

Metformin Induced Vitamin B12 deficiency: A Cross sectional study. Untangling the connection

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Abstract

Background: Metformin is a widely popular drug to treat type 2 diabetes as it is efficacious, inexpensive and relatively well tolerated with minimal side effect profile. It is known that long term metformin use predisposes a person to develop Vitamin B12 deficiency, however guidelines to screen and treat are yet to be well established. Vitamin B12 deficiency is known to cause peripheral neuropathy and anemia.

Methods: Ours is a prospective, observational, cross sectional study based in a hospital setting in a tertiary care center. Study participants were subjected to serum Vitamin B12 analysis and Michigan neuropathy screening instrument was used to screen for peripheral neuropathy.

Results: We report statistically significant association between metformin use and development of Vitamin B12 deficiency. The average duration of metformin use that resulted in development of Vitamin B12 deficiency was 13.6 years. We also found statistically significant association of metformin use with development of peripheral neuropathy.

Conclusion: Long term metformin leading to Vitamin B12 deficiency is common knowledge, however we need more targeted guidelines on when to screen and treat for B12 deficiency. Some subsets of the population such as elderly and vegetarians are more prone and hence we need to educate more physicians and patients on the same.

Plain language summary

Metformin Induced Vitamin B12 deficiency

Diabetes is a hugely prevalent disease resulting from a persistently elevated blood glucose level. Its adverse effects on overall lifespan and lifestyle are well known. Long standing diabetes is so dangerous as it affects blood vessels of different calibers which eventually leads to injury of the organs it supplies. Diabetic peripheral neuropathy is a term used when there is injury to nerves supplying the limbs because of long standing and often uncontrolled diabetes. A similar neuropathy/nerve damage may result from other causes such as Vitamin B12 deficiency. A popular drug used to control blood sugars is Metformin. It is considered effective and relatively safe and cost effective, making it a popular choice to treat Type 2 diabetes. Metformin has been known to contribute towards Vitamin B12 deficiency in a small sub group of users when used for a long duration. In this prospective observational study our intent primarily was to explore this association. Results from our study show that there is a direct association between the dose and duration of metformin use with the development of Vitamin B12 deficiency. This would mean that a person on long term metformin is more likely to develop Vitamin B12 deficiency as an undesired effect. This is in line with other Indian and International studies which have showed similar results as ours. Although our study also showed an increased likelihood of neuropathy with metformin use, the results were not statistically significant to make an association. New guidelines have since been set forth by the American diabetic association to screen for Vitamin b12 deficiency among people with diabetes on metformin. As this is a easily preventable side effect, when screened and treated, it is important to create awareness among both physicians and people with diabetes regarding this association.

Keywords

metformin, vitamin b12 deficiency, peripheral neuropathy, anemia

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Introduction

Insulin resistance is one of the major contributors to the growing diabetes epidemic. This is largely due to excess body weight and sedentary lifestyle that lacks physical activity. Among the different types, Type 2 diabetes is overwhelmingly the most common type, resulting from a direct consequence of Insulin resistance.^{1,2}

Metformin is approved for use as first line medication both as monotherapy and in combination, given its high efficacy, relative safety, favorable effects on cardiovascular system and weight.³

Given its widespread use, it is imperative that we understand, screen and treat all side effects related to its long-term consumption. Vitamin B12 deficiency is one such effect, all though a well-known association, not truly screened, quantified, and treated in a timely manner. Vitamin B12 deficiency is known to adversely affect the hematological and nervous system to varying degrees.

Long term metformin use is known to cause clinical Vitamin B12 deficiency with the predominant mechanism being due to calcium mediated reduction in intestinal absorption. It is seen more commonly in elderly, vegetarians. More recent studies and guidelines have highlighted this very fact and advocated for testing in at risk population and long-term users.^{4,5,8,11}

Aim

To study the association between Metformin use and Vitamin B12 deficiency in Type 2 diabetics

Primary Objectives

To study the association between Metformin use and Vitamin B12 deficiency in Type 2 diabetics.

