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Deficiency of Vitamin B12 in Type 2 Diabetic Patients Receiving Metformin Therapy at HMC Hospital Peshawar

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Abstract

Background: Diabetes mellitus is on the rise at an alarming rate, and it has now become a global issue. Type 2 Diabetic Mellitus is a disease characterized by disturbances in glucose, protein, and fat metabolism. Diabetes has been increasingly common in recent decades, causing significant socioeconomic burden, particularly in poorer countries.

Objective: To investigate the prevalence of vitamin B12 deficiency in Type 2 diabetes patients taking metformin.

Methodology: This study was conducted on T2 diabetic patients in the Diabetic Department of Diabetes and Endocrinology HMC Hospital, Peshawar, for a year (10 February 2019 to 12 March 2020). The demographic data of the recruited patients was obtained after they gave their informed written consent. Patients inquired about their metformin use history, dosage, and duration of type 2 diabetes mellitus. A 5cc venous blood sample was taken from the arm and kept at 4 degrees Celsius. Vitamin B12 levels were measured using enzyme-linked immunoassay assays after serum was withdrawn. ELISA was used to determine the Vitamin B12 level in serums.

Results: A total of 149 people were enrolled in this trial. The patients' average age was 55 years. In this study, there were 67 (38.8%) males and 82 (55.2%) females. The individuals had a 5.12-year history of diabetes mellitus. The average HbA1c level was 8.280.32. The individuals that were included have taken metformin for at least 4.8 years. There were 25 (22.6%) patients using 1000-1500 mg metformin daily, 76 (46.4%) receiving 1500-2000 mg metformin daily, and 48 (40.7%) taking greater than 2000 mg metformin daily. There were 44 patients with a normal BMI, 80 patients who were overweight, and 25 patients who were obese. The average B12 level in the blood was 223pg/ml. Vitamin B12 deficiency was found in 96 (49.1%) of the patients. There was no vitamin B12 deficiency in 53 (45.4%) of the patients.

Recommendations: It is strongly advised based on the findings of this study that Serum cobalamin levels should be measured in Type II diabetes patients who are taking metformin, and patients should be given R.D.A (Recommended Dietary Allowance) multivitamins to avoid sequela of cobalamin deficiency.

Keywords: Frequency, Deficiency, Vitamin B12, Type2 Diabetic, Metformin Therapy

Introduction

Diabetes currently affects 240 million people worldwide, and this figure is expected to rise significantly to 380 million by 2026, with low and middle-income countries bearing the lion's share of the burden.² Pakistan is a high-frequency area, with 6.9 million affected people currently, with projected estimates of 11.5 million affected people by 2026, posing a significant socioeconomic burden to this developing country.¹ Pakistan is currently ranked seventh in the world with 6.9 million diabetics. The number of diabetics is expected to double (11.5 million) by 2025, propelling Pakistan to fourth place. According to the World Health Organization, type II diabetes affects 88 percent of all diabetics. Metformin is the first-line treatment of type II diabetes treatment. According to the UKPDS, this drug has miraculously improved diabetes-related vascular complications, all-cause mortality, had fewer hypoglycemic events, improved insulin sensitivity, weight loss, and euglycemia. Diabetes-related memory loss was also reduced by up to 20% when compared to SU therapy.⁴

The drug, on the other hand, has been blamed for lowering B12 levels by up to 30%.⁵ Multiple studies have found that Metformin-induced B-12 deficiency is caused by one or more of the following factors: decreased intestinal motility, disrupted B12 absorption from the gut, bacterial overgrowth, cobalamin-IF malfunction, and, last but not least, inhibited absorption of cobalamin-IF complex.^{6,7} There is also a concurrent folate deficiency of unknown aetiology. Hyperhomocysteinemia develops as a result of double deficiency, resulting in vascular myocardial events.⁸ If no serious complications occur, the majority of metformin-treated diabetics complain of paresthesia and altered sensations, particularly in the legs, which many treating physicians treat as peripheral neuropathy due to the primary disease⁹, and patients are prescribed neuropropics, anticonvulsants, and standard antidepressants without screening for cobalamin deficiency.¹¹

After 16 weeks to five years of metformin therapy, the symptoms of cobalamin deficiency become clinically evident. A high total daily dose (>2gm/day) and the patient's age are both risk factors.¹⁰ Medical practitioners should be cautious about prescribing metformin to type II diabetics who are at low risk of cobalamin deficiency as well as those who are at high risk of developing cobalamin deficiency or other neurological sequelae should be screened or treated empirically with B12 or calcium supplements¹⁰. Using cobalamin supplements to treat neuropathic sequelae improves quality of life¹².

