

VITAMIN B12 DEFICIENCY IN TYPE II DIABETIC PATIENTS ON METFORMIN THERAPY; A STUDY CONDUCTED IN TERTIARY CARE HOSPITAL OF PESHAWAR

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ABSTRACT

Objective: To evaluate the frequency of Vitamin B12 deficiency in local Type II diabetic patients using Metformin.

Materials and Methods: A Cross Sectional study was conducted in the department of General Medicine, Khyber Teaching Hospital, Peshawar from August, 2016 to January, 2017 after designing proper inclusion and exclusion criteria and getting approval from Ethical and Research committee of hospital. A total of 130 Type II diabetic patients were selected from OPD with 14.1% proportion of vitamin B12 deficiency, 95% confidence interval & 6% margin of error using WHO sample size calculator. Those with Vitamin B12 levels less than 100 pg/mL were considered as deficient. Vitamin B12 deficiency was stratified among age, gender and duration of metformin usage to see the effect modifications.

Results: Study showed presence of vitamin B12 deficiency in 19 (14.61%) patients whereas in 111 (85.38%) patients it was not detected.

Conclusion: Modest prevalence of vitamin B12 deficiency among Type II diabetic patients treated with Metformin was observed.

Key words: Diabetes Mellitus (DM), Vitamin B12, Metformin..

This article may be cited as: Hayat W, Faisal MS, Inayat A, Khalil KUR.. Vitamin b12 deficiency in type ii diabetic patients on metformin therapy;a study conducted in tertiary care hospital of peshawar. J Med Sci 2018; 26: (2) 151-154.

INTRODUCTION

Diabetes Mellitus (DM), a very common non-communicable disease worldwide, is considered to be the fourth most frequent cause of death in developed countries¹. According to survey conducted by WHO in 1995, among top ten countries with highest diabetes mellitus prevalence, Pakistan was eighth on list with 4.3 million diabetic patients. It is proposed that Pakistan will be on same rank in this list with 14.5 million diabetic patients by year 2025². Prevalence of diabetes in the urban areas of Pakistan is 6% in males and 3.5% in females, whereas in the rural areas the estimated prevalence in males is 6.9% and 3.5% in females³.

Metformin is the first-line medication used in the treatment of Type II diabetes but it has been shown in multiple studies to reduce serum B₁₂ levels in 10-30% of patients⁴. In medical literature, metformin induced vitamin B₁₂ deficiency has now become a traditional myth⁵. In a survey conducted by National Health and Nutrition Examination, out of 1621 diabetic patients using metformin, 575 showed B₁₂ deficiency⁶. In addition, metformin induced vitamin B₁₂ deficiency may iatrogenically exacerbate peripheral neuropathy in Type II diabetic patients. A decrease in blood levels of vitamin B₁₂ and folate might result in elevation of homocysteine levels, which is reported as an independent risk factor for development of cardiovascular disease, especially in patients of Type II diabetes^{7,8,9}. Doing a thorough literature search, we found that very small data exist regarding metformin induced vitamin B₁₂ deficiency in our local adult diabetic population. This study was an attempt to establish data for target population, the results will serve as guidelines for devising future research strategies and identifying means to prevent vitamin B12

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Date Received: September 26, 2017

Date Revised: March 26, 2018

Date Accepted: April 20, 2018

deficiency in Type II diabetics using metformin.

MATERIAL AND METHODS

A descriptive (Cross Sectional) study was designed to determine the frequency of metformin induced vitamin B₁₂ deficiency in Type II diabetic patients. The study was conducted at the Department of General Medicine, Khyber Teaching Hospital, Peshawar from August, 2016 to January, 2017. Study was carried out after recommendation from the hospital ethical and research committee. Sample size of 130 Type II diabetic patients on Metformin therapy was taken, using 14.1% proportion of vitamin B₁₂ deficiency, with 95% confidence interval and 6% margin of error. Patients were enrolled through OPD by consecutive, non-probability sampling. Before taking a written informed consent, purpose and benefits of the study were properly explained to the patients.

Patients of either gender, between 30 to 65 years of age with history of Type II DM of minimum five years duration and using Metformin within a dose range of 1000-1500 mg/day for atleast one year were included in the study. Patients with history of gastrectomy, ileal resection, pernicious anemia, renal/hepatic diseases, on lipid lowering drugs or multi-vitamin supplements and Type I DM were excluded to control the confounders and bias in results. All patients were subjected to detailed history and clinical examination followed by routine baseline investigations. From all the patients, a blood sample was obtained after an overnight fast to measure the vitamin B₁₂ levels. Those with Vitamin B₁₂ levels less than 100 pg/mL were considered as deficient while with Vitamin B₁₂ levels more than 350 pg/mL were considered as normal. In addition, those with blood levels of Vitamin B₁₂ in range of 100 to 350 pg/mL were labelled as indeterminate. Vitamin B₁₂ deficiency was stratified among age, gender and duration of metformin usage to see the effect modifications.

Data was stored and analyzed by using SPSS version 16. Means and Standard Deviations were calculated for quantitative variables like age and vitamin B₁₂ levels. Percentages and frequencies were calculated for categorical variables like age, gender and vitamin B₁₂ deficiency and the results were presented in table form.

