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PREVALENCE OF VITAMIN B12 DEFICIENCY AND ITS ASSOCIATED NEUROPATHY IN PATIENTS TAKING LONG TERM METFORMIN THERAPY IN TYPE 2 DIABETES MELLITUS

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ABSTRACT
Background: Diabetic people on metformin are more likely to develop vitamin B12 deficiency. There has been little research into the duration of therapy and dose of metformin that causes B12 deficiency and peripheral neuropathy. This study is being done to determine the same. **Objective:** To determine the association between vitamin B12 deficiency and its neuropathy to long-term metformin therapy in diabetic patients. **Study design:** This observational cross-sectional study was conducted at SRIHER Chennai. Patients on long-term metformin were taken and separated into two groups: B12 Vitamin deficiency and normal Vitamin B12 levels. **Results:** B12 Vitamin deficiency was found in 15.72% of 159 patients on metformin. Only 2 of the 59 people on vitamin supplements in our study showed Vitamin B-12 deficiency, whereas 23 out of 100 people in the non-supplemented group had Vitamin B-12 deficiency. The difference (OR - 0.11; P 0.005) was statistically important. There was a statistically important difference observed between the prevalence of deficiency of vitamin B-12, Duration (>5 years), and dosage (>1 g/day) of Metformin use (p-value - <0.0001). Among the study group with neuropathy, the duration of metformin in the normal b12 group is 5.6 ±4.69 yrs. vs. 11±4.019 yrs. in b12 deficiency group (mean difference = 5.4; p <0.0004). **Conclusion:** The study found that metformin uses for a long time (> 5 years) and dose > 1g/day are linked to B12 Vitamin deficiency and neuropathy in diabetic patients.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic metabolic condition is growing more widespread both in developed and emerging nations. Metformin is an anti-diabetic medicine that is taken orally and is often used to treat type 2 diabetes mellitus (T2DM). The majority of metformin side effects are modest and gastrointestinal symptoms, for example stomach discomfort and diarrhoea. The occurrence of B12 vitamin insufficiency is around 22% among diabetics [1]. Evidence from observational and interventional research indicates that the link between B12

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vitamin insufficiency and Diabetes type 2 (T2DM) is related to metformin's long-term and higher use dosage as the least prevalent adverse effect [2,3]. Because B12 Vitamin deficiency-related hematologic and neurologic problems are treatable with early identification, continuous monitoring of Vitamin B12 levels is required to initiate treatment [4,7-9].

MATERIALS & METHODS

This cross-sectional analysis was carried out at Sri Ramachandra Medical College and Research Institute, Chennai, to assess the prevalence of a lack of vitamin B12 in diabetic individuals taking metformin and the risk of peripheral neuropathy Diabetics who are deficient in vitamin B12 in these patients. Data was collected over 16 months, from September 2020 to December 2021. Ethics committee approval: Approval for the study is obtained from the institutional ethics committee (Ref no: CSP-MED/20/SEP/61/79)

Inclusion criteria: All type 2 diabetes mellitus individuals with more than one year of metformin therapy with good compliance are included.

Exclusion criteria:

- Patients consuming alcohol,
- Taking B12 supplements,
- HIV positive status
- Post gastric surgery,
- Pancreatic disease

The patients are assessed for peripheral neuropathy using a diabetic neuropathy score [5]. Serum B12 was considered by the electrochemiluminescence method. It was established that there is a link between Vitamin B12 and peripheral neuropathy using binary and continuous variables. All patients tested for routine blood investigations include hemoglobin, MCV, renal function test, HbA1c, urine protein dipstick. Data was manually retrieved from medical records, imported into Microsoft Excel, and analysed with the statistical software for social services (SPSS). The mean, standard deviation, frequency and proportions for quantitative variables, and frequency and proportions for qualitative variables were used to calculate descriptive statistics for the explanatory and outcome variables. According to Altman (1991), the odds ratio (OR), standard error, and 95% confidence range are calculated. To compare, the Chi-Square test was utilized Vitamin B12 levels between groups. $p = 0.05$ is used as the significance threshold.

RESULTS

25 patients out of 159 (15.72%) were Vitamin B12 deficient, of which 17 were male and 8 were female. Levels vary from 41 to 2122, with a mean of 802.76. The mean vitamin B12 level was higher among females (857) when compared to males (751). The older population with age > 70 years was found to have higher vitamin B12 levels with a mean of 930 (Figure 1).