Secondary Objectives

- 1) To study the correlation between dose and duration of Metformin use and Vitamin B12 deficiency.
- 2) To study the occurrence of diabetic peripheral neuropathy (PN) due to vitamin B12 deficiency in Type 2 diabetics
- 3) To study the occurrence of macrocytic anemia due to Vitamin B12 deficiency in Type 2 diabetics on metformin.

Methods

Study Design

Prospective, observational, cross sectional, hospital-based study on 205 patients from the Department of General Medicine at Kasturba Hospital, Manipal between March 2021 to October 2022.

Inclusion Criteria

- Type 2 Diabetics as per American Diabetes Association guidelines

- Age 30 to 80 years
- On Metformin

Exclusion Criteria

- Patients with liver failure, chronic liver disease
- Pregnancy
- Hypothyroidism, autoimmune thyroid disease
- Patients with Renal failure (Creatinine Clearance <30 ml/min/stage 4 and above)
- People suffering from bowel disorders such as—Atrophic gastritis, Pernicious anemia, IBD, Chronic Pancreatitis, Whipple's disease, Parasitic Infections.
- Post bowel surgeries such as Gastrectomy, Terminal Ileal resection surgeries and Bariatric surgeries.
- Patients treated for Vitamin B12 deficiency with a course of Injection Vitamin B12.

Methodology: Patients attending Kasturba hospital who satisfied the inclusion and exclusion criteria were included in the study after obtaining informed consent from all participants. Detailed history and examination details were obtained based on a proforma. All patients were tested for peripheral neuropathy using Michigan Neuropathy Screening Instrument (MNSI).⁶ The collected data was compiled, and statistical analysis was done.

Statistical Analysis: Comparison of quantitative variables was done using ANOVA. Comparison of categorical data was done using Chi Square. A *P* value less than .05 was considered statistically significant.

Results

AGE: Subgroup of population more than 60 years of age were 48.8% with a mean age of the study group being 59 years. Males were in small majority at 58.5%. Up to 26.8% of the subjects were vegetarian.

Baseline Characteristics: The baseline characteristics have been depicted in Table 1. Half the subjects were on metformin for a duration between 5 and 10 years with a mean duration of 9.62 years.

Duration Of Diabetes (in years): Half the subjects were on metformin for a duration between 5 and 10 years with a mean duration of 9.62 years.

Duration Of Metformin use (in years): Majority of the subjects, 54% of them were on sulfonylureas in addition to Metformin. The second most common being DPP4 inhibitors, followed by Alpha-glucosidase inhibitors.

Complications:

