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A Study On The Prevalence Of Vitamin B12 Deficiency In Eastern Indian Type 2 Diabetes Mellitus Patients With Peripheral Neuropathy On Metformin Presenting To A Tertiary Care Hospital

Abstract

Introduction:

The association between long-term metformin use in type 2 diabetes mellitus (T2DM) and low vitamin B12 levels has been proven and screening for the same is recommended by American Diabetes Association (ADA) guidelines. The potential of the deficiency to cause or worsen diabetic peripheral neuropathy (DPN) in T2DM patients has been investigated in previous studies. However, the prevalence estimates of vitamin B12 deficiency in T2DM patients treated with long term metformin and having established DPN is lacking in our country. The aim of our study was to estimate the prevalence of vitamin B12 deficiency in T2DM patients with DPN on metformin and find out the risk factors for vitamin B12 deficiency in these patients.

Methods:

This cross-sectional study was conducted in the department of endocrinology in a tertiary care hospital on T2DM patients with DPN on long term metformin therapy. Vitamin B12 levels were estimated in all the subjects and the prevalence and risk factors for Vitamin B12 deficiency were assessed.

Results:

The prevalence of vitamin B12 deficiency in our patients was 32%. Based on the correlation estimates, none of the factors studied were significantly associated with variations in Vitamin B12 levels.

Conclusion:

Our study found that a third of metformin treated T2DM patients with peripheral neuropathy had vitamin B12 deficiency with no specific clinical predictor for the same. We thereby recommend screening for vitamin B12 deficiency in T2DM patients on long-term metformin and with established DPN.

Keywords

Vitamin B12 deficiency Distal Peripheral Neuropathy Type 2 Diabetes Mellitus Metformin

Authors

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Introduction

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 [1-4]. The relationship between vitamin B12 deficiency and peripheral neuropathy has been shown in previous studies [5,6]. Recent American Diabetes Association (ADA) guidelines recommend periodic testing of vitamin B12 in metformin-treated patients, especially in those with peripheral neuropathy [5]. The prevalence of Vitamin B12 deficiency in patients with T2DM with established DPN and on treatment with long standing metformin has not been studied in India. Our study was designed to estimate the prevalence of vitamin B12 deficiency in eastern Indian T2DM patients with DPN on metformin therapy, majority of whom take a non-vegetarian diet (primary source of Vitamin B12).

Materials And Methods

Study design

Cross sectional study

Inclusion criteria:

1. Type 2 Diabetes Mellitus patients with a duration of more than 5 years with peripheral neuropathy established with VPT on Metformin dose of more than 1000 mg.
2. Consenting participants between 18 and 60 years of age.
3. Ambulant patient.

Exclusion criteria:

1. Patients on supplementation with vitamin B12 either orally or parenterally.
2. Patients with overt features of malabsorption.
3. Patients with chronic diarrhoea.
4. Patients with severe hepatic, renal, pulmonary, cardiac or neurological disease.
5. Patients with advanced malignancy.
6. Patients with dementia.

7. Patients with alcohol abuse, smoker
8. Family history of peripheral nerve disease
9. History of toxic exposure and drug exposure causing peripheral neuropathy
10. Patients with autoimmune disorder or pregnancy
11. Unconscious and severely ill patients
12. Patients who are mentally impaired and/or unable to give consent

Sample size calculation

This study was a cross sectional prevalence study and hence the following expression was used to calculate the sample size.

$$n = \frac{z^2\ p\ (1-p)}{d}$$

Where n = sample size, z = z statistic for a level of confidence, p = expected prevalence or proportion and d = precision. According to existing data from the study by Yajnik et al [6] the prevalence of vitamin B12 deficiency was taken to be 60% and the precision was taken as 10%. With

the above figures a sample size of 94 was arrived at. Our study included 100 participants.

Biochemical estimation of vitamin B12

Vitamin B12 in the serum samples was measured by Beckman Coulter Access 2 Immunoassay System.

Statistical analysis

Data was entered into and analysed using Statistical Package for the Social Sciences (SPSS) software package (version 16). The chi-square test was used for comparison of categorical variables. Odds ratios (OR) and confidence intervals (CI) were calculated and a ‘p’ value less than 0.05 was considered statistically significant. All reported p values are two-sided. Continuous variables were handled with the help of the student t tests and ANOVA tests.

Results

The baseline characteristics of the participants are shown in Table 1. The study population had 53 males and 47 females with a mean age of 54.9 ± 12.94 years. The mean body mass index of the patients was 27.89 ± 2.464 kg/m^2. The mean HbA1C level of the patients was 7.833 ± 1.009 %. The mean duration of diabetes was 7.81 ± 2.688 years.

The prevalence of vitamin B12 deficiency in our patients was 32%.

The general characteristics of the patients and the laboratory values are summarized in Table 1.