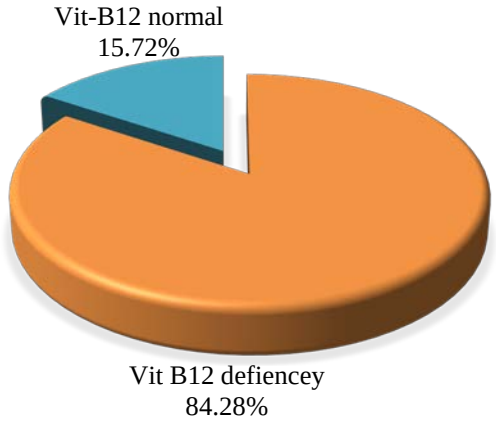

Figure 1: Prevalence of Vitamin B12 deficiency

Most of the study population consumed metformin for 1 to 3 years duration with a range between 1 to 20 years. The mean duration of metformin intake among the study population was 5.32 years (Figure 2).

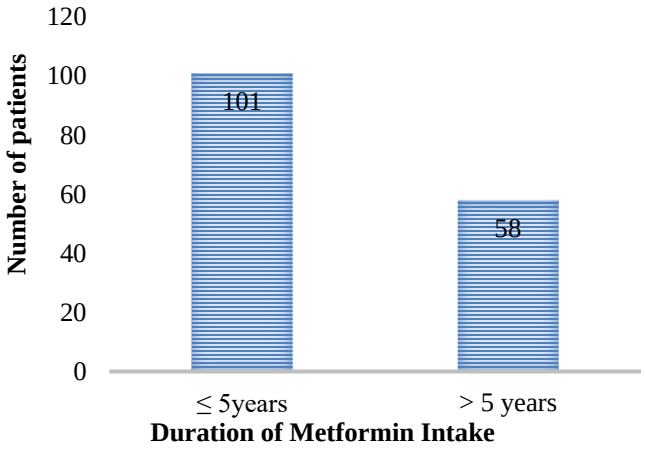

Figure 2: Distribution of metformin based on duration of intake

Most of the study population consumed 500 mg to 1gm metformin (49.1%), followed by 1 to 2 grams (Figure 3). The diabetic neuropathy examination score ranged from 0 to 12. Mean DNE score of the population was 2.849. Subjects > 70 years in age had highest DNE score with mean of 3.86, followed by the 41 - 50-year age group. Males were found to have higher scores with mean of 3.03 than females with mean of 2.534 (Figure 4).

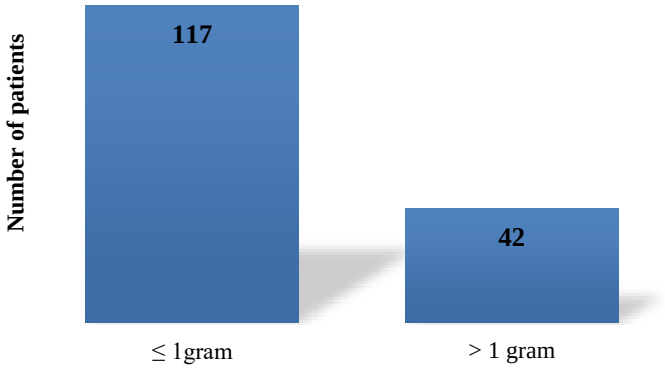

Figure 3: Distribution of Metformin based on dosage

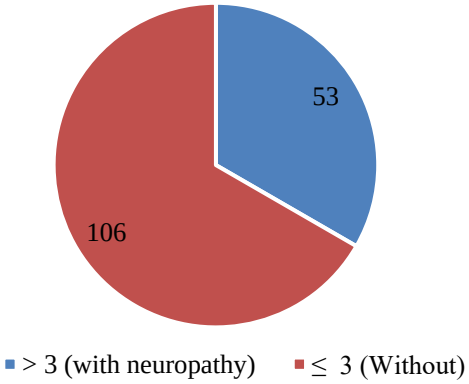

Figure 4: Distribution of Neuropathy based on DNE among the group

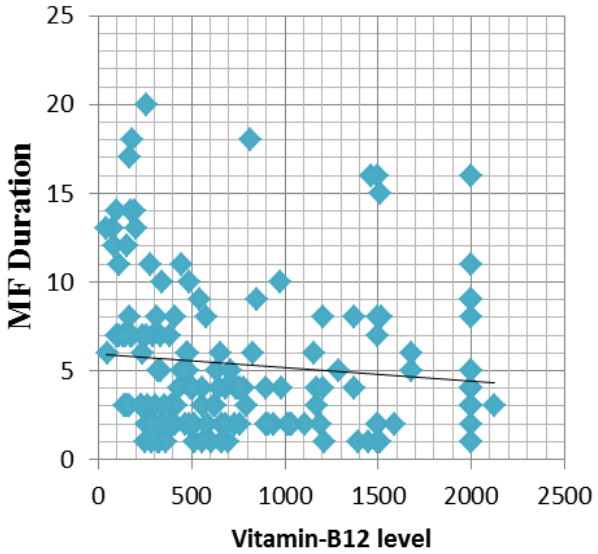

Figure 5: Scatter plot of Vitamin B12 insufficiency with metformin duration

Vitamin B12 deficiency was highest among the 31 -40-year age group of 33%. This age group was also found to have a higher mean dose of Metformin at 1.33 grams when compared to the rest (Table 1). Metformin duration is one of the significant variables assessed in this study. Those with a duration of Metformin consumption of more than 5 years were discovered to have the highest Vitamin B12 deficiency of 80%.

