Original Article

Correlation of Vitamin B12 Deficiency with Metformin Therapy in Indian Type 2 Diabetes Mellitus Patients

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ABSTRACT

Introduction: Diabetes is non-communicable disease prevalent all over the world. Metformin is most commonly prescribed and first line anti-hyperglycaemic medication of type 2 diabetes mellitus patients. Vitamin B12- Intrinsic factor complex uptake by ileal cell surface receptors is a known to be a process dependent on calcium availability. Metformin affects calcium dependant membrane action. Hence intestinal absorption of Vitamin B12 is often decreased during chronic metformin therapy.

Aims & Objectives: This study is done to assess the prevalence, severity and clinical implication of vitamin B12 deficiency in type 2 diabetes mellitus patients taking chronic metformin therapy.

Methods: The study included total 50 type 2 diabetes patients as per inclusion and exclusion criteria. Detailed history, physical examination and laboratory evaluation CBC, peripheral blood smear, renal function test, FBS,PPBS, HbA1c, serum vitamin B12 assay, urine routine & microscopy of all 50 patients. Analysis was done with help of SPSS software and using Microsoft Excel 2012.

Results: In our study, dosage of the metformin was highest among deficient group followed by borderline and normal. The mean duration of therapy with metformin is high in the deficient group. Hence the duration of therapy with metformin and the dose determines the development of vitamin deficiency. With duration of metformin and duration of diabetes showed non-significant P value which may be due to the small sample size. As it is a cross sectional study, the population is very low and it is difficult to study the P value in this population. But the mean value shows good correlation with duration and dosage of metformin therapy and duration of diabetes with B12 deficiency.

Conclusion: Chronic metformin therapy is associated with B12 deficiency by causing asymptomatic vitamin B12 deficiency. Vitamin B12 level in the patients who were on chronic metformin therapy is useful to predict B12 deficiency as they are prone for B12 deficiency. The duration and dose of metformin therapy has affected the vitamin B12 status of type 2 diabetes mellitus patients.

Key words: Type 2 Diabetes mellitus, Metformin, Vitamin B-12

INTRODUCTION

Diabetes is non-communicable disease prevalent all over the world but the rate of rapidly rising newer cases of diabetes in India leads to our country as "diabetes capital of the world."[1] Over past three decades, diabetes is rising as one of the major causes of mortality and morbidity among elderly population.

It is observed that prevalence of diabetes is increasing worldwide. Although there is an increase in the prevalence of type 1diabetes also, the major driver of the epidemic is type 2 diabetes mellitus which accounts for more than 90 percent of all diabetes cases.[2] Metformin is most commonly prescribed and first line anti-hyperglycaemic medication of type 2 diabetes mellitus patients. It is also observed that metformin has mortality and morbidity benefits in cardiovascular patients.[3]

Vitamin B12 deficiency associated with metformin use is thought to occur due to vitamin B12 malabsorption. Initial theories included alteration of bile acid metabolism, small intestinal bacterial overgrowth, or effects on intrinsic factor secretion, but a more currently accepted explanation is the interference by metformin on calcium-dependent membrane action responsible for vitamin B12-intrinsic factor absorption in the terminal ileum.[4-6] Hence intestinal absorption of Vitamin B12 is often decreased during

chronic metformin therapy.[7] Decrease in vitamin B12 level is an independent risk factor for cardiovascular disease, especially among individuals with type 2 diabetes. 10-30% of diabetic patients on long term treatment with metformin had vitamin B12 deficiency.[8]

Many studies were done globally to establish the vitamin B12 deficiency as a complication of metformin therapy. Few studies were done in India to know the prevalence and severity of vitamin B12 deficiency due to metformin therapy. I had taken up this study to assess the prevalence, severity and clinical implication of vitamin B12 deficiency in type 2 diabetes mellitus patients taking chronic metformin therapy.

AIMS & OBJECTIVES

The study was conducted to determine prevalence of VitaminB12 deficiency in type 2 diabetes mellitus patients on metformin therapy; and to correlate the severity of vitamin B12 deficiency with duration and dose of metformin therapy.