RESULTS

This study was carried out on 130 patients out of which 19 (14.61%) patients were in age group of 30-37 years, 32 (24.61%) in 38-44 years, 38 (29.23%) in 45-51 years, 21 (16.15%) in 52-58 years and 20 (15.38%) were in age group of 59-65 years. The Mean and SD for Age was 48+9.24. In terms of gender distribution, Male

patients were 109 (83.84%) while female patients were 21 (16.15%). Frequencies of vitamin B₁₂ deficiencies were found in 19 (14.61%) patients whereas not detected in 111 (85.38%) patients. Stratification of vitamin B₁₂ deficiencies with age distribution were carried out as shown in Table-1 with P Value 0.970. Stratification of vitamin B₁₂ deficiencies were also carried out with gender distribution which can be seen in Table-2 with P Value 0.0008. In Table-3, stratification of vitamin B₁₂ deficiencies with duration of metformin use is given with P Value 0.452.

Table 1: Stratification of vitamin b12 deficiency with age

Age	Vitamin b12 deficiency	No of patients and percentages	P value
30-37 Years	Yes	03 (2.30%)	0.970
	No	16 (12.30%)	
38-44 Years	Yes	04 (3.07%)	
	No	28 (21.53%)	
45-51 Years	Yes	05 (3.84%)	
	No	33 (25.38%)	
52-58 Years	Yes	04 (3.07%)	
	No	17 (13.07%)	
59-65 Years	Yes	03 (2.30%)	
	No	17 (13.07%)	

Table 2: Stratification of vitamin b12 deficiency with gender

Gender	Vitamin b12 deficiency	No of patients and percentages	P value
Male	Yes	11 (8.46%)	0.0008
	No	98 (75.38%)	
Female	Yes	08 (6.15%)	
	NO	13 (10%)	

Table 3: Stratification of vitamin b12 deficiency with duration of metformin use

Duration of metformin use	Vitamin b12 deficiency	No of patients and percentages	P value
= 12 Months	Yes	05 (3.84%)	0.452
	No	39 (30%)	
> 12 Months	Yes	14 (10.76%)	
	No	72 (55.38%)	

DISCUSSION

Metformin is considered to be one of the mainstay therapy in Type II diabetes but it is proposed to be associated with vitamin B₁₂ deficiency^{12,14}. After detailed literature search, it was found that very few studies have been carried out on Pakistani diabetic population regarding this topic. Main objective of this study was to determine the prevalence of metformin induced vitamin B₁₂ deficiency in local Type II diabetic patients. Our study proposed only modest prevalence of vitamin B₁₂ deficiency i.e. Vitamin B₁₂ deficiency was found in 19 (14.61%) patients whereas in 111 (85.38%) patients it was not detected. The exact mechanism for this deficiency is unknown but it is proposed that process of uptake of Vitamin B₁₂-Intrinsic factor complex by cell membrane of ileum is calcium-dependent. It is a known fact that metformin alters this action, thus results in deficiency of serum Vitamin B₁₂ levels¹⁵. According to study done in 2010, the mean serum level of vitamin B₁₂ among Type II diabetics using metformin was 317.5 pmol/L while in 16.2%, only the borderline B₁₂ deficiency was found⁵. In another report, in Type II diabetics not taking metformin, the prevalence of B₁₂ deficiency was only 4.4% as compared to 14.1% in metformin users which is very similar to our results i.e. 14.61%¹⁰.

In a study done by Long AN et al, the prevalence of metformin induced Vitamin B₁₂ deficiency among diabetic patients was found to be 21.9%¹¹. In 2009, another study was carried out by Pflipsen et al, which has revealed B₁₂ deficiency in 22% diabetic patients using metformin. In comparison to our study, these studies were more sensitive as the data were taken from past medical records and survey was conducted regarding use of insulin and other hypoglycemic agents. Moreover, in contrast to our study, levels of methyl-malonic acid were also measured, which can identify B12 deficiency even in initial asymptomatic phase^{16,18,19}.

According to an American study, there was no significant correlation found between Vitamin B₁₂ deficiency and metformin usage. However, a trend of lower B¹² level was existing in diabetic patients on prolonged metformin therapy¹⁷. Bivariate analysis of our study demonstrated, no significant association between age, gender and B₁₂ deficiency.

Many patients who develop Vitamin B₁₂ deficiency, also suffer from anaemias and paraesthesias consequently. Most of the times, Physicians mistakenly link it to the underlying diabetes and thus never address the issue¹³. But this statistically significant percentage of vitamin B₁₂ deficiency serves the physicians a useful tool while considering these associated complications in diabetic patients specially those who are on prolonged

or high dose metformin therapy²⁰. According to study done on Type II diabetic patients with complications like neuropathic pains and anemia, Vitamin B₁₂ supplementation showed improvement in these symptoms²¹. Keeping this fact in mind, physicians must identify and screen Type II diabetics on metformin for existing Vitamin B₁₂ deficiency specially in those presenting with complications like neuropathies.

CONCLUSION

The level of vitamin B₁₂ did not drop in most of the Type II diabetic patients using oral metformin.

RECOMMENDATIONS

Further studies are needed to see the correlation between frequency of B₁₂ deficiency at different Metformin doses. Moreover, the effect of Vitamin B₁₂ supplements in these patients regarding improvement of B₁₂ deficiency and its associated complications.

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CONFLICT OF INTEREST: Authors declare no conflict of interest
GRANT SUPPORT AND FINANCIAL DISCLOSURE NIL

AUTHOR'S CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under:

Hayat W: Concept and design, manuscript writing.

Faisal MS: Data collection

Inayat A: Bibliography

Khalil KUR: Statistical analysis

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.