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Original Research Article

Correlation of Vit B12 levels with metformin usage among type 2 diabetic patients in a tertiary care hospital

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ABSTRACT

Background: T2DM is a metabolic disorder that is increasingly becoming a public health concern. The disease is associated with a variety of systemic macrovascular and microvascular complications. Diabetic peripheral neuropathy (DPN) is the most common complication, and it may eventually develop in up to 50% of patients. It is assumed that prolonged use of metformin causes vitamin B12 deficiency. The clinical presentation of vitamin B12 deficiency generally includes haematological and neurological manifestations. The aim of the study is to correlate vit b12 levels in relation to duration of usage of metformin for a period of more than 1 year.
Methods: The study was conducted from November 2017 to June 2018 for a period of 7 months which included 50 subjects from both sex groups, aged 18 years and above, on metformin with subjective evidence of neuropathy and compared with vit b12 levels.
Results: The study results indicate that there is no significant drop in vit b12 levels in metformin users in significant proportions to cause vitb12 deficient-neuropathy. The p value being 0.658 comparing vit b12 with metformin usage years (<2 yrs, 2-5yrs, 5-8yrs, ≥8yrs).
Conclusions: This cross-sectional study indicates that diabetic patients who were on metformin were not having any vit b12 deficiency, though all patients had subjective neuropathy. This suggests that neuropathy is not related to metformin induced Vit B12 deficiency. Therefore, prescribing of vit b12 supplementation in any long term metformin treated patients is no longer necessary and reduces patients financial burden.

Keywords: Metformin, Peripheral neuropathy, Type 2 diabetes mellitus, Vitamin B12

INTRODUCTION

T2DM is a metabolic disorder that is increasingly becoming a public health concern. The disease is associated with a variety of systemic macrovascular and microvascular complications. Diabetic peripheral neuropathy (DPN) is the most common complication, and it may eventually develop in up to 50% of patients.[1] Metformin is the indispensable first-line treatment for type 2 diabetes mellitus (DM) worldwide. It is believed that it prevents the absorption of vitamin B12 in the ileum and this is caused by inhibition of calcium dependent channels in the ileum. It is known that prolonged use of metformin causes vitamin B12 deficiency by this mechanism.[2-6] Both American and European guidelines recommend metformin as the first-line agent for the pharmacological management of T2DM. Accumulating evidence suggests that long-term use of metformin is associated with low vitamin B12 levels, and findings from both observational and interventional studies have

confirmed this association.[7-11] Since vitamin B12 is essential for the remethylation of homocysteine to methionine, metformin-induced vitamin B12 deficiency could be associated with hyperhomocysteinemia, a condition with a questionable detrimental impact on macrovascular disease in T2DM patients.[12]

Metformin acts primarily at the liver by reducing glucose output and, secondarily, by augmenting glucose uptake in the peripheral tissues, chiefly muscle. These effects are mediated by the activation of an upstream kinase, liver kinase B1 (LKB-1), which in turn regulates the downstream kinase adenosine monophosphatase protein kinase (AMPK). AMPK phosphorylates a transcriptional co-activator, transducer of regulated CREB protein 2 (TORC2), resulting in its inactivation which consequently downregulates transcriptional events that promote synthesis of gluconeogenic enzymes.[13] Inhibition of mitochondrial respiration has also been proposed to contribute to the reduction of gluconeogenesis since it reduces the energy supply required for this process.[14] The clinical presentation of vitamin B12 deficiency generally includes haematological and neurological manifestations. Neuropathy can be the only manifestation of the deficiency, without a haematologic presentation.[15] It is also well known that Vitamin B12 deficiency also causes hematological anemia.[16] It is however noteworthy that subtle neurological manifestation appears earlier than hematological changes.[17]