According to the literature, metformin-related cobalamin deficiency has not been studied previously in Asian populations.

Methods

This hospital-based cross-sectional study was conducted on T2 diabetic patients at Diabetic Department of diabetes and Endocrinology HMC Hospital, Peshawar, for a period of one year (10-02-2019 to 12-03-2020). The sample was 149 patients presenting in Department of diabetes and Endocrinology, HMC, Peshawar. The general characteristic of patients was 51-90 years, either gender, type 2 diabetes on metformin therapy for one year were included. The researchers did not include the following patients in the study; Patients who are or have been vitamin B12 deficient in the last two months, pregnant women with mal-absorption disorders, or any abdominal surgery colectomy or gastrectomy patients with any blood disorder such as anaemia

or hemoglobinopathies. Following the signature of consent, demographic information was recorded on the study proforma, followed by a history of metformin use, metformin dosage, and duration of type II diabetes mellitus. A 5cc venous blood sample was taken from the arm and stored at 4 degrees Celsius. ELISA was used to determine the Vitamin B12 level in serums. Continuous data, such as age, duration of diabetes and Metformin use, weight, height, and BMI, were summarised using Mean+SD. Gender, marital status, education level, smoking history, and other nominal variables were summarised using frequencies and proportions. The data was stratified by age, gender, BMI, metformin duration, and HbA1C. The Chi-square test was used, with P 0.05 considered significant.

Results

Tables 1 and 2 show the demographics of patients. There were 25 (22.6%) patients taking 1000-1500mg metformin, 76 (46.4%) taking 1500-2000mg metformin, and 48 (40.7%) taking more than 2000mg metformin daily. The mean serum B12 level was 225.79pg/ml, with a minimum of 128pg/ml and a maximum of 344pg/ml. Vitamin B12 deficiency was associated with all female genders (p 0.017; BMI) (p 0.028). Duration of metformin use (p 0.000), HbA1c (p 0.000).

Table 1: Statistics and Variables of the Researched Population

Variable	Parameter	B 12 Deficiency		Chi square	P value
		Yes, 96 (49.1%)	No, 53(45.4%)		
Age	51-65	27(55.1%)	22(44.9%)	1.41	0.49
	65-90	46 (46%)	54(54%)		
Gender	Male	28(41.79%)	39(58.21%)	5.74	0.017
	Female	49(59.76%)	33(40.24%)		
BMI	Normal	35(64.81%)	19(35.19%)	7.13	0.028
	Overweight	21(47.73%)	23(52.27%)		
	Obese	17(33.33%)	34(66.67%)		

Table 2: Duration of Metformin Usage

Variable	Parameter	B 12 Deficiency		Chi square	P value
		Yes, 96 (49.1%)	No, 53(45.4%)		
Years	3 - 6	26(54.17%)	22(45.83%)	44.21	0.000
	7 - 9	46 (45.54%)	55(54.46%)		
HbA1C 8.28+0.32(6-12)	9 - 12	63 (42.28%)	86(57.72%)	19.84	0.000

Discussion

In T2 diabetics, this study found a strong association between cobalamin deficiency and metformin treatment (48 percent). This is in contrast to various studies that have been cited internationally. A study on metformin patients with the frequency of deficiency vitamin B12 (41 percent) & 29.66 percent respectively, B12 deficiency in metformin treated Type II diabetic patients was found to be only 8.6 percent & 19 percent in two different studies.^{13,14} Report from an early hospital To avoid borderline vitamin B12 deficiency manifesting clinically, it may be appropriate to advocate for Cobalamine deficiency screening prior to metformin use.¹⁰ It is strongly advised based on the findings of this study that Serum cobalamin levels should be measured in Type II diabetes patients who are taking metformin, and patients should be given R.D.A (Recommended Dietary Allowance) multivitamins to avoid sequela of cobalamin deficiency²¹. There are some limitations to this study; the study focused on the relationship between B12 deficiency and metformin duration and HBA1C. If the relationship between metformin dose and the severity of B12 deficiency had been studied, the results could have been astonishing and variable. One limitation of this study was that the researchers did not measure methyl malonic acid levels, which could improve the sensitivity of the results by detecting B12 deficiency in the early asymptomatic stage. Homocysteine levels in the blood, as well as methyl malonic acid levels in the blood and urine, are elevated in B12 deficiency. Because of a slower rate of metabolism Patients with B12 deficiency were not followed to see how B12 replacement affected them.

Conclusion

It is concluded that cobalamin deficiency, a water-soluble vitamin B12 deficiency, is common in Type 2 diabetics taking metformin. Screening for and treatment of B12 deficiency prior to metformin use is recommended to avoid deficiency-related morbidity.

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