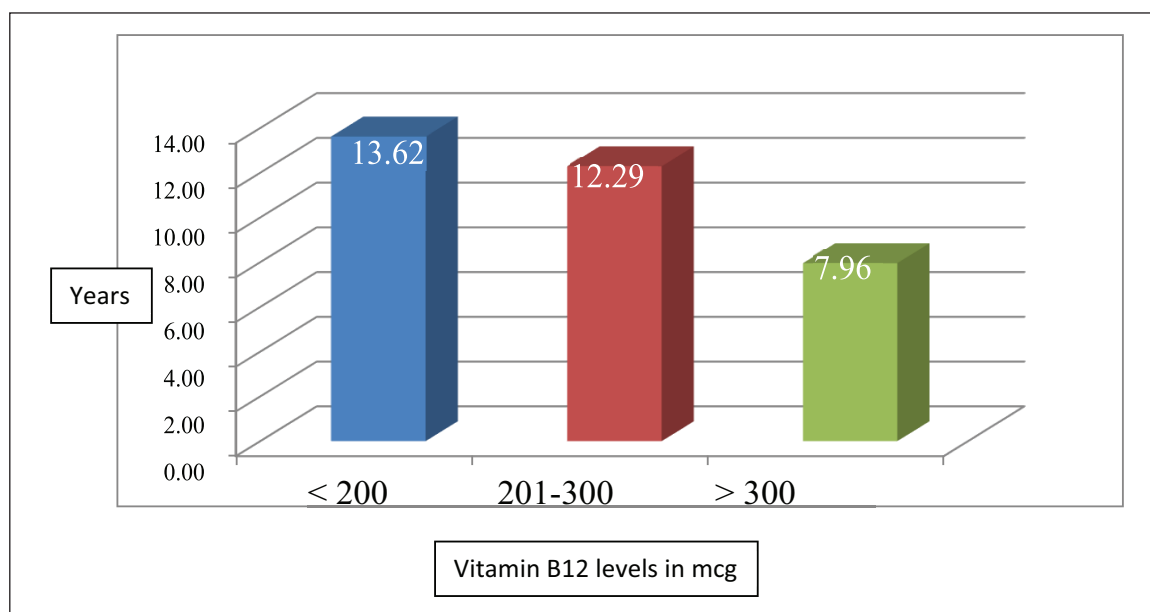
Macrovascular: Among the macrovascular complications, CAD was the most common, seen in 18.5% of the total subjects. This was followed by CVA seen in 9.8% and PVD in 3.4% of the subjects.

Microvascular: Peripheral neuropathy was the most common microvascular complication, seen in 22% of the subjects, followed by diabetic nephropathy and retinopathy in 19.5% and 7.8% respectively.

Vitamin B12 Deficiency: Vitamin B12 deficiency was seen in a total of 35 subjects accounting to 17.1% of total. Absolute deficiency (B12 levels <200 pg/ml)—10.2%

Table 1. Baseline characteristics of study population.

Baseline characteristics	Minimum	Maximum	Mean	Standard deviation
Age (in years)	33	83	59.5	10.98
Duration of diabetes(in years)	1	30	9.6	6.62
Duration of metformin use(in years)	1	30	8.8	5.8
HB (g/dl)	4.9	17	11.6	2.3
Hba1c	4.7	14	8.4	1.98
Serum B12 levels (pg/ml)	100	2000	1010.1	698.8

**Figure 1.** Duration of metformin (in years) and B12 deficiency.**Table 2.** Comparison of type of anemia with b12 levels.

Parameters	Number of patients	Percentage	Number of patients	Percentage	Number of patients	Percentage	Total
Serum B12 levels	<200	<200	201-300	201-300	>300	>300	
Type of anemia							
Macrocytic	3	75.0%	3	42.9%	1	2.2%	7
Microcytic	1	25.0%	1	14.3%	20	43.5%	22
Normocytic	0	0.0%	3	42.9%	25	54.3%	28
Total	4	100.0%	7	100.0%	46	100.0%	57

Intermediate deficiency (B12 levels 201-300pg/ml)—6.8%.

Anemia: 52 subjects were found to be anemic which accounted to 25.4% of the total study population.

Peripheral Neuropathy: PN was identified amongst 22% of the subjects, which equates to 45 subjects.

Duration Of Metformin and Vitamin B12 Deficiency:

We report a statistically significant correlation between duration of metformin and B12 deficiency (as shown in Figure 1). Mean duration of 12.29 years was associated with intermediate Deficiency and 13.62 with absolute deficiency while a normal B12 levels were seen with a mean duration of 7.96 years. (as shown in Table 2)

Duration Of Metformin and Peripheral Neuropathy: Among patients with PN, 71% were on metformin for >10 years, 28% were on metformin for a duration between 5 and 10 years.

Dose Of Metformin and Peripheral Neuropathy: Among patients with PN, majority that is, 71% were on doses of metformin between 500 and 1000mg, while majority without PN—66.9% were on doses of $\leq$ 500mg/day. (as shown in Figure 2 and Table 3)

Vitamin B12 Deficiency and Peripheral Neuropathy (in pg/ml): Among subjects with low B12 levels of <200 pg/ml, 71% had PN and with subjects having Normal B12 levels, only 13.5% had PN.