MATERIAL & METHODS

It is a cross sectional study that included 50 type 2 diabetic patients who were on metformin therapy for more than 2 years from outdoor patients of department of medicine at C. U. Shah medical college and hospital, Surendranagar. We have excluded the patients who were known case of vitamin B12 deficiency, history of prior treatment with B12 injection, comorbidities like liver cirrhosis, operative history like gastrectomy or colectomy, intestinal infection, malabsorption syndrome and patients having type 1 diabetes mellitus.

The study included detailed history, physical examination and laboratory evaluation CBC, peripheral blood smear, renal function test, fasting blood sugar, post-prandial blood sugar, HbA1c, serum vitamin B12 assay, urine routine & microscopy of all 50 patients after taking informed consent.

Analysis was done with help of SPSS software and using Microsoft Excel 2012. To interpret the other results Mean, SD, percentage and Chi square Test were used.

OBSERVATIONS & RESULTS

The study included 50 total no. of diabetic patients out of which 26 were males and 24 were females. 66% of the participants were more than 55 years of age in this study (Table 1).

Study participants taking Metformin less than 8 years of duration and more than 8 years of duration were equal. (Table 2)

Among study participants, 26 had borderline vitamin B12 deficiency irrespective of the glycaemic tatus, duration of diabetes and metformin therapy 52% of the total participants had borderline deficiency (Table 3).

24% of Study participants had macrocytosis, 14% had microcytosis and majority of had normocytosis (Table 4).

Table 1: Age and sex wise distribution of study population

Age	Male	Female	Total
< 55 Years	10	7	17
>55 Years	16	17	33
Total	**26**	**24**	**50**

Table 2: Metformin treatment duration wise distribution of the study participants

Duration of metformin therapy	Participants	%
<8 YRS	25	50%
>8 YRS	25	50%

Table 3: Vitamin b12 level wise distribution of the study participants

Vitamin B12 Level	Participants	Percentage
Deficient	13	26%
Borderline	26	52%
Normal	11	22%

Table 4: MCV wise distribution of the study participants

Cell Morphology	Participants	Percentage
Macrocytic	12	24%
Microcytic	7	14%
Normocytic	29	58%

Table 5: Correlation of macrocytosis & b12 level of the study participants

Vitamin B12 Level Among Macrocytic	Cases (n=12)	Percentage
Deficient	5	41.66%
Borderline	4	33.33%
Normal	3	25%

Table 6: correlation of duration of metformin and duration of diabetes with B12 level of the study participants

Vitamin B12 Level	Duration Of Metformin (N=50)		Duration of DM (N=50)	
	>8 Yrs	**<8 Yrs**	**>10 Yrs**	**<10 Yrs**
Deficient	7	6	4	9
Border Line	11	15	9	17
Normal	7	4	1	10
P Value	**0.469**		**0.277371**	

Table 7: Correlation of mean of metformin dose and vitamin B12 level in study participants

Vitamin B12 level	Mean dose of metformin
Deficient	1230.76
Borderline	1115.38
Normal	1045.45

Table 8: Correlation of mean duration of metformin and vitamin B12 level in study participants

Vitamin B12 Level	Mean Duration of Metformin
Deficient	10.33
Borderline	08.26
Normal	09.36

Table 9: Correlation of mean duration of DM with vitamin B12 levels of the study participants

Vitamin B12 Level	Mean Duration of DM
Deficient	7.66
Borderline	8.23
Normal	6.72

Among macrocytic cell picture, maximum number of patients (41.66%) was found B12 deficient. There is no significant correlation between duration of metformin and development of vitamin B12 deficiency. There is no significant correlation between duration of diabetes mellitus and development of vitamin B12 deficiency (Table 6).

The mean dose of metformin was highest in B12 deficient group followed by borderline and normal level (Table 7).

The mean duration of metformin therapy was highest in the deficient group (Table 8).

The mean duration of diabetes was highest in the Borderline group. Lowest in normal group and intermediate in deficient group (Table 9).

DISCUSSION

Metformin is most commonly prescribed drug for the treatment of diabetes mellitus and there are mechanism through which metformin interacts with vitamin B12 absorption and causes deficiency of vitamin B12. It is a cross sectional study where the serum B12 level of type 2 Diabetic patients were measured and correlated with other investigations like complete blood count, fasting and post prandial blood sugar level and duration of metformin therapy, duration of diabetes mellitus.

