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Research Article

DETERMINE THE FREQUENCY OF VITAMIN B12 DEFICIENCY IN TYPE 2 DIABETIC PATIENTS TAKING METFORMIN THERAPY

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Abstract:

Objectives: To determine the frequency of vitamin B12 deficiency in type 2 diabetic patients taking metformin therapy.

Materials and methods: This Cross-Sectional Study was conducted at in/out patient department of General Medicine in Fuji Foundation Hospital Rawalpindi during 1st Sep 2017 to 28th Feb 2018. The sample size will be 218 patients. The data was collected through non-probability consecutive sampling. Sample was drawn by the postgraduate resident under full aseptic measures and stored in two serum bottles. Both samples were clearly marked with patient's name and admission number/OPD number. Sample bottles were sent to Fuji Foundation Hospital Rawalpindi laboratory for measurement of Serum B12 level and HbA1c. Serum B12 level was checked by Roche B12 kit. The rationale to check HbA1c is to look for the control of sugars.

Results: Total 218 patients were included according to the inclusion criteria of the study. Descriptive statistics of age (years) of patient was also calculated in terms of mean and standard deviation. Mean age (years) in the study was 54.08±13.74 with ranges from 20 to 80 years. Distribution of gender of patient was also calculated in terms of frequency and percentage of male and female patients. There were 61 (28.0) male and 157 (72.0) female patients who were included in the study according to the inclusion criteria. Descriptive statistics of plasma sugar level was calculated in terms of mean and standard deviation. Mean duration of plasma sugar level was 16.02±3.55 in the study. **Conclusion:** The study concluded that frequency of vitamin B12 deficiency is substantial in type 2 diabetic patients taking metformin therapy.

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INTRODUCTION:

A fasting plasma glucose >7.0 mmol/L (126 mg/dL) or an HbA1C $>6.5\%$ warrant the diagnosis of Diabetes Mellitus. Type 2 DM is a heterogeneous group of disorders characterized by variable degrees of insulin resistance, impaired insulin secretion, and increased glucose production. Diabetes is sometimes present in a subclinical or undiagnosed form for years before diagnosis and 25–50% of patients have some evidence of vascular complications at that time [1].

The worldwide prevalence of DM has risen dramatically in past two decades, an estimated 30 million cases in 1985 to 285 million in 2010 and according to International Diabetes Federation it will be 438 million by the year 2030 [2]. The prevalence of type 2 DM is rising much more rapidly mainly because of reduced physical activity levels as countries are becoming more industrialized, increasing obesity and the aging of the population. In 2010, the prevalence of diabetes ranged from 11.6 to 30.9% in the countries with the highest prevalence (United Arab Emirates, Saudi Arabia, Bahrain, Kuwait, Oman, and Malaysia). In the United States, diabetes is the seventh leading cause of death and a recent estimate suggested that diabetes is the fifth leading cause of death worldwide [3].

Deficiency of vitamin B12 affects both men and women in equal numbers. The prevalence of deficiency varied by age group $\leq 3\%$ in aged 20–39 yrs, $\approx 4\%$ in aged 40–59 yrs and $\approx 6\%$ in aged ≥ 70 y [4]. The reported prevalence of deficiency is much higher in African and Asian countries i.e 70% in Kenyan school children, 80% in Indian preschoolers, and 70% in Indian adults [5].

In 2009, Pflipsen et al. showed that 22% of patients with Type 2 DM had a vitamin B12 deficiency and those on metformin had reduced serum vitamin B12 levels with an increased risk of vitamin B12 deficiency. Moreover, it has been shown that the dose and duration of metformin use is directly correlated to vitamin B12 deficiency [6].

We know that Metformin is the first-line oral treatment in overweight and obese type 2 diabetics. Metformin use is significantly associated with vitamin B12 deficiency, but exact frequency is yet unknown in Pakistan [7]. Physicians most of the times consider B12 deficiency associated neurological symptoms as a part of Type 2 Diabetes Mellitus i.e Diabetic neuropathy and treat them accordingly because no guidelines recommend estimation of serum vitamin B12 levels in diabetics, hence this side effect of metformin goes unnoticed [8]. To determine the frequency of vitamin B12 deficiency in type 2 diabetic patients taking metformin therapy.

PATIENTS AND METHODS:

This Cross-Sectional Study was conducted at in/out patient department of General Medicine in Fauji Foundation Hospital Rawalpindi during 1st Sep 2017 to 28th Feb 2018. The sample size will be 218 patients. The data was collected through non-probability consecutive sampling.

Inclusion criteria: The patients of both genders, aged between 30–80 years, diagnosed cases of Diabetes Mellitus type 2 and on metformin therapy for more than one year was included in this study.

Exclusion criteria:

- Abdominal Surgery (by taking history and looking for scar mark on abdominal examination).
- Crohn's disease (by taking history from the patient).
- Celiac disease (by taking history from the patient and asking about wheat sensitivity).
- Excessive alcohol consumption (by taking history from the patient).

Data Collection Procedure: An ethical approval for the study was gained from the hospital ethics committee before initiating study enrollment. After taking consent from the patient and explaining the procedure of blood sampling, sample was drawn by the postgraduate resident under full aseptic measures

and stored in two serum bottles. Both samples were clearly marked with patient's name and admission number/OPD number. Sample bottles were sent to Fauji Foundation Hospital Rawalpindi laboratory for measurement of Serum B12 level and HbA1c. Serum B12 level was checked by Roche B12 kit. The rationale to check HbA1c is to look for the control of sugars. The reports were collected by post graduate resident. The results were noted on proforma accordingly. Variables which were noted include patient's age, gender, blood sugars and serum Vitamin B12 level.