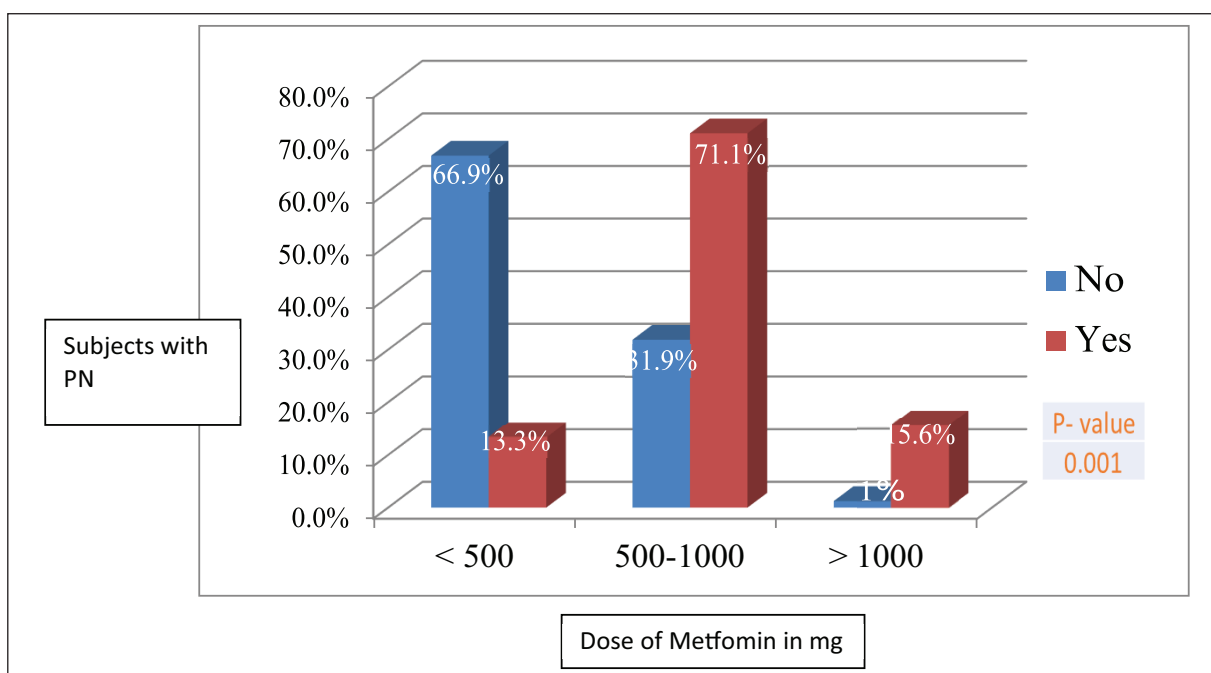


Figure 2. Dose of metformin and PN.

Table 3. Multivariate analysis between serum vitamin b12 levels and duration of diabetes/duration of metformin use.

Parameters	Serum B12 levels						Total	Chi-square value	P-value
	<200	201-300	>300						
5. Duration of diabetes (in years)	<5	2 9.5%	5 35.7%	80 47.1%	87		17.832	.001	
	5-10.0	7 33.3%	1 7.1%	46 27.1%	54				
	>10	12 57.1%	8 57.1%	44 25.9%	64				
Total	21	100.0%	14	100.0%	170	100.0%	205		

Parameters	Serum B12 levels						Total	Chi-square value	P-value
	<200	201-300	>300						
6. Duration of Metformin use (in years)	<5	2 9.5%	5 35.7%	84 49.4%	91		25.548	.001	
	5-10.0	7 33.3%	1 7.1%	53 31.2%	61				
	>10	12 57.1%	8 57.1%	33 19.4%	53				
Total	21	100.0%	14	100.0%	170	100.0%	205		

Type of Anemia and Vitamin B12 Levels: Among anemics with low B12 levels, 75% showed a peripheral smear consistent with macrocytic anemia. Normocytic anemia was present majority—54.3% of subjects with normal B12 levels (As shown in Table 4).

