ORIGINAL ARTICLE

Prevalence of Vitamin B12 Insufficiency in Type 2 Diabetic patients on Metformin Therapy

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ABSTRACT

Background: Type 2 DM is a syndrome with hallmark features of disturbance in metabolism of glucose, proteins and fats. The prevalence of diabetes has alarmingly risen in the past couple of decades, impacting a great socioeconomic stress especially in the developing countries.

Aim: To determine the prevalence of B12 insufficiency in Type 2DM patients on metformin treatment

Methodology: This survey was conducted over a period of 6 months (1-8-2019 to 1-2-2020) on T2 diabetic patients at Diabetic Clinic, Shaikh Zayed Hospital, Lahore. After informed written consent, demographic data of the enrolled patients were recorded. Patients were asking about history of metformin usage, dosage of metformin and duration of type 2 Diabetes Mellitus. A 5cc venous blood sample was drawn from the arm and stored at 4 C. Serums were extracted and Vitamin B12 level was determined using ELISA.

Results: The mean age of patients was 50.02±9.14 years. There were 87(44.8%) males and 107(55.2%) females in this study. The participants had history of diabetes mellitus over 7.27 years. The mean HbA1c was 8.81±0.76. The included patients had history of intake of metformin over 6.10 years. There were 25(12.9%) patients taking 1000-1500mg metformin, 90(46.4%) were taking 1500-2000mg and 79(40.7%) were taking more than 2000 mg metformin daily. There were 66(34%) patients with normal BMI, 63(32.5%) were overweight and 65(33.5%) were obese. The mean serum B12 level was 225pg/ml. There were 101(52.1%) patients having vitamin B12 deficiency and 93(47.9%) patients had no vitamin B12 deficiency.

Conclusion: It is concluded from this study that prevalence of B12 insufficiency is high among type II diabetic patients taking metformin.

Keywords: B12 insufficiency, Type II diabetics, Metformin treatment.

INTRODUCTION

The prevalence of diabetes mellitus has alarmingly risen in the past couple of decades, impacting a great socioeconomic burden especially in the developing countries.[1] Pakistan is currently ranked 7th with 6.9 million diabetics. The number of diabetics are expected to double (11.5 million) by 2025 which will shift up Pakistan to 4th position. World Health Organization estimates that amongstall diabetics, 90% are sufferers are of type II. Metformin is first line treatment of type II diabetes. According to UKPDS, this drug has magically improved diabetes related vascular complications, all causes mortality, had less hypoglycemic events, enhanced insulin sensitivity in addition to weight reduction and achievement of euglycemia. The diabetes related memory loss had also decreased upto 20% as compared to SU therapy[4].

On the other hand, the drug has been blamed to lower B12 level upto 30%.[5] Multiple authors have studied that Metformin induced B-12 inufficiency attributes to either or more, decreased intestinal motility disrupted B12 absorption from the gut, bacterial over growth, cobalamin-IF malfunction and last but not the least inhibited absorption of cobalamin-IF complex[6],[7] Also there is concomitant folate deficiency of unknown etiology. As a result of double deficiency, hyperhomocysteinemia develops, resulting in vascular myocardial events[8].

If no serious sequelae, most of metformin treated diabetics complain of paranesthesia and altered sensations esp. in legs and many of the treating physicians treat as peripheral neuropathy attributable to primary disease[9] and patients are advised neuropropics, anticonvulsants, a typical antidepressants without screening for cobalamin deficiency[11].

The symptoms attributable to cobalamin deficiency become clinically evident after 16 weeks to five years of metformin therapy. High total daily dose (>2gm/day) and age of the patient are important risk factors[10]. We should be choosy to prescribe metformin in those type II diabetics who are at low risk of cobalamin deficiency and those at risk of developing cobalamin deficiency or related neurological sequalae should either be screened or treated empirically with B12 or calcium supplements[10]. Managing neuropathic sequalae with cobalamin supplements results in improved quality of life[12].

This study was done on Pakistani population as per literature metformin related cobalamin deficiency in not studied before in Asian population.

MATERIALS AND METHODS

It was a cross sectional study done for 6 months from 1-8-2019 to 1-2-2020, on 194 patients presenting in Diabetic Clinic, Shaikh Zayed Hospital, Lahore. Age group 35-65 years from either gender, type 2 diabetes with metformin therapy for ≥6 months were included. We excluded following group of patients. Patients who are or had l vitamin B12 within last 3 months, pregnant women,

subjects with malabsorption disorder, or any abdominal surgery colectomy or gastrectomy subjects with any blood disorder like anemia or hemoglobinopathiesy,. After signed consent. Demographic data was recorded on study proforma, following by history of metformin usage, dosage of metformin and duration of type II Diabetes Mellitus. A 5cc venous blood sample was drawn from the arm and stored at 4 C. Serums were extracted and Vitamin B_{12} level was determined using ELISA. Continuous data e.g. age, duration of diabetes mellitus & Metformin usage, weight, height, BMI was summarized using Mean+SD. Nominal variables e.g. gender, marital status, education level, smoking history etc. were summarized using frequencies and proportions. Data was stratified for age, gender, BMI duration of metformin, HbA1C Chi-square test was applied taking P <0.05 as significant.