Table 1: Characteristics of the study population

	Total	Control/ Normal	B12 deficient (<190 pg/ml)	p- value
N	100	67	32	
Age (in years)	54.9 ± 12.94	56.33 ± 12.36	51.34 ± 13.46	0.0713
Weight (in kg)	69.79 ± 2.469	69.45 ± 2.293	70.52 ± 2.735	0.0453*
BMI (kg/m^2)	27.89 ± 2.464	27.56 ± 2.292	28.61 ± 2.727	0.0479*

Duration of Diabetes (years)	7.81 ± 2.688	7.821 ± 2.634	7.844 ± 2.864	0.9688
FPG (mg/dl)	166.7 ± 2.56	166.4 ± 2.464	167.3 ± 2.729	0.1088
PPBG (mg/dl)	213.4 ± 9.43	213.3 ± 9.243	213.7 ± 10.03	0.8431
HBA1c	7.833 ± 1.009	7.779 ± 1.056	7.962 ± 0.9187	0.4042
SBP	132.8 ± 2.688	132.8 ± 2.634	132.8 ± 2.864	0.9688
DBP	85.81 ± 2.688	85.82 ± 2.634	85.84 ± 2.864	0.9688
Vit B12 (pg/ml)	247.2 ± 83.25	286.8 ± 73.94	166 ± 14.27	<0.0001***
eGFR, ml/min per 1.73 m^2	79.73 ± 5.721	79.95 ± 4.843	79.28 ± 7.345	0.5893
Creatinine	1.077 ± 0.1409	1.082 ± 0.1257	1.062 ± 0.1694	0.5538
Albumin (mcg/L) to creatinine	25.81 ± 2.688	25.82 ± 2.634	25.84 ± 2.864	0.9688

Although the weight and BMI were statistically different between the normal and B12 deficient individuals, the difference does not appear clinically relevant.

Based on the correlation estimates (Table 2), none of the factors studied were significantly associated with variations in Vitamin B12 levels.

Table 2: Correlation estimates of Vitamin B12 with different parameters

Variables	r	95% confidence interval	P value
Age (in years)	-0.02166	-0.2172 to 0.1755	0.8306
Weight (in kg)	-0.07878	-0.2710 to 0.1195	0.4359
BMI (kg/m^2)	-0.07569	-0.2681 to 0.1225	0.4542
Duration of Diabetes (years)	-0.0314	-0.2264 to 0.1660	0.7565
FPG (mg/dl)	-0.04635	-0.2406 to 0.1514	0.647
PPBG (mg/dl)	-0.09083	-0.2822 to 0.1075	0.3688
HBA1c	0.08116	-0.1171 to 0.2732	0.4221
SBP	-0.0314	-0.2264 to 0.1660	0.7565
DBP	-0.0314	-0.2264 to 0.1660	0.7565
eGFR, ml/min per 1.73 m^2	-0.01645	-0.2132 to 0.1816	0.8716
Creatinine	0.06821	-0.1300 to 0.2611	0.5001
Albumin (mcg/L) to creatinine	-0.0314	-0.2264 to 0.1660	0.7565

Discussion

Metformin remains the first line treatment for type 2 DM in the absence of a contraindication. Although gastrointestinal side effects are the most common problem with the use of metformin, it can also lead to serious side effects, such as lactic acidosis and vitamin B12 deficiency [7][8]. 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, subacute combined degeneration of the spinal cord, megaloblastic anemia and pancytopenia.

Our study found a 32% prevalence of Vitamin B12 deficiency in T2DM patients with a duration of more than 5 years on Metformin dose of more than 1g and with established DPN. In a study by Ko et al., the prevalence of vitamin B12 deficiency was 9.5% in a cohort of 76 patients. Vitamin B12 deficient patients had longer duration of metformin use (≥4 years) and higher daily metformin dose (>1000 mg) than non-deficient patients [9]. An Indian study from Ranchi, Jharkhand by Singh et al. reported that the use of metformin was significantly associated with vitamin B12 deficiency and peripheral neuropathy and found the prevalence of Vitamin B12 deficiency to be 21.4% among 84 metformin users [10]. Differences in prevalence of Vitamin B12 deficiency among studies could be on account of differences in dose and duration of use of Metformin. Ethnic and dietary differences could also be contributory.

In a study from South Africa by Ahmed et al., the prevalence of Vitamin B12 deficiency was 28.1% among 121 participants but interestingly it did not have any association with DPN [11]. This study also found African ethnicity to be a protective factor for Vitamin B12 deficiency. In our study, none of the common clinical and biochemical parameters studied were significantly associated with variations in Vitamin B12 levels.

In an Indian study by Raizada et al, no significant increase in the prevalence of neuropathy was found in vitamin B12-deficient patients compared with patients with normal vitamin B12 levels [12]. A letter by Chowta and Tiwary commenting on the article by Singh et al mentions that exhaustion of vitamin B12 stores usually occurs after 12–15 years of absolute vitamin B12 deficiency and duration of diabetes might be the most crucial factor in the development of vitamin B12 associated neuropathy [13]. In our study, the mean diabetes duration was 7.81 ± 2.69 years. Our study was different from earlier studies in the fact that all our patients had established DPN which also could be a reason for higher prevalence of Vitamin B12 deficiency in our study compared to others. A limitation of this study was the small sample size although it was adequately powered to look at outcome. Larger trials including patients with established DPN and metformin use might shed further light on the prevalence and predictors of Vitamin B12 deficiency in this population.

Conclusion

Our study found that a third of metformin treated T2DM patients with peripheral neuropathy had vitamin B12 deficiency with no specific clinical predictor for the same. We thereby recommend screening for vitamin B12 deficiency in T2DM patients on long-term metformin and with established DPN.

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