Diet and Vitamin B12 Levels: We found no statistically significant correlation between B12 and diet.

Multi-variate analysis:

A multi-variate analysis was done between the different variables/factors affecting the vitamin b12 in the study population (as shown in Table 3). We found that the duration of diabetes and the duration of metformin use was statistically significant ($P=.001$).

We also noted a statistically significant association between Vitamin b12 levels and the microvascular complications of diabetes as shown in Table 4. We analyzed

the association between microvascular retinopathy, nephropathy and neuropathy in our study population. We noted that nephropathy and neuropathy has a statistically significant association with serum vitamin b12 levels ($P=.001$).

Discussion

The primary objective of the study was to find an association between metformin use and Vitamin B12 deficiency. In addition, we studied the relation of duration and dose of metformin use with development B12 deficiency, anemia, and peripheral neuropathy.

Diabetes is a widely prevalent chronic disease and metformin is the most common diabetic medication prescribed for it. In the Indian population, as much as 90% of people

Table 4. Multivariate analysis between serum vitamin b12 and microvascular complications of diabetes.

Microvascular complications of diabetes	Serum B12 levels							Total	Chi-square value	P-value
		<200		201-300		>300				
Microvascular—Retinopathy		4	19.0%	4	28.6%	42	24.7%	50	0.908	.923
	No	16	76.2%	9	64.3%	114	67.1%	139		
	Yes	1	4.8%	1	7.1%	14	8.2%	16		
Microvascular—nephropathy		2	9.5%	0	0.0%	0	0.0%	2	20.708	.001
	No	18	85.7%	12	85.7%	133	78.2%	163		
	Yes	1	4.8%	2	14.3%	37	21.8%	40		
Microvascular—Neuropathy	No	6	28.6%	6	42.9%	139	81.8%	151	34.605	.001
	Yes	15	71.4%	8	57.1%	31	18.2%	54		
Total		21	100.0%	14	100.0%	170	100.0%	205		

with diabetes are being treated with metformin.⁷ The association between metformin causing B12 deficiency, although widely known, lacks backing with strong evidence from large scale RCTs and metanalysis. There are few large international studies and only one large Indian study exploring this association.^{8,9}

Recent studies and guidelines have addressed the need for testing in long term metformin users, especially so in high risk patients.

Study Population

Age group of the subjects in our study included predominantly middle to elderly population with a mean age of 59 years. This is comparable with other studies where the mean age was in the range of 50-60 ± 10 years.^{8,10,11} We had 58.5% males and 41.5% females in our study, a distribution which is a good representation of the general population.

Of the total study population, 26.8% were vegetarians. A similar study was done in Bangalore by Shivaprasad et al in which 33.3% of their participants were vegetarians.⁸ The relatively high number can be attributed to a higher group of vegetarian population found in this southern part of the country. As vegetarian diet is a well-known risk factor for B12 deficiency, we expected a bias, however, we found no statistically significant association between the two. One of the reasons for this could be because among a large subset of non-vegetarians, meat consumption was limited to once a week, which is not sufficient to meet the dietary requirement of B12. The mean duration of diabetes and metformin use we found were 9.62 and 8.62 years. Other studies had a mean duration of diabetes ranging from 4.6 to 11.1 years.^{8,12}

The mean HbA1c in this study was 8.45. This indicates that the study population predominantly had uncontrolled T2DM. This is interesting as the study population is from the patient pool regularly visiting the hospital. Singh et al reported a mean HbA1c of 8.2 in their cross-sectional study that included 136 subjects.¹³ As this is a hospital-based study, majority of the subjects were middle age-elderly population with a long-standing history of T2DM and metformin use. This study population included predominantly long-standing uncontrolled diabetics, which could have a

bearing on increased prevalence of macro and microvascular complications of T2DM.