RESULTS

Demographics of patients are tabulated in Table 1. 25(12.9%) patients taking 1000-1500mg metformin, 90(46.4%) were taking 1500-2000mg and 79(40.7%) were taking more than 2000mg metformin daily. The mean serum B12 level was 225.79pg/ml the minimum serum B12 level was 130pg/ml and maximum was 349pg/ml. Vitamin B12 deficiency was significantly associated with all of female gender (p 0.017; BMI (p 0.028). duration of metformin usage (p 0.000), HbA1c (p 0.000).

Table 1:Demographics and variables of studied population

	Vitamin B 12 Deficiency		Chi square	P value
	Yes	No		
	101(52.1%)	93(47.9%)		
Age(years)				
35-45	36(53.7%)	31(46.3%)	1.41	0.49
46-56	38(55.9%)	30(44.1%)		
57-67	27(45.8%)	32(54.2%)		
Gender				
Male (87)	37(42.5%)	50(57.5%)	5.74	0.017
Female (107)	64(59.8%)	43(40.2%)		
BMI				
Normal (34%)	43(65.2%)	23(34.8%)	7.13	0.028
Overweight (32.5%)	30(47.6%)	33(52.4%)		
Obese (33.5%)	28(43.1%)	37(56.9%)		
Duration (years)of Metformin use6.1+1.24(3-9)				
3-6	49(36.3%)	86(63.7%)	44.21	0.000
7-10	52(88.1%)	7(11.9%)		
HbA1C 8.81+0.76(8-10)				
8-9	67(43.8%)	86(56.2%)	19.84	0.000
10-11	34(82.9%)	7(17.1%)		

DISCUSSION

Our study shows strong association between cobalamin deficiency and metformin treatment in T2 diabetics i.e., 52.1%. This is in contrast to various studies quoted internationally. Owhin et al in 2019[13], & Khan et al (2017)[14] conducted a study on patients on metformin the prevalence of B12 insufficiency (41%) & 29.66% respectively, B 12 deficiency inmetformin treated Type II diabetic patients was found to be only 8.6% & 19% in 2 different studies by Akinlade et al[16] & Jager et al[10] report from an early clinical

observational study by Tomkin et al[17] among Irish diabetic patients on long-term metformin therapy with concomitant dietary management indicated a prevalence of 30% for vitamin B12 malabsorption. DeFronzo et al also reported a prevalence of 29% among American type 2 Diabetes mellitus patients using metformin.[18] Another study by Sparre Hermann et al reported a 26.7% prevalence of vitamin B12 deficiency in metformin-treated type 2 diabetes mellitus patients in Sweden.[19] Additionally, a study by Damiao et al[20] and Pflipsen et al[21] found a 22.5% and 22% prevalence of B12 deficiency among Brazilian and American type 2 Diabetes mellitus patients using metformin. Wulffele et al also reported a vitamin B12 deficiency prevalence of about 14% among type 2 diabetes mellitus patients treated with metformin in the Netherlands[22,23].

Other studies by Reinstatler et al[24] De Groot-Kamphuis et al[25] and Iftikhar et al[26] also reported lower prevalence of vitamin B12 deficiency in metformin-treated type 2 diabetes mellitus patients. The reason for differences in the prevalence of vitamin B12 deficiency among this study's participants may be multifactorial: Some of the factors include; borderline low B12 status of the participants[15] and concomitant malabsorption & high dose of metformin to non-urbanethnicity, low socioeconomic status difference in laboratory method of vitamin B 12 variable cut-off values for cobalamindeficiency[27].Owhin et el 2019[28] concluded that 9.8%diabetics of > 60 years were vitamin B12 deficient in contrast to our study 45.8%[29]. Many researchers have concluded comparable results, but on the exact cause for this deficiency has not been established yet[30].

It may therefore be appropriate to advocate for Cobalamine deficiency screening before metformin use to avoid borderline vitamin B12 deficiency manifest clinically. Through this study, it is strongly recommended that serum cobalamin levels should be done in Type II diabetes patients if put on metformin and patients must be prescribed multivitamins as per RDDA to prevent sequaela of cobalamin deficiency[21].

There are limitation to our study, we studied association of B12 deficiency with the duration of metformin and HBA1C. Had the relation of dose of metformin with the severity of B12 deficiency been studied, the results might have been astonishing and variable. One of limitation of our study was that we didn't measured methyl malonic acid levels which can improve the sensitivity of results by identifying B12 deficiency in early asymptomatic stage. Serum concentrations of homocysteine as well as serum and urinary concentrations of methyl malonic acid are elevated in B12 deficiency, due to a decreased rate of metabolism. Patients with B12 deficiency were not followed to see effect of replacement of B12[31].

CONCLUSION

It is concluded that the as prevalence of cobalamin deficiency is highly prevalent in Type 2 diabetics on metformin. B12 deficiency screening prior to metformin use is advised and pretreated to prevent deficiency related morbidity.

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