

Original Research Article

A study on Vitamin B12 assay in type 2 diabetes mellitus on chronic metformin therapy in a tertiary care centre


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Abstract

Background: Metformin is considered as the first-line antidiabetic agent in the treatment of type 2 diabetes mellitus (T2DM) due to its effect on glucose and lipid metabolism. However various reports have recognized long-term treatment with metformin as a pharmacological cause of vitamin B12 deficiency. On the other hand, the exact prevalence of vitamin B12 deficiency among diabetic patients described in different literature is not constant.

Aim of the study: The study was conducted to assess Serum Vitamin B12 levels in Type – 2 Diabetes mellitus patients who were on chronic metformin therapy.

Materials and methods: The study population consists of 50 Type-2 Diabetes patients attending the Department of Diabetology OPD, Government Mohan Kumaramangalam Medical College Hospital, Salem, who was on metformin therapy for more than 5 years. Age, Sex, History of the duration of Diabetes and Metformin therapy and Examination were done. Blood samples were taken in the morning fasting sample for estimating Serum Vitamin B12 levels.

Results: Out of the 50 patients, 12 (24%) had deficient state and 30 (60%) had borderline lower Serum Vitamin B12 levels. It was assessed by Correlation Study and Frequency Analysis using SPSS version 20.

Conclusions: Chronic Metformin therapy is associated with a higher prevalence of Serum Vitamin B12 deficiency. Hence, testing Serum Vitamin B12 levels in chronic metformin-treated patients should be considered and subsequent follow up needed.

Key words

Diabetes mellitus, Metformin, Serum Vitamin B12.

Introduction

Metformin is first-line and the most frequently prescribed medication for the treatment of Type 2 Diabetes Mellitus. It is the first-line drug in the treatment of newly diagnosed T2 Diabetes Mellitus by various International recommendations and guidelines after lifestyle intervention [1]. Apart from Glycemic control, Metformin has a beneficial effect on lipid metabolism, inflammation and oxidative stress [2]. Metformin has been proven to reduce the myocardial infarction risk and all-cause mortality in overweight newly diagnosed T2 Diabetes Mellitus patients as it promotes weight loss as well [3]. Metformin use was linked with reduced risk in the development of T2 Diabetes Mellitus by several studies [4]. Metformin therapy should be considered in Prediabetes in those with BMI \geq 35 Kg/m², < 60 years of age, women with prior gestational diabetes mellitus and/or those with raising A1c despite lifestyle intervention for prevention of type 2 diabetes [1]. The main side effects of metformin include gastrointestinal disturbances such as vomiting and diarrhoea [5]. Individuals with renal, hepatic insufficiency and / or congestive heart failure have an increased risk of lactic acidosis while on Metformin therapy [6]. Vitamin B12 is also known as cobalamin is a water-soluble vitamin that is essential for red blood cell formation, nerve cell physiology and homocysteine metabolism. Vitamin B12 deficiency has been associated with Megaloblastic anemia, peripheral neuropathy, and cardiovascular disease [7]. Lately, many studies have linked metformin use in the long term with biochemical Vitamin B12 deficiency and anemia [8]. Several studies have indicated the association of Vitamin B12 deficiency with the dosage as well as the duration of metformin use [9]. The clinical symptoms of Vitamin B12

deficiency are anemia, peripheral neuropathy, depression, and cognitive impairment. But the symptoms are usually absent in those with Serum Vitamin B12 deficiency. Several types of research have made a recommendation to screen for Vitamin B12 in those Type 2 Diabetes Mellitus on Metformin [10].

Materials and methods

The patients enrolled in this study were recruited from the outpatient clinic of the Department of Diabetology, Government Mohan Kumaramangalam Medical College and Hospital, Salem during the period August 2015 to August 2016. The study was approved by the ethical committee of our hospital. Informed consent was obtained from the patients after explaining the need to take a blood sample. The study population included were 50 types of 2 Diabetes Mellitus patients who were on Metformin therapy for more than 5 years. Type 1 Diabetes Mellitus patients, Gestational Diabetes Women, Prior Vitamin B12 injection, Gastrectomy, Colectomy, IBD and Vegetarian patients were excluded. The mode of evaluation of patients includes history, anthropometric measurements, and clinical examination. A blood sample was drawn in vacutainer, immediately centrifuged and serum kept frozen and Vitamin B12 assay was determined from serum samples by chemiluminescence method.