We found that 74% of the subjects were on oral hypoglycemics in addition to metformin, sulphonyl urea being the most common in upto 54%. These are comparable to the Indian study done by Singh et al that reported 60% of their subjects on sulfonylureas.¹³ This could be explained by the effectiveness and relatively cheaper cost of sulfonylureas. Prescription of gliptins are fast catching up as they have fewer side effect profile such as hypoglycemia as compared to sulfonylureas and increasing affordability in recent times. Gliptins were prescribed in addition to metformin in 19% of the study population. Gliptins have an added benefit due to their cardioprotective effects. Prescription of gliptins are fast catching up as they have fewer side effects such as hypoglycemia as compared to sulfonylureas and increasing affordability in recent times. A small population—0.5% were also on gliflozins, which have significant cardiac and renal benefits, independent of their glucose lowering abilities.

Complications of Diabetes

In our study population we found macrovascular complications in the form of Cerebrovascular accident (CVA), coronary artery disease (CAD) and Peripheral vascular disease (PVD) with CAD being the most common, seen in 18.5% of the subjects. Other Indian studies report similar prevalence of CAD at 21% among people with diabetes and 11% among non-diabetics.^{14,15} Diabetes is an important risk factor for atherosclerotic CAD and various studies Indian and global have projected as much as 2 to 4 times higher risk of CAD among people with diabetes when compared with non-diabetics. CAD also accounts for the most common cause of mortality among people with diabetes because of acute coronary syndromes.

Among microvascular complications, peripheral neuropathy (PN) or diabetic peripheral neuropathy (DPN) was the most common. We used the Michigan Neuropathy Screening Instrument (MNSI) to check for DPN. This is widely accepted and used tool for testing DPN. It has been used in large, randomized control studies (RCTs) and in cross sectional studies.^{16,17} Almost 22% of our subjects had DPN.

This is in line with other international studies and Indian studies reporting prevalence ranging between 18.5 and 28.3%. The prevalence is directly related to the duration of diabetes, metformin use and uncontrolled sugars. DPN is a well-known complication in long standing diabetics occurring because of microvascular ischemia affecting the vasa-nervorum. PN can occur secondary to Vitamin B12 deficiency and due to T2DM, however we were unable to differentiate the cause of DPN from among the two.

Among microvascular complications the second most common was diabetic nephropathy at 19.5%. Other similar Indian studies report a prevalence ranging from 18.8% to 26.9%.^{18,19} Diabetic nephropathy is another devastating complication of uncontrolled T2DM with as high as 20% of diabetic kidney disease patients ending up in end stage renal disease. It greatly adds to the overall morbidity and mortality in diabetics.

Metformin Induced Vitamin B12 Deficiency

The association dates to 1969 to 1971 when Berchtold et al and Tomkin et al reported the evidence of B12 deficiency in metformin users with cross sectional studies. Since then, case reports, cross-sectional, retrospective, and longitudinal, observational studies, as well as research on the use of metformin for an extended period, have revealed a clinical link between the two. There

Are very few prospective placebo-controlled trials comparing this association.^{20,21}

One such trial done by De Jager et al studied effects of metformin on the incidence of Vitamin B12 in patients with Type 2 diabetes. A total of 390 patients were randomized to receive 850 mg of metformin or placebo. In comparison to placebo, metformin group had a mean decrease in B12 concentration of 19% (95% CI: 24%-14%; $P < .001$). The absolute risk of low B12 concentration was 11.2% higher in the metformin arm.²¹

Another large-scale placebo RCT was conducted by Aroda et al from UK in 2018, who studied the risk of B12 deficiency with metformin use in the diabetes prevention program as part of a secondary analysis. The study had 2146 subjects divided equally into a metformin arm and a placebo arm. B12 levels were assessed at 5 years. The study found lower B12 levels among subjects on metformin ($P = .02$).⁸ Both these RCTs expressed the need for regular measurement of B12 levels in patients on long term metformin.^{8,12}

The present study showed a positive correlation with development of B12 deficiency and metformin use. 17% of our subjects on metformin developed B12 deficiency.