DATA ANALYSIS:

The data was analyzed by SPSS software version 16. Descriptive statistics was calculated for all variables like age, gender, plasma sugar level and serum Vitamin B12 level. Frequency and percentage are presented for qualitative and quantitative variables like gender, HbA1c, and serum vitamin B12 level.

RESULTS:

Total 218 patients were included according to the inclusion criteria of the study. Descriptive statistics of age (years) of patient was also calculated in terms of mean and standard deviation. Mean age (years) in the study was 54.08+13.74 with ranges from 20 to 80 years.

Table. No. 01 Descriptive statistics of patients

	n	Minimum	Maximum	Mean	Std. Deviation
Age (years)	218	30	80	54.08	13.74
Plasma Sugar level	218	11	24	16.02	3.55
Serum Vitamin B12 level	218	40	147	102.67	28.100

Distribution of gender of patient was also calculated in terms of frequency and percentage of male and female patients. There were 61 (28.0) male and 157 (72.0) female patients who were included in the study

according to the inclusion criteria. Descriptive statistics of plasma sugar level was calculated in terms of mean and standard deviation. Mean duration of plasma sugar level was 16.02+3.55 in the study.

Table. No. 02: Frequency and percentage of HbA1C (control of diabetes)

	Frequency	Percentage
< 6.0%	0	0
6.0% - 9.0%	55	25.2
> 9.0%	163	74.8
Total	218	100.0

Descriptive statistics of serum vitamin B12 level was calculated in terms of mean and standard deviation. Frequency of hbA1C > 9.0% and 6-9.0% was 163 (74.8) and 55 (25.2) respectively. The primary objective of the study is to determine the frequency of

vitamin B12 deficiency in type 2 diabetic patients taking metformin therapy. Out of 218 patients, there were 65 (29.8) patients of vitamin B12 deficiency (<148 mpol/L).

Table. No. 03: Effect modifier like Age stratification with Serum Vitamin B12 level deficiency

Table. No. 03: Effect modifier like Age stratification with Serum Vitamin B12 level deficiency					
			Serum Vitamin B12 level deficiency (<148 mpol/L)		p-value
			yes	no	
Age group	30 - 50 years		23	42	0.241
			35.4%	27.5%	
	51 - 80 years		42	111	
			64.6%	72.5%	
Total			65	153	
			100.0%	100.0%	

DISCUSSION:

Metformin is the most prescribed anti-diabetic drug in patients with type 2 diabetes mellitus (T2DM) and hence, considered a cornerstone in the treatment of T2DM [7]. It is an anti-hyperglycaemic agent that is usually well tolerated in most of the patients (except for mild gastrointestinal side effects) and it is characterized by excellent improvement in the cardiovascular morbidity and mortality associated with T2DM. Due to the numerous clinical benefits associated with metformin, some side effects with potential adverse health effects associated with its use are usually ignored and rarely investigated. One of such side effects is vitamin B₁₂ deficiency [8].

Vitamin B₁₂, also called cobalamin, is a water-soluble vitamin involved in the optimal functioning of the hemopoietic, neuro-cognitive and vascular systems. It is involved in DNA synthesis, fatty acid metabolism and energy production [9]. Vitamin B₁₂ exerts its physiological effects by facilitating the methylation of homocysteine to methionine which is later activated into S-adenosyl methionine that donates its methyl group to methyl acceptors. Similarly, vitamin B₁₂ mediates the conversion of methyl malonyl coenzyme A (coA) to succinylcoA, a process when hindered, results in accumulation of serum methylmalonic acid (MMA) thereby causing defective fatty acid synthesis of the neuronal membranes [10].

Reports have shown that there is an association between metformin use and vitamin B₁₂ deficiency. However, the mechanism through which metformin induces vitamin B₁₂ deficiency (VBD) in patients with T2DM is presently unclear. Some of the suggested mechanisms include alteration in small bowel motility, which stimulates bacterial overgrowth and consequential vitamin B₁₂ deficiency [11]. Others include competitive inhibition or inactivation of vitamin B₁₂ absorption, alteration in intrinsic factor levels and interaction with the cubulinendocytic receptor [12]. Also, inhibition of the calcium dependent absorption of vitamin B₁₂-intrinsic factor (IF) complex at the terminal ileum has been suggested as one of the mechanisms [13].

Assessment of vitamin B₁₂ deficiency in patients with T2DM is of clinical importance. It can present as peripheral neuropathy and may be mistaken for diabetic neuropathy in patients on metformin treatment. Also, low vitamin B₁₂ levels have been reported to be associated with poor nerve conduction velocities and poorer responses to light touch by monofilament detection. This may lead to unnecessary

use of anticonvulsants, tricyclic antidepressants and other medications for diabetic neuropathy [14].

CONCLUSION:

The study concluded that frequency of vitamin B12 deficiency is substantial in type 2 diabetic patients taking metformin therapy. Thus, there is a need to seriously check and monitor the nutritional status of those treated patients with metformin in order to prevent B12 deficiency associated sign and symptoms and also to prescribe vitamin B12 supplements if there is definitive deficiency.

CONFLICT OF INTEREST:

There is no conflict of interest.

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