India has more people with diabetes than any other country in the world.[18] The pre-existing cobalamine deficiency as a result of dietary habits poses an additional burden of neuropathy.[19] Animal studies have recently shown that metformin can exert neuroprotective and antineuropathic activities that are independent of its euglycemic effect. Metformin protects against numbness and neuropathic pain induced by chemotherapy in mice.[20] The sensory symptoms of pain, dysaesthesia, and paraesthesia characterize both diabetic PN and chemotherapy-induced PN, signifying the impact of these findings. Animal studies have also reported that metformin abolished pain resulting from the activation of sensory neurons as well as resolved neuropathic allodynia, protected against ethanol-induced neuronal apoptosis, and enhanced neurogenesis.[21-24] It also suppressed cortical neuronal apoptosis and exerted neuroprotective effects in Parkinson's disease.[25,26]

In this study we are aiming to compare vitamin B12 levels in T2DM patients and duration of Metformin usage and also its correlation in different age groups and both sexes.

METHODS

This Prospective hospital-based study extended from November 2017 to June 2018. A total of 50 patients were studied who were attending Medicine OPD and inpatients in the medicine department of Narayana Medical College, Nellore, Andhra Pradesh, India. Vit B12 levels were collected. Complete hemogram was also done to exclude pernicious anaemia and any cellular level changes in blood cells due to borderline Vit B12 deficiency. Normal Vit B12 levels range from 200-832, of which 200-250 were considered borderline, and below 200 were considered deficient.

The patients included in the study group fulfilled the following inclusion criteria:

- Type 2 DM patients, 18 years and above who fulfilled WHO diagnostic criteria (Blood Sugar Fasting >126 or Blood Sugar >200, 2 h after glucose challenge) and
- Patients who were on metformin treatment for at least one year.

The exclusion criteria included patients who were non-consenting; had type 1 diabetes mellitus; had other causes of cobalmine deficiency like malabsorption syndrome or Gastro-Intestinal surgery, Pernicious anaemia, chronic kidney disease and who are "at risk" and "heavy" alcoholics according NIAAA (National Institute on Alcohol Abuse and Alcoholism) Criteria. Approval for this study was received from the ethics board.

RESULTS

Patients using metformin were grouped under 4 categories of <2 years,2-5 years,5-8years, ≥8years and the mean Vit B12 levels in each category are 627.25, 496.87, 394.44, 498.60 respectively (Table 1) with normal range being 200-832 and the total mean of all the groups being 475.04 which indicates there has been no significance of metformin on Vit B12. P value 0.658 that is not significant (Table 1).

Table 1: Comparison of Vit B12 levels among the metformin groups.

Grouping of patients on metformin	No. of patients	Mean vitamin B_{12} level	Std. deviation	F value	P value
<2 Years	4	627.25	277.257		
2-5 Years	15	496.87	385.598		
5-8 Years	16	394.44	321.114	0.540	0.658 (Not Sig.)
≥8 Years	15	498.60	393.468		
Total	50	475.04	356.813		

When depicted graphically there has been a substantial fall in Vit B12 levels among the patients in 5-8 years of metformin usage category, when compared with <2 years, 2-5 years. There was a peak initially and progressive fall is noted when it came to 2-5 year category (Figure 1).

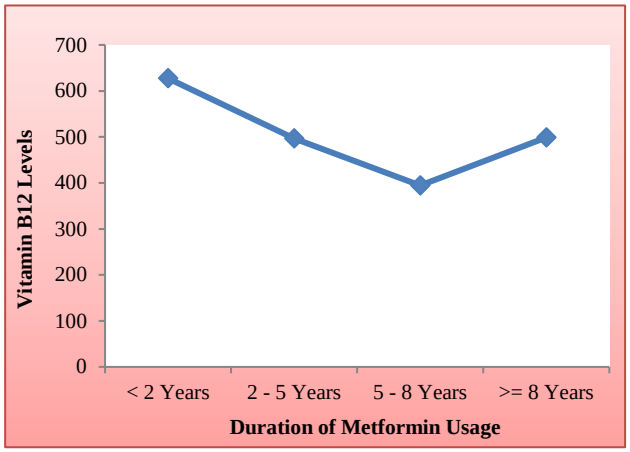

Figure 1: Vit B12levels with metformin years.