A prospective observational study from Bangalore conducted by Shivaprasada et al in 2020, in which 2887 people were examined to determine how long and how much metformin were taken before developing B12 deficiency. They detected B12 levels <200 pg/ml in 24.5% metformin users and intermediate B12 levels of <300 pg/ml in 34.5%. We reported in our study, B12 levels of <200 pg/ml in 10.2% and B12 of <300 pg/ml in 17.1% of metformin users.⁸ We report a relatively smaller percentage of B12 deficiency

among metformin users in comparison to similar Indian studies. This could be partly due to multivitamin supplements that few of our subjects were on, that could have masked the effect of metformin on B12 levels.

Dose of Metformin and B12 Deficiency

A cross sectional study done by Kim et al studied 1111 patients on metformin and found a statistically significant correlation of doses of metformin >1500 mg, with B12 deficiency,¹² however for doses 500-1000 and 1000-1500 mg they reported no statistically significant results.

Another study comparing the dose of metformin with B12 levels by Ko et al reported low B12 levels with doses of >1000 mg/day of metformin ($P = .02$).²² Patients receiving more than 2 g metformin had a significantly greater chance of developing B12 insufficiency as shown by a meta-analysis by Yang et al of 23 trials (RR-3.26 $P = .001$).²³ In a cross-sectional investigation, Singh et al discovered a negative relationship between cumulative metformin dose and B12 levels ($r = .6$, $P < .01$).¹³

While most studies declare a positive correlation with dose and duration of metformin use with B12 deficiency, some studies have not.¹⁷ We report a statistically significant association with dose of metformin and B12 deficiency ($P = .001$). In our study we found a mean metformin dose of 964 and 1130 mg for B12 levels between 200-300 and <200 pg/ml respectively. Most studies have shown a positive correlation of B12 deficiency with metformin dose >1000 mg/day. We report a similar association. Higher dose of metformin causes more significant interference with B12 absorption from the gut, leading to more likely occurrence of B12 deficiency.

Duration of Metformin and B12 Deficiency

It has been found that, longer the duration metformin use higher is the risk of developing B12 deficiency. A study done by Ko et al stated that B12 deficiency was associated with metformin consumption of >4 years.²³ Our study showed a mean duration of 12 years for development of B12 deficiency among metformin users. It also showed a mean duration of 7.9 years of metformin in subjects with normal B12 levels.²⁴

According to a meta-analysis by Yang et al of 23 trials, people taking metformin for more than 3 years had a greater risk of having a B12 deficiency than people taking it for less than 3 years (RR-2.88 $P = .001$).²³

Shivaprasad et al used Metformin usage index in their study (MUI=Duration of metformin in years multiplied by dose in mg/day divided by 1000). They found B12 deficiency associated more closely with an MUI >5 as compared to subjects with a lesser MUI.⁸

Although duration of metformin in our study is an indicator of cumulative metformin usage over time, a tool such as MUI would have been more effective in assessing dose and duration of metformin use and its effects on B12 levels.

Metformin and Peripheral Neuropathy

Metformin induced cobalamin deficiency (MCD) can cause new onset PN or worsen nerve damage in patients with pre-existing DPN or cause a mixed “diabetic and MCD-related neuropathy.”

When compared to the metformin group with normal B12 levels, a subsequent analysis of the diabetes preventive program study during a 9-year follow-up showed a statistically significant greater prevalence of PN. However, the cases of neuropathy ($n=13$) were too small to draw a meaningful inference from ($n=15$).

