ORIGINAL ARTICLE

Correlation of Vitamin B12 Deficiency with Peripheral Neuropathy in Diabetes Mellitus

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ABSTRACT

Aim: To evaluate the correlation between Vitamin B12 deficiency and peripheral neuropathy in diabetic patients.
Methods: The descriptive study was performed on 100 T2DM patients and divided into three groups, based on drugs used in treatment as group A (Metformin with other drugs), Group B (Metformin only) and Group C (drugs other than Metformin). Detailed demography, drug intake history and biochemical parameters (blood glucose, postprandial blood glucose, HbA1c, and vitamin B12) were recorded. Peripheral neuropathy was assessed by nerve conduction velocity study.Whitney U test, Wilcoxon signed-rank test, and chi-square test were used to analyse the data and study the correlation.
Results: Pronounced Vitamin B12 deficiency was observed in 29% of patients whereas, 33% of patients had intermediate levels of deficiency. PN was found significantly associated with drugs used and the duration of metformin use ($P<0.01$). A significant association was noted between PN and vitamin B12 ($p<0.05$) but, no association was found between vitamin B12 and drug used.
Conclusion: A significant association was noted between PN and vitamin B12. Metformin was found to have a significant association with PN. Vitamin B12 can be a contributing factor in DPN.
Keywords: Diabetes mellitus, Metformin, Vitamin B12.

INTRODUCTION

Metformin is the first-line drug used for the management of T2DM, with associated adverse effects such as abdominal distress and diarrhoea[1-2]. It is also reported to decrease vitamin B12 absorption in the terminal ileum[3]. Literature suggests that prolonged use of Metformin causes improper absorption of vitamin B12, leading to decreased blood concentration of vitamin B12[4]. Deficiency of vitamin B12 causes hypomethylation in the central nervous system which is associated with diabetic PN[4-6]. Further, decreased concentration of vitamin B12 can increase the risk of cardiovascular complications in T2DM due to its incorporation in homocysteine metabolism[7].

Although the association between the use of Metformin and deficiency of Vitamin B12 is proven, the extent of this problem has not been quantified. There have been various studies which have shown the occurrence of vitamin B12 deficiency associated with Metformin use but the results varied greatly from 14 to 30%[4,6,8,10]. This wide range can be attributed to differences in cut-offs chosen to define the participants mean age, deficiency, study settings, and the dose of Metformin as also the duration of use. Also, there are no set guidelines for screening or providing supplementation for this deficiency in diabetic patients. Therefore, the study was undertaken to ascertain if neuropathy due to vitamin B12 deficiency is indeed due to Metforminand find a correlation between Vitamin B12 deficiency and the occurrence of peripheral neuropathy in diabetic patients.

MATERIAL AND METHODS

The descriptive study was performed on 100 patients in a tertiary care centre at Kolhapur. Inclusion criteria for patients were type 2 DM of more than 5 years whereas, patients with PN due to other causes were excluded. Written informed consent from patients and ethical approval from the Institutional Ethics Committee were obtained before initiation of the study.

Patients were diagnosed as per the American Diabetes Association guidelines[8]. Subjects were divided into three groups, based on drugs used in the treatment of DM as Group A (Metformin in combination with other drugs), Group B (Metformin only), and Group C (drugs other than Metformin). Detailed demographic data of patients were recorded and appropriate tests were performed to obtain the values of fasting blood glucose, postprandial blood glucose, HbA1c, and vitamin B12. Drug intake history and peripheral neuropathy were assessed by nerve conduction velocity study. The values of vitamin B12 <200pg/ml were considered as deficiency whereas, between 200 and 350 pg/ml and more than 350 pg/ml was considered as intermediate and normal respectively. The nerve conduction tests were performed using NeuroStim 2. Median, ulnar, peroneal nerve conduction studies, F-wave, and median ulnar and sural nerve conduction velocity were recorded at room temperature. Standard nerve conduction velocities were used. Polyneuropathy was diagnosed as:

- A reduction of conduction velocity of at least 40% in at least 2 motor or 1 sensory nerve.
- Prolongation of terminal motor latencies.
- Prolonged or even absent F-wave latency in 2 or more motor nerves.
- The size of the compound muscle action potential as also sensory nerve action potentials were decreased in at least two 2 motor and 1 sensory nerve.

The sample size was calculated by R studio v 1.2.5001 software using pwr.chisq.test (w=, n=, sig,level=, power=)

R code. The calculated sample size was n=80 and the power of study was 90%.

