ, Emanuele MA, Durazo-Arvizu R, Camacho P. Effect of metformin therapy on vitamin D and vitamin B₁₂ levels in patients with type 2 diabetes mellitus. Endocr Pract. 2012 Mar-Apr;18(2):179-84. doi: 10.4158/EP11009.OR.

14. Qureshi SA, Ainsworth A, Winocour PH. Metformin therapy and assessment for vitamin B12 deficiency: is it necessary?. Practical Diabetes. 2011 Sep 1; 28 (7):302-4.

15. Yajnik CS, Deshpande SS, Lubree HG, Naik SS, Bhat DS, Uradey BS, Deshpande JA, Rege SS, Refsum H, Yudkin JS. Vitamin B12 deficiency and hyperhomocysteinemia in rural and urban Indians. J Assoc Physicians India. 2006 Oct;54:775-82.

16. Shobha V, Tarey SD, Singh RG, Shetty P, Unni US, Srinivasan K, Kurpad AV. Vitamin B12 deficiency & levels of metabolites in an apparently normal urban south Indian elderly population. The Indian journal of medical research. 2011 Oct;134 (4): 432.

17. DeFronzo RA, Goodman AM. Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. The Multicenter Metformin Study Group. N Engl J Med. 1995 Aug 31;333(9):541-9.

18. 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: randomizedplacebo-controlled trial. BMJ. 2010 May 20; 340:c2181. doi: 10.1136/bmj.c2181.

19. Carmel R. Mandatory fortification of the food supply with cobalamin: an idea whose time has not yet come. J Inherit Metab Dis. 2011 Feb; 34(1):67-73. doi: 10.1007/s10545-010-9150-2. Epub 2010 Jun 25.

20. Bell DS. Metformin-induced vitamin B12 deficiency presenting as a peripheral neuropathy. South Med J 2010; 103: 265-7.

21. Leishear K, Boudreau RM, Studenski SA, Ferrucci L, Rosano C, de Rekeneire N, Houston DK, Kritchevsky SB, Schwartz AV, Vinik AI, Hogervorst E, Yaffe K, Harris TB, Newman AB, Strotmeyer ES; Health, Aging and Body Composition Study. Relationship between vitamin B12 and sensory and motor peripheral nerve function in older adults. J Am Geriatr Soc. 2012 Jun;60(6):1057-63. doi: 10.1111/j.1532-5415.2012.03998.x.

22. Naha K, Dasari S, Vivek G, Prabhu M. Vitamin B₁₂ deficiency: an unusual cause for recurrent generalised seizures with pancytopenia. BMJ Case Rep 2012. doi: 10.1136/bcr-2012-006632.

23. Durand C, Mary S, Brazo P, Dollfus S. [Psychiatric manifestations of vitamin B12 deficiency: a case report]. Encephale. 2003 Nov-Dec; 29 (6):560-5.

24. Hin H, Clarke R, Sherliker P, Atoyebi W, Emmens K, Birks J, Schnee J, Ueland PM, Nexo E, Scott J, Molloy A. Clinical relevance of low serum vitamin B12 concentrations in older people: the Banbury B12 study. Age and ageing. 2006 May 18;35(4):416-22.

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