Present study includes total of 50 patients with males=34, females=16 patients. when analysed in both males and females. Of all the categories, 5-8 years category show decreased level of Vit B12 of mean 404.69 in males and 350.00 in females. Mean vitamin B12 levels in males and females are 478.00 and 468.75 respectively (Table 2).

Table 2: Age wise comparision of metformin with Vit B12in both sex.

Sex	Grouping of patients on metformin in years	Mean vitamin B12 levels	Std. deviation of Vit B12	No. of patients
Males	2-5 Years	542.30	467.101	10
	5-8 Years	404.69	349.754	13
	≥8 Years	506.18	453.303	11
	Total	478.00	412.177	34
Females	< 2 Years	627.25	277.257	4
	2-5 Years	406.00	118.341	5
	5-8 Years	350.00	189.058	3
	≥8 Years	477.75	191.681	4
	Total	468.75	205.126	16
Total	<2 Years	627.25	277.257	4
	2-5 Years	496.87	385.598	15
	5-8 Years	394.44	321.114	16
	≥8 Years	498.60	393.468	15
	Total	475.04	356.813	50

DISCUSSION

The 2018 ADA Clinical Practice Recommendations endorse screening Metformin users for vitamin B12deficiency and the 2017 ADA diabetic neuropathy statement recommends that all patients with diabetic neuropathy should be assessed for B12 deficiency, to exclude a treatable cause of neuropathy.[27] Lower prevalence of B12 deficiency in patients taking Metformin, were assessed confounding factors such as other medications, which may alter B12 levels. Sulfonylurea use in combination with Metformin is a significant independent risk factor for B12 deficiency.[28] B12 levels have also been reported to be lower in older adults with prolonged PPI and H2 blocker use in one study.[29]

Vitamin B12 deficiency can lead to clinically significant but treatable conditions. These include a wide range of clinical conditions, such as memory impairment, peripheral neuropathy, dementia, delirium, sub acute combined degeneration of the spinal cord, megaloblastic anemia and pancytopenia. Accumulating evidence suggests that long-term use of metformin is associated with low vitamin B12 levels, and findings from both observational and interventional studies have confirmed this association.[7-11]

As far as our study is concerned there has been no correlation of metformin with Vit B12levels which maybe supporting as well as contradicting some studies. in our study no. of patients on metformin for >8 years in both males and females are 11 (22%) and 4 (8%) constituting a total of 30% of population. further studies should be encouraged to conduct vit B12 levels in prolonged metformin users of more than 10 years to substantiate any significant correlation.

Clinically, a retrospective chart review also reported the association between metformin use and a decrease in lumbar radiculopathy pain.[30] Antineuropathic effects of metformin may be mediated by 5-adenosine monophosphate-activated protein kinase (AMPK) activation.[31]

Impaired AMPK signaling was linked to PN in animals.[32] So, in contrary to the above mentioned citations and research, there has been exerted a neuroprotective effect in animal studies, and not yet confirmed on humans. If there is neuropathic effect in metformin users, molecular level evidence is not yet found to substantiate. Whereas animal studies 5AMPK signaling impairment was found to be the culprit.

However, unless proven otherwise vitamin b12 supplementation in metformin users must be withheld causing a financial burden among many patients.[27,28] Many patients suffering from pernicious anemia with type 2 diabetes mellitus have been with held metformin even it is first line of treatment according to current guidelines.[7-11]

Limitations of this study were that previous vitamin supplementation history was not available among patients and neuropathy in patients was completely subjective and no objective evidence is available.[7]

CONCLUSION

There has been a negative correlation in between vitamin B12 levels and metformin usage. There was no significant reduction in the patients even on prolonged usage of 5-8years. In the metformin usage patients for more than 8 years have a normal levels when compared to previous group. Thereby indicating that our study shows there is no significance of vitamin B12 supplementation in metformin users as these are not the culprits in occurrence of peripheral neuropathy. Financial burden both for patients and government can be reduced to a great extent since it takes a great amount of effort and money to supply a broad base of patients for a long-term of period.