Study included type 2 diabetes patients 50 in number and on metformin for more than 2 years. Patients were selected under the inclusion criteria. Hence all patients were taking metformin for more than 2 years. 33 patients out of 50 people were having age more than 55 years. Out of the study population 26 had borderline deficiency in vitamin B12 Irrespective of the glycaemic status, duration of diabetes and metformin therapy. 52% of the total patients had borderline deficiency. 24% of Study population had macrocytosis, 14% had microcytosis and majority of had normocytosis. Macrocytosis is mostly seen in the deficient group. There were 8 patients who had not shown macrocytosis in the peripheral smear in the vitamin B12 deficient group.

The significance between the sex and vitamin B12 deficiency had no significant p value. The males were 26 and females were 24 in study so relation not found between sex and development of vitamin B12 deficiency. Patients were also sub-grouped based on age but no specific relation established between age and B12 deficiency. There is no significant correlation between duration of metformin or duration of diabetes and development of vitamin B12 deficiency.

In the US from 1999-2006 The National health & Nutritional survey had found the vitamin B12 deficiency in both diabetics with and without metformin therapy also the biochemical B12 deficiency was higher with metformin group. It correlates with our study where we found the relation with mean duration of metformin and B12 deficiency.

In our study total 50 participants were taken compared to 121 in study by Marwan A. Ahemed et al.[9] There were 52% male and 48% female in our study compared to 34% male and 66% female in Marwan A. Ahmed et al. The prevalence of vitamin B12 deficiency was 26% in our study compared to 28.1% in Marwan A. Ahmed et al.

Owhin SO et al showed 41% prevalence of vitamin b12 deficiency among metformin treated type 2 diabetes mellitus patients whereas in our study prevalence of vitamin b12 in 26%.[10]

In study done by Vineetha Shobha et al, among urban population who were on metformin therapy showed higher prevalence of asymptomatic vitamin B12 deficiency.[11] Hence there can be associated preexisting vitamin B12 deficiency due to causes other than diabetes and Metformin, like vegetarianism.

Matthew C Pflipsen et al, showed prevalence of vitamin B12 deficiency among 22% of diabetics taking chronic metformin. They measured methyl malonic acid and homocysteine in the borderline B12 deficient cases; to confirm those cases as deficiency cases.[12] In our study we had high borderline patients. If we do methyl malonic acid and homocysteine in this subgroup we can also diagnose higher number of absolute deficient cases.

Metformin as a first-line oral treatment for hyperglycemia in diabetes is generally regarded as having few

side effects.[13] However, since Berchtold et al first reported in 1969 that metformin could cause vitamin B12 deficiency by reducing vitamin B12 absorption in the gastrointestinal tract, such findings have been constantly published.[4] It has been reported that an average of 6% to 30% of patients could show vitamin B12 deficiency due to metformin use.[14,15] In addition, some studies have reported that serum vitamin B12 levels were inversely related to the duration and dose of metformin use.[16-18] Since large prospective studies have clarified this relationship recently,[19,20] the 2017 American Diabetes Association treatment guidelines now recommend regular monitoring of vitamin B12 levels in patients with diabetes taking metformin.[21]

CONCLUSION

In our study population, it is proven that vitamin B12 deficiency is more prevalent among type 2 diabetic patients. The mean dose and duration of metformin therapy was highest in B12 deficient group followed by borderline and normal level. Hence the duration of therapy with metformin and the dose determines the development of vitamin deficiency. With duration of metformin and duration of diabetes showed non-significant P value which may be due to the small sample size. As it is a cross sectional study, the population is very low and it is difficult to study the P value in this population. In these subgroups the number of population decreases in each subgroup and the significance decreases further as we do subgroup study. But the mean value shows good correlation with duration and dosage of metformin therapy and duration of diabetes with B12 deficiency. So, it is concluded that study of vitamin B12 level in the patients who were on chronic metformin therapy is useful to predict B12 deficiency as they are prone for it.

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