In contrast, a meta-analysis of 6 studies by Yang et al that included a total of 1058 patients and they reported no significant risk of B12 deficiency in subjects on metformin compared with non-users ($RR=1.09$ $P=.68$).²³

A cross sectional study with 162 subjects done by Alvarez et al found a significant negative correlation with B12 levels and PN. They reported low or borderline B12 levels in 64% of patients with DPN.²⁵

An Indian study done by Hashem et al carried out a prospective case control study on 150 adults in which 75 were on metformin for 6 months or more and 75 were not.²⁶ The study showed a higher frequency and severity of DPN in metformin users. Additionally, median conduction velocity and sensory nerve action potential on NCS were considerably lower among metformin users. They also reported an inverse correlation between B12 levels and PN.²⁵

Our study had showed 86.5% of DPN with low and intermediate B12 levels and among patients without PN, 13.5% had low or borderline B12 levels.

In our study population with PN, 71% of them were on metformin for 10 years or more and were taking metformin at doses between 500 and 1000 mg/day. We report a statistically significant positive correlation between dose and duration of metformin with PN. This increase in PN in long term metformin is a known entity in long term diabetics and another reason for the increase could be due to B12 deficiency from metformin use, which led to PN. The latter can be justified as most of the DPN subjects had low to intermediate B12 levels. B12 deficiency is known to cause new onset PN or worsen pre-existing DPN.

Metformin and Anemia

Aroda et al as part of a sub analysis of the diabetic prevention program study, investigated the relation of metformin and anemia. They found a non-significant increase of anemia in metformin users ($P=.25$).⁸ Our analysis also showed similar results with a statistically insignificant increase in anemia with metformin use ($P=.18$), however we found that 75% of subjects with low B12 levels showed a macrocytic anemia picture (.001). Even though we could not make any statistically significant association, our results of predominant macrocytic anemia in B12 deficiency subjects are consistent with the known knowledge that Vitamin B12 deficiency leads to poor maturation of RBCs in the marrow and a macrocytic anemia on peripheral smear.

Although we have accumulated significant evidence associating metformin use and B12 deficiency, as well as a

potential clinical sequelae such as peripheral neuropathy and macrocytic anemia, diagnosing, and treating B12 deficiency has not been implemented in long term metformin users.²¹

Given the global usage of metformin in diabetic and non-diabetic illnesses (PCOS, gestational DM) and chronicity of the conditions it is used for, there is a need to recognize adverse consequence such as B12 deficiency. As stated by other trials, regular identification of B12 deficiency in long term metformin treated individuals must be considered.

Limitations of the study: This being an observational study, real world derivation of the results will be less useful. Sample size was not derived from statistical analysis. A significant portion of the subjects were vegetarians and hence could be a confounding factor for development of Vitamin B12 deficiency.

Conclusion

Patients on long term metformin therapy are at a high risk of developing B12 deficiency and PN. The risk is incremental among “at risk” population which includes elderly and vegetarians. B12 deficiency can increase the risk of early onset DPN in addition to causing neuropathy on its own. Interval screening for B12 deficiency in patients on long term metformin would be useful in preventing further complications. The same has been addressed in the latest ADA guidelines which advocates for screening Vitamin B12 deficiency in long term metformin users.^{4,5,8,11}

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Ethical Considerations

Ethical clearance was obtained from the KMC-Kasturba hospital Institutional Ethics Committee (IEC:909/2020) on 9/12/2020.

Consent to Participate

A written informed consent was obtained from each study participant.

Consent for Publication

All participants have provided an informed consent to participate in this study and to have their data published.

Author Contributions

Arjun Ballal: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing—original draft, Writing—review & editing. Sudha Vidyasagar: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Visualization. Cynthia Amrutha Sukumar: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing—original draft, Writing—review & editing.

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Declaration of Conflicting Interests

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Data Availability Statement

Available on contacting the corresponding author.

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