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REFERENCES

1. Tesfaye S, Boulton AJ, Dyck PJ, Freeman R, Horowitz M, Kempler P et al. Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. Diabetes Care. 2010 Oct 1;33(10):2285-93.
2. Chapman LE, Darling AL, Brown JE. Association between metformin and vitamin B (12) deficiency in patients with type 2 diabetes: A systematic review and meta-analysis. Diabetes Metab. 2016;42:316-27.
3. Iftikhar R, Kamran SM, Qadir A, Iqbal Z, bin Usman H. Prevalence of vitamin B12 deficiency in patients of type 2 diabetes mellitus on metformin: a case control study from Pakistan. Pan Afr Med J. 2013;16:67.
4. Ko SH, Ko SH, Ahn YB, Song KH, Han KD, Park YM, et al. Association of vitamin B12 deficiency and metformin use in patients with type 2 diabetes. J Korean Med Sci. 2014;29:965-72.
5. Mazokopakis EE, Starakis IK. Recommendations for diagnosis and management of metformin-induced vitamin B12 (Cbl) deficiency. Diabetes Res Clin Pract. 2012;97:359-67.
6. Kumthekar AA, Gidwani HV, Kumthekar AB. Metformin associated B12 deficiency. J Assoc Physicians India. 2012;60:58-60
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 May 20;340:c2181.
8. Ting RZ, Szeto CC, Chan MH, Ma KK, Chow KM. Risk factors of vitamin B12 deficiency in patients receiving metformin. Arch Internal Med. 2006 Oct 9;166(18):1975-9.
9. Nervo M, Lubini A, Raimundo FV, Faulhaber GA, Leite C, Fischer LM et al. Vitamin B12 in metformin-treated diabetic patients: a cross-sectional study in Brazil. Revista Da Associacao Medica Brasileira. 2011 Feb;57(1):46-9.
10. Sparre Hermann L, Nilsson BO, Wettre S. Vitamin B12 status of patients treated with metformin: a cross-sectional cohort study. Br J Diab Vascu Dis. 2004 Nov;4(6):401-6.
11. Pflipsen MC, Oh RC, Saguil A, Seehusen DA, Seaquist D, Topolski R. The prevalence of vitamin B12 deficiency in patients with type 2 diabetes: a cross-sectional study. J Am Board Fam Med. 2009 Sep 1;22(5):528-34.
12. Russo GT, Di Benedetto A, Magazzù D, Giandalia A, Giorda CB, Ientile R et al. Mild hyperhomocysteinemia, C677T polymorphism on methylenetetrahydrofolate reductase gene and the risk of macroangiopathy in type 2 diabetes: a prospective study. Acta Diabetol. 2011 Jun 1;48(2):95-101.
13. Shaw RJ, Lamia KA, Vasquez D. The kinase LKB1 mediates glucose homeostasis in liver and therapeutic effects of metformin. Science. 2005;310:1642-6.
14. El-Mir MY, Nogueira V, Fontaine E. Dimethylbiguanide inhibits cell respiration via an indirect effect targeted on the respiratory chain complex I. J Biol Chem. 2000, 275: 223-228. 10.1074/jbc.275.1.223.
15. Healton EB, Savage DG, Brust JC, Garrett TJ, Lindenbaum J. Neurologic aspects of cobalamin deficiency. Medicine. 1991 Jul;70(4):229-45.
16. Ismail II, John JK, Ibrahim M. Neurological, hematological and dermatological manifestations of vitamin deficiency secondary to pernicious anemia. J Neurol Stroke. 2015;3(3):00095.
17. Oh R, Brown DL. Vitamin B12 deficiency. Am Fam Physician. 2003 Mar 1;67(5):979-86.
18. Kaveeshwar SA, Cornwall J. The current state of diabetes mellitus in India. Australasian Med J. 2014;7(1):45-48.
19. Pawlak R, Parrott SJ, Raj S, Cullum-Dugan D, Lucus D. How prevalent is vitamin B12 deficiency among vegetarians?. Nutri Rev. 2013 Feb 1;71(2):110-7.
20. Mao-Ying QL, Kavelaars A, Krukowski K, Huo XJ, Zhou W, Price TJ et al. The anti-diabetic drug metformin protects against chemotherapy-induced peripheral neuropathy in a mouse model. PloS One. 2014 Jun 23;9(6):e100701.
21. Melemedjian OK, Khoutorsky A, Sorge RE, Yan J, Asiedu MN, Valdez A et al. mTORC1 inhibition induces pain via IRS-1-dependent feedback activation of ERK. PAIN®. 2013;154(7):1080-91.
22. Melemedjian OK, Asiedu MN, Tillu DV, Sanoja R, Yan J, Lark A et al. Targeting adenosine monophosphate-activated protein kinase (AMPK) in preclinical models reveals a potential mechanism for

