An assessment of Vitamin B12 deficiency in Diabetic patients on Metformin therapy

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ABSTRACT

Objective: To evaluate the prevalence of Vitamin B12 deficiency in type 2 Diabetes Mellitus patients on Metformin therapy.
Study Design: An observational analytic cross-sectional study
Place and Duration: Department of Medicine Jinnah Medical College Hospital from 1st January 2018 to 30th March 2019.
Methodology: All patients having type 2 diabetes mellitus of age 31-84 years of either gender, taking metformin, were included in the study. The data included demographic characteristics, duration of diabetes and metformin treatment. A blood sample of all patients was obtained after an overnight fasting and samples were then sent to the hospital's laboratory to measure the vitamin B12 levels. Serum vitamin B12 levels less than 170pg/ml were regarded as biochemical deficiency.
Results: Out of 215 patients, frequency of vitamin B12 deficiency was found to be 29.3 %. About 55 vitamin B12 deficient patients were on metformin therapy from more than 4 years and showed statistically significant difference ($p<0.05$) . Average age was reported as 58.89±13.12 years. The average duration of Diabetes mellitus and metformin therapy were reported as 9.93±6.82 years and 9.60±6.15 years respectively
Conclusion: Vitamin B12 deficiency is prevalent in patients on metformin therapy especially above 50 years of age and taking metformin for more than four years which strongly suggests the routine screening of vitamin B12 in diabetic individual on metformin.
Keywords: Diabetes mellitus, Metformin, Vitamin B12, Megaloblastic anemia, Diabetic neuropathy, Anti-diabetic drugs

INTRODUCTION

Globally incidence of diabetes mellitus is growing at alarming rate. According to WHO, the number of persons suffering from diabetes mellitus has increased from 108-422 million in year 1980 to year 2014[1]. In 2014 the worldwide prevalence of diabetes among adults (>18 years) was reported as 8.5%. In 2016, it is estimated that 1.6 million deaths occurred due to diabetes and diabetes became the 7th leading cause of death[1,2]. According to IDF(International diabetic federation),men (215.2 million) are slightly more affected by diabetes than women (199.5 million)[3].

The first line oral hypoglycemic agent for type 2 diabetes mellitus (T2DM) is biguanides, commonest of which is metformin (met). It acts by increasing the glucose uptake in liver and muscle tissues. It also contributes to weight reduction and increases insulin sensitivity[4]. Although the safety and efficacy of metformin for the treatment of type 2 diabetes mellitus have been well established by its long-term clinical use, the administration of this drug is sometimes associated with certain adverse effects. Gastrointestinal adverse events including diarrhea, anorexia and dyspepsia are common during treatment with metformin, but are not serious in most cases. In contrast, lactic acidosis, which occurs infrequently during metformin treatment, sometimes progresses to a serious condition[4]. Another common side effects of metformin is vitamin B12 deficiency related to slow absorption. Vitamin B12 deficiency can result in a wide spectrum of abnormalities such as gastrointestinal, hematological, neurological and psychiatric disorders, moreover it increases the intensity of diabetic peripheral neuropathy[5]. The other mild symptoms due to deficiency of vitamin B12 are anemia, memory loss, low mood and fatigue[6].

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The level vitamin B12 is inversely associated with duration and dose of metformin[7]. Literature showed an incidence of vitamin B12 deficiency from 15 % to 32% due to metformin therapy among Type 2 diabetic patients[8,9]. Mastroianni et al evaluated the level of vit B12 after metformin treatment among Type 2 diabetic patients which showed that vit B12 reduced by 32% compared to placebo(9). In another comparative trial, the proportion of vit B12 deficiency was higher in the metformin group (4.3%) as compared to placebo (2.4%) (p<0.05)[10].

Currently there are no proper published guidelines advocating for routine screening for deficiency of vitamin B12 among patients taking metformin. The aim of the present study is to evaluate the frequency of Vitamin B12 deficiency in Type 2 diabetic patients on metformin therapy. This would be helpful in monitoring of vitamin B12 deficiency in patients after starting of metformin therapy, which can significantly reduce the morbidity and improve the quality of life among these patients by timely start B12 supplementation as required. So this study was conducted with an objective to evaluate the prevalence of vitamin B12 deficiency in type 2 Diabetes Mellitus patients on Metformin therapy.