Results

The majority of the study population were taking metformin less than 10 years of duration (74%). 26% of the population were taking metformin more than 10 years of duration. Out of the 50 patients, almost 30 had a borderline deficiency in vitamin B12. Irrespective of the glycemic status, duration of diabetes and metformin therapy, 60%

of the total patients had a borderline deficiency. The mean duration of diabetes was higher in the deficient group as seen in the mean duration of metformin lowest in the normal group. So both the mean duration of diabetes and the mean duration of metformin was higher in the deficient group (Table – 1 to 9).

Table – 1: Mean values of all observations.

Mean values of parameters	
Age	58.64 years
Duration of metformin	9.3 years
Duration of DM	10.4 years
FBS	166.26 mgs%
PPBS	267.8 mgs%
Blood urea	23.42 mgs%
Serum creatinine	0.974 mgs%
SGOT	23.04 IU
SGPT	23.56 IU
ALP	95.04 IU
Total bilirubin	0.712 mgs%
Direct bilirubin	0.344 mgs%
Total protein	6.924 gms%
Albumin	3.8 gms%
WBC	7380 Cells
RBC	3.27 Million/
Platelet	2.3 Lakhs
ESR 1 hr	13.16 mm
ESR 2 hr	24.16 mm
Hb%	10.43 gms%
PCV	32.16
Polymorphs	65.40%
Lymphocytes	32.40%
Eosinophils	2.20%
MCV	99.16 fl
MCH	32.22 pg
MCHC	31.88 gm/dl
Vitamin B12	296.62 pg/dl

Table – 2: Differentiation based on duration of metformin.

Duration of metformin	Result
< 10 years	37(74%)
>10 years	13(26%)

Table – 3: Distribution of macrocytosis.

	MCV
Normal	32(64%)
High	18(36%)

Table – 4: Relationship between Vitamin B12 and peripheral smear.

Smear	Vitamin B12 level		
	Deficient	Borderline	Normal
Macrocytosis	7	2	3
Microcytic	0	6	0
Normal	5	22	5

Table – 5: Significance of Vitamin B12 and sex distribution.

Vitamin B12 levels	Sex	
	Male	Female
Deficient	7	5
Borderline	12	16
Normal	5	3
P value	0.416	
Significance	Non-significant	

Table – 6: Significance of Vitamin B12 deficiency and duration of metformin.

Vitamin B12 levels	Duration of metformin	
	> 10 years	< 10 years
Deficient	4	8
Borderline	7	23
Normal	2	6
P value	0.511	
Significant	Non-significant	

Table – 7: Mean duration of metformin in all groups.

Vitamin B12 levels	Mean duration of metformin
Deficient	10.33
Borderline	9.07
Normal	8.63

Table – 8: Distribution based on Vitamin B12 level.

	Vitamin B12
Normal	8
Borderline	30
Deficient	12

Table – 9: Mean duration of diabetes mellitus and Vitamin B12 levels.

Vitamin B12 levels	Mean duration of diabetes mellitus
Deficient	11.17
Borderline	10.4
Normal	9.25

Discussion

Vitamin B12 malabsorption in patients who had been treated with Metformin for as little as 3 months was reported as early as 1961 by Berchtold, et al. [11]. As early as 1971, Tomkin, et al. based on a cross-sectional evaluation recommended that all patients on long term metformin therapy have annual Vitamin B12 testing [12]. The water-soluble Vitamin B12 also known as Cobalamin is essential for hematopoietic and neurological functions in the body. Metformin since its introduction in 1950 is considered the most frequently prescribed drug for the treatment of Type 2 Diabetes Mellitus. Metformin has a beneficial effect on lipid metabolism, inflammation and oxidative stress beyond glycemic control. The malabsorption of Vitamin B12 induced by Metformin is Calcium-dependent and be reversed with increased calcium intake was demonstrated in a study [13]. Older individuals have a greater risk of developing Vitamin B12 deficiency. Chronic metformin therapy may exacerbate Vitamin B12 deficiency among older adults with low serum B12. The daily diet should also be considered as a possible cause of B12 deficiency as vegetarians tend to have a higher prevalence of B12 deficiency compared to that of Non – vegetarians.

Conclusion

Long term use of metformin was associated with Serum B12 deficiency. A relationship exists between metformin and reduced serum B12 levels beyond the background prevalence of serum B12 deficiency. Vitamin B12 deficiency associated complications and symptoms are rarely seen clinically. Vitamin B12 deficiency was seen even in the absence of anemia. The

lower levels of Serum vitamin B12 are demonstrated in Type 2 Diabetic patients who were on chronic metformin therapy in our study. Hence, people with Type 2 Diabetes Mellitus on chronic metformin therapy should have their Vitamin B12 levels tested at least once a year. Measurement of serum Vitamin B12 levels should be considered at the initiation of metformin therapy and subsequent annual follow up.

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