Statistical analysis: Data were analyzed using R studio v 1.2.5001 software. Categorical data were expressed in frequency and percentage whereas, continuous data were expressed in mean±SD. Mann Whitney U test and Wilcoxon signed-rank test were used to find the difference and the chi-square test was used to find the association between the variables. P<0.05 was considered as statistical significant.

RESULTS

A total of 100 diabetes patients (64 males and 36 females), were divided into 3 groups. Group A, Group B and Group C, comprising of 31, 37 and 32 patients respectively. A significant difference was observed between age (p<0.05) and the duration of DM (P<0.001) in patients of different groups. It was observed that 30% of patients of group C had neuropathy whereas, 28% and 24% NP was observed in group A and B respectively (Table 1). Overall among the sample, 29% of all the diabetics had pronounced Vitamin B 12 deficiency and 33% had intermediate levels of vitamin B12. The distribution of levels in each group is illustrated in Table 2. The duration of Metformin use also had significant association with the serum levels of vitamin B12 (P<0.05). PN was to be found significantly associated with drugs used and the duration of metformin use (P<0.01). There was a significant association observed between PN and deficiency of vitamin B12 (p<0.05).

Table 1: Participant's demographic and clinical characteristics, divided according to treatment.

Variables	Group A	Group B	Group C	P
Age (years)	58.87±9.55	53.65±11.32	62.69±11.07	0.05
Duration of DM (years)	11.39±4.44	8.24±3.38	14.38±6.28	0.00
Diagnosed neuropathy (%)	28	24	30	-

DM- diabetes mellitus

Table 2: Levels of vitamin B12 according to groups

Groups	Levels of vitamin B12		
	Deficiency (%)	Intermediate (%)	Normal (%)
Group A	29.03	45.17	25.80
Group B	27.03	24.32	48.65
Group C	31.25	31.25	37.50

DISCUSSION

Prolonged treatment of T2DM using Metformin tends to reduce vitamin B12 levels and manifests as peripheral neuropathy, memory impairment, subacute degeneration of cord with macrocytic anaemia[9]. This study was undertaken to ascertain deficiency of vitamin B12 is indeed a contributing factor in DPN. Therefore, the study was aimed to find a correlation between Vitamin B12 deficiency and PN in diabetic patients treated with Metformin and other drugs.

The study by Roy RP et al. showed lower mean vitamin B12 levels in patients taking metformin only than in patients taking other drugs in combination with metformin and patient who were not taking metformin at all[9]. Similarly, the study of Alharbi TJ et al. showed a decreased level of vitamin B12 in patients treated with Metformin[10]. In contrast with these results, the study showed lower mean vitamin B12 in a patient taking metformin along with other drugs than patients taking only metformin and no metformin. Wile and Toth concluded that prolonged treatment beyond 6 months with Metformin could result in low level of vitamin B12 and an increased levels of Homocysteine associated with PN[11]. A systematic review of Chapman showed an association between reduced values of vitamin B12 and Metformin[12]. Similarly, levels of vitamin B12 was associated with Metformin use. Regarding PN, resulted from hypo methylation in the central nervous system which is may be due to deficiency of vitamin B12[4-6]. Previous reports showed an association between metformin with B12 levels and neuropathy[11,13]. Similar results were observed in present study. The study of Zagar BR et al. suggested that no association was seen between levels of vitamin B12 and PN[14]. Contrary result was observed in the study with a significant association between PN and vitamin B12.

The differing results of various studies firmly establish the complex interaction of the link between Vitamin B12, metformin, and DPN. In the study, we found a significant association between Vitamin B12 and Metformin with PN. The limitations of the study are the duration and sample size was small. Biomarkers such as homocysteine and MMA were not evaluated. In India, 8.8% adults are diabetic, due to combination of genetic susceptibility and high calorie diet and sedentary life style[15]. Since deficiency vitamin B12 is common in vegan population compared to non-vegan population due to less vitamin B12 diet, deficiency of vitamin B12 can further decrease by use of metformin[16]. A study with a large sample size could be better to study association including vegan and non-vegan samples.

CONCLUSION

The study demonstrates significant association between the presence of PN and use of Metformin and between Metformin and serum levels of Vitamin B12, thus demonstrating the complex interaction between the three. Limitations of the study would include the limited sample size and lack of inclusion of biochemical markers for Vitamin B12 deficiency such as Homocysteine and methylmalonic acid which could pave way for further research in the arena.

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