METHODOLOGY

This single centre observational analytic cross-sectional observational study conducted at the diabetic clinic, Department of Medicine Jinnah Medical College Hospital Karachi, Pakistan from 1st January 2018 to 31st March 2019 for total duration of 14 months. The convenient sampling technique was used for sample collection. Inclusion criteria included a diagnosis of type 2 Diabetes Mellitus, age between 31-84 years of either gender and history of using metformin for more than 6 months. Exclusion criteria included patients on strict vegetarian diet, any history of malabsorption/worm infestation (ruled out by stool analysis), history of gastrointestinal surgery ,pregnancy, renal failure, hepatic failure and intake of B12 supplements (excluded on the basis of history and medical records) .

The data was collected by researchers/trained house physicians under supervision. Before enrollment participants were explained about the details of study and utilization of data and informed consent was taken from all the patients.

All the information was recorded on structured questionnaire. The data included patient's age, gender, duration of diabetes mellitus and duration of metformin use. After collecting above information from patients and medical records, 5 ml of blood was collected in sample tube after an overnight fasting and sent hospital's laboratory to measure serum vitamin B12 levels. Serum vitamin B12 levels less than 170 pg /ml were regarded as biochemical deficiency.

Data Analysis: SPSS version 23 was used to analyze data. Mean and SD were calculated for quantitative variables whereas frequencies and percentages were calculated for qualitative variables. Chi-square was applied. P≤0.05 was taken as statistically significant.

RESULTS

A total of 215 patients were enrolled in the study and among them 63(29.3%) patients were found vitamin B12 deficient (Figure-1). According to general characteristics of the participants, mean age of the patients was calculated as 58.89±13.12 years. Majority of them were females 138(64.2%) and 77 (35.8%) were males .The average duration of diabetes mellitus and metformin therapy were reported as 9.93±6.82 years and 9.60±6.15 years respectively (Table -I).
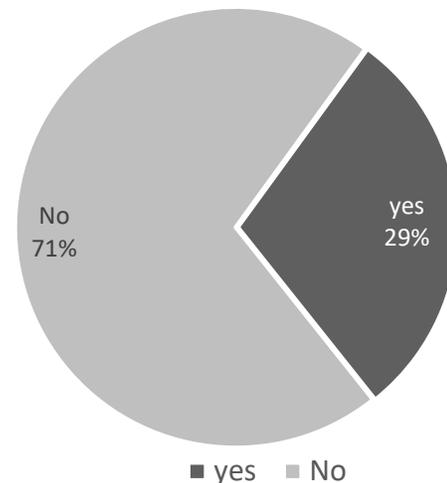

Figure-1: Frequency of vitamin B12 Deficiency = 63(29.3%)

Table-I: Frequency of different variables (N=215)

Variables	Frequency
Age (years) mean+ SD	58.89+13.3
Males	77(35.8%)
Females	138(64.2%)
Duration of Diabetes Mellitus (years) mean + SD	9.95+ 6.74
Duration of Metformin therapy (years) mean + SD	9.61 + 6.61

Table-II: comparison of VIT B12 deficiency with age, gender and duration of metformin therapy, N=63(29.3%)

Variables	Vitamin B12 Deficiency			p-Value
	Yes	No	Total	
Age groups				
<=50years	16	50	66	0.278
>50years	47	102	149	
Duration of met therapy				
<=4 years	8	42	50	0.018
>4 years	55	110	165	
Gender				
Male	26	51	77	0.283
Female	37	101	138	

On comparing patients with normal verses low B12 levels, majority of the patients with vitamin B12 deficiency were found to be age more than 50 years (n=47) however this was

not statistically significant difference (p>0.05). On comparing the duration of metformin therapy, 55 out of 63 B12 deficient patients were using metformin therapy from more than 4 years and this difference was statistically significant (p<0.05). In Comparison of gender, majority of vitamin B12 deficient patients were females however this difference was not statistically significant (p>0.05) (Table-II).