the treatment of neuropathic pain. Molecular Pain. 2011 Dec;7(1):70.
23. Ullah I, Ullah N, Naseer MI, Lee HY, Kim MO. Neuroprotection with metformin and thymoquinone against ethanol induced apoptotic neuro-degeneration in prenatal rat cortical neurons. BMC Neurosci. 2012 Dec;13(1):11.
24. Wang J, Gallagher D, DeVito LM, Cancino GI, Tsui D, He L et al. Metformin activates an atypical PKC-CBP pathway to promote neurogenesis and enhance spatial memory formation. Cell Stem Cell. 2012 Jul 6;11(1):23-35.
25. El-Mir MY, Detaille D, Gloria R, Delgado-Esteban M, Guigas B, Attia S, Fontaine E, Almeida A, Leverve X. Neuroprotective role of antidiabetic drug metformin against apoptotic cell death in primary cortical neurons. J Molecular Neurosci. 2008 Jan;34(1):77-87.
26. Patil SP, Jain PD, Ghumatkar PJ, Tambe R, Sathaye S. Neuroprotective effect of metformin in MPTP-induced Parkinson's disease in mice. Neuroscience. 2014 Sep 26;277:747-54.
27. Pop-Busui R, Boulton AJ, Feldman EL, Bril V, Freeman R, Malik RA, et al. Diabetic neuropathy: a position statement by the American Diabetes Association. Diabetes Care. 2017;40:136-54.
28. Kang D, Yun JS, Ko SH, Lim TS, Ahn YB, Park YM, et al. Higher prevalence of metformin-induced vitamin B12 deficiency in sulfonylurea combination compared with insulin combination in patients with type 2 diabetes: a cross-sectional study. PLoS One. 2014;9:e109878.
29. den Elzen WP, Groeneveld Y, de Ruijter W, Souverijn JH, le Cessie S, Assendelft WJ, et al. Long-term use of proton pump inhibitors and vitamin B12 status in elderly individuals. Aliment Pharmacol Ther. 2008;27:491-7.
30. Taylor A, Westveld AH, Szkudlinska M, Guruguri P, Annabi E, Patwardhan A et al. The use of metformin is associated with decreased lumbar radiculopathy pain. J Pain Res. 2013;6:755-763.
31. Ma J, Yu H, Liu J, Chen Y, Wang Q, Xiang L. Metformin attenuates hyperalgesia and allodynia in rats with painful diabetic neuropathy induced by streptozotocin. Eur J Pharmacol. 2015;764:599-606.
32. Roy Chowdhury SK, Smith DR, Saleh A, Schapansky J, Marquez A, Gomes S et al. Impaired adenosine monophosphate-activated protein kinase signalling in dorsal root ganglia neurons is linked to mitochondrial dysfunction and peripheral neuropathy in diabetes. Brain. 2012 May 4;135(6):1751-66.

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