It was seen that there was a suitable link in comparison to metformin duration and consumption and deficiency of vitamin B12 prevalence, statistically ($p< 0.05$) (Table 2 and figure 5).

Table 1: Age distribution among Vitamin B12 deficiency group

Age (years)	Vit B12 deficient	Patient with age group (%)	Mean duration of metformin	Mean dose of metformin intake
≤30	0	0	3	1
31-40	2	33	3.83	1.33
41-50	5	16	3.86	1.16
51-60	7	15.9	4.52	1.25
61-70	6	14.6	5.56	1.109
≥ 71	5	13.8	7.63	1.09

Table 2: Individuals with Vitamin B12 deficiency and metformin usage correlate

Metformin Duration	Vit B deficiency	Vit B Non-deficient	OR	p Value
>5 Years	20	38	10.1	<0.0001
≤ 5 Years	5	96		

Table 3: Correlation of DM duration, Metformin duration and Dosage with vitamin B12 related Neuropathy groups

Parameter	Vit B12 deficient*	Vit B-12 non deficient*	Mean difference	p-values
Diabetes duration	14.5±8.873	15.2±10.64	0.7	>0.05
Metformin use duration	11±4.019	5.6±4.69	5.4	<0.0005
Metformin use	1.64±0.36	1.025±0.396	0.615	<0.0001

*Mean±SD;

DISCUSSION

Metformin is known to cause vitamin b12 deficiency. In this study, the main findings assessed are the metformin treatment duration and dosage linked to neuropathy as demonstrated by

Aroda VR et al [2]. It was seen that those with metformin use of more than 5 years duration were more likely to develop B12 vitamin deficiency than those with ≤ 5 years duration and this finding was significant p <0.0001. This finding was also observed in a previous study done by Kim J et al. [6]. The dosage of metformin therapy is another significant variable in the development of neuropathy [7]. Of the 25 patients with vitamin B12 deficiency, 7 patients took ≤ 1 gram metformin and 18 patients took > 1 gram. In patients with normal B12 levels, 110 had ≤ 1 gram per day of Metformin whereas, 24 had > 1 gram per day. Hence there is a statistically significant correlation of vitamin B12 deficiency and Metformin dose (p value -<0.0001). Similar outcome was observed in study done by Kim, J et al. [6].

Diabetic neuropathy examination (DNE) score was used to determine neuropathy in this study population. DNE score of >3 was considered as the criteria for defining neuropathy. (5) DNE score of >3 was observed among 53 individuals in the study population. Among which 14 individuals had B12 deficiency and 39 individuals had normal vitamin B12 Levels. It was seen that those with DNE > 3 were thrice more likely to have Vitamin B12 deficiency than those without neuropathy and this is significant (p = 0.01). The average diabetes duration among those with neuropathy and vitamin B12 deficiency was 14.5 years, and the average usage of metformin was 11 years. And average dose of metformin intake 1.64 grams. In those individuals with normal levels of vitamin B12 and neuropathy, the average length of diabetes was 15.2 years, the average duration of metformin administration was 5.6 years, and the average dosage of metformin consumption was 1.025 grams. However, there was no significant mean distinction between the duration of diabetes in both cohorts. Hence, the duration of diabetes was adequately matched between both groups and could not behave as a confounding factor. In short, this study concludes that, in diabetics using metformin who develop neuropathy, Vitamin B12 insufficiency was related to longer duration of metformin usage (p 0.05) (Table 3). More investigation is required to determine the function of metformin treatment in developing neuropathy and other vitamin B12 deficiency-related problems [10].

CONCLUSION

We propose that metformin usage for a long time (> 5 years) and intake of metformin > 1 gram significantly increase the risk of B12 vitamin deficiency and related neuropathy among the diabetic population. The limitation of this study is the smaller sample size. Further, RCT is required to substantiate this finding and to form guidelines for screening and treatment of B12 deficiency in diabetic patients on metformin therapy,

FINANCIAL ASSISTANCE

Nil

CONFLICT OF INTEREST

The authors declare no conflict of interest

AUTHOR CONTRIBUTION

Sivaprakash Varadan designed the entire work. Sivaprakash Varadan, Suresh Kumar, Viswanathan P, Vaishnavi S, Tanisha Singh, RB Sudagar Singh contributed to making necessary corrections. All the authors checked the final draft.

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