DISCUSSION

Vitamin B 12 deficiency is a known side effect of metformin therapy[11].Vitamin B 12 required for formation of cellular DNA and myelin sheath, so can lead to megaloblastic anemia, dementia and peripheral neuropathy. Clinical symptoms of Vitamin B12 deficiency in T2DM are comparable to those in the general population. Worsening of diabetic neuropathy has been described among patients with co-existing vitamin B12 deficiency[12]. Furthermore, vitamin B12 replacement has been shown to cause symptomatic improvement, reduction in pain, and parasthesias among patients with severe diabetic neuropathy, suggesting that functional vitamin B12 deficiency in T2DM patients is clinically significant. Sensory polyneuropathy caused by vitamin B12 deficiency mimics diabetic neuropathy. Overlapping symptoms between neuropathy and vitamin B12 deficiency may complicate the diagnosis of actual diabetic neuropathy[12] that's why patient who are on long-term metformin therapy should have screening of vitamin B12 level regularly[12,13]. But on contrary its noted that this is not a frequent practice in primary healthcare. In the present study we have evaluated the frequency of vitamin B12 deficiency in T2DMpatients using metformin therapy for greater than 6 months.

We observed that 63(29.3%) of our diabetic participants had Vit B12 deficiency. This observation was compared to other studies in different areas of the world. In a RCT (randomized controlled trial) conducted by Defronzo et al. found that use of met reduced vit B12 level by 29%[14]. Najam and colleagues has concluded that B12 deficiency was more common in patient taking metformin > 2 years[15]. In another study by Kim et al, 22% people had B 12 deficiency[16]. The Mulla and colleagues studied one fifty seven T2DM females who were on metformin therapy and found 10% of patients had vit B12 deficiency[17]. Hermann et al reported that 26.7% patient had B12 deficiency with long term metformin therapy[18]. Similarly, the Nervo et al observed 36.8% patient had B12 deficiency most of them were older than 55 year of age[19]. In a systematic review by Chapman et al observed that there is a clear relationship between use of met therapy and low concentration of vit B12[20]. Similar results were observed again proven in several subsequent case reports, cross-sectional research and randomized controlled trials[21-23].

In our study the mean age of the patients was reported as 58.89 years and average duration of metformin therapy was reported as 9.60 years and most of the patients were females (64.2%). In a clinical audit by Haeusler and colleagues found the overall mean age of patients on met therapy as 61.05 years and average duration of met therapy was reported as 7.61 years

however most of them were males (53%)[13].Whereas in another study by Mulla et al observed dissimilar results of average age and duration of met therapy as 63.4 years and 6.4 years[17]. In a study conducted by Alharbi and colleagues, enrolled 319 patients who were met therapy and reported almost similar mean age as 57.8 years[23]. Similarly, the Wong et al observed that elderly people living in long term care institutions are particularly at risk of vitamin B_{12} deficiency[24].

We observed that 55 vitamin B12 deficient patients were on met therapy from more than 4 years and had statistical relationship was found to be significant (p<0.05). Haeusler and colleagues in their study found strong correlation between vitamin B12 concentration and duration of metformin therapy[13]. Alharbi et al has also showed vit B12 deficiency occurred when met was taken for more than 4 years with adjusted odd ratio as 6.35 (P<0.05).(23,24)).In a study by Wai et al, they did the stratification of one seventy four met users and also found that vit B12 deficiency were significantly related with duration of met use[25]. Kumthekar in a case report[26] and Kos et al in a study also observed B12 deficiency is more common with longer duration of metformin therapy[27].

CONCLUSION

Vitamin B12 deficiency is prevalent in patients on metformin therapy especially above 50 years of age and taking metformin for more than four years which strongly suggests the routine screening of vitamin B12 in diabetic individual on metformin.

AUTHOR'S CONTRIBUTION

Kumar A: Conceived idea, Designed research methodology and referencing
Kumar D: Major Conceived idea, Designed research methodology, Bibliography
Razzaque S: Data analysis, Manuscript writing
Kumar R: Data collection, Literature search
Kumar A: Data collection, Data analysis
Ghauri MI: Literature review, Data analysis

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