

FREQUENCY OF VITAMIN B12 DEFICIENCY IN PATIENTS WITH TYPE II DIABETES MELLITUS WITH AND WITHOUT METFORMIN THERAPY

Kalim Ullah Khan¹, Jehan Anjum¹, Muhammad Fayaz¹, Wajeeh Ur Rehman², Daneet Kumar¹, Jasvinder Kumar³, Uroosa Arif⁴

ABSTRACT

Objective: To find out the frequency of vitamin B12 deficiency in patients with type II diabetes mellitus with and without metformin therapy.

Materials and Methods: This was a cross sectional study conducted at Department of Medicine Hayatabad medical Complex Peshawar. To find the frequency of vitamin B12 Deficiency in patients with type-II diabetes mellitus with Metformin therapy a total of 183 patients were included in the study. There was 6 month duration of our study **from 14-02-2019 to 14-08-2019**. WHO sample size calculator was used to determine sample size. Sample size was taken 183 keeping proportion of 21.9% of vitamin B12 deficiency among DM patients on metformin, with 95% confidence level & 6% absolute precision. Sampling technique was Consecutive nonprobability sampling.

Results: Age wise distribution amongst 183 patients was analyzed as n=1.5 years (29 %) 30-40 years (20.2%) 41-50 year (27.3%) 51-60 years (23.5%) 61-70 Mean age was 2.45 years with standard deviation ± 1.142 . Gender distribution amongst 183 patients was examined as n= (37.7%) were male patients and (52.30%) were female patients. 25% of Vitamin B12 Deficiency was observed amongst type II Diabetic Patients.

Conclusion: Greater probabilities of increasing biochemical vitamin B12 deficiency in the patients of type II diabetes mellitus, associated with the continuing cure with metformin and parallel usage of blocker of acid were confirmed from this cross-sectional study. Medical physician should keep this in mind and it should be distinguished from other factors. The diabetic patients on metformin treatment for secondary vitamin B12 deficiency and other patient who have any distressed neurologic symptoms should be screened. Additionally, by the regular intake of added multivitamins and supplements vitamin B12 deficiency can be prevented.

Key Words: Frequency, metformin therapy, type II diabetes mellitus, Vitamin B12 deficiency

INTRODUCTION

The most common non-communicable disease on this globe is now Diabetes Mellitus (DM). In advanced countries it is the 4th or 5th foremost cause of death¹. In the united states from 2009 to 2034, there will be increase in the both the diagnosed and undiagnosed people with diabetes and it will range from 23.7 million to 44.1 million². It is estimated that in the world, there will be 418 million people with impaired glucose tolerance and about 380 million people with type II diabetes by

2025³. increase in disability, reduction of life prospect and huge health cost for every culture are resulted from the complication due to diabetes like stroke, diabetic neuropathy, coronary artery and peripheral vascular disease, amputation, blindness and failure of kidneys¹. In a study from Pakistan the estimated prevalence in urban areas in male is 6% and in female it is estimated 3.5% while in rural area it is estimated as, 6.9% in male while in female it was 3.5%.⁴ In the top ten countries, Pakistan was on 8th in the list of diabetes with high prevalence and there were about 4.3 million people with diabetes mellitus in a report of WHO, though it is estimated that there will be 14.5 million people with this problem in Pakistan and will be on 4th in list⁵.

For managing type II diabetes (T2DM) the metformin is the most commonly used remedy⁶. People using high dose of metformin for longer period of time have well known vitamin B12 deficiency in the type II diabetes patient⁷. This remedy might hinder with the calcium-dependent absorption of vitamin B₁₂ and with the central element in the ileum and this influence can be retreated by increased calcium intake⁸. The result of decrease in vitamin B12 concentration in case of clinically important problems such as neuropathy, mental changes and macrocytic anemia, could be irreversible

1 Medical C Ward Hayatabad Medical Complex, Peshawar

2Resident Physician, Hayatabad Medical Complex, Peshawar

Complex, Peshawar

3 Medical Officer BHU Langow Buner

4 MBBS

Address for correspondence:

Dr. Kalim Ullah Khan

Specialist Registrar, Medical C Ward Hayatabad Medical Complex, Peshawar

Cell No # 0332-9285524

Email: kalim83@yahoo.com

and intense⁹. Moreover the deficiency of vitamin B12 symptoms can lead to unnecessary treatment if it is misdiagnosed with peripheral diabetic neuropathy. There should be strong consideration of Vitamin B12 concentration in blood, during the long term type II diabetes and high dose of metformin and should be monitored regularly. This was suggested by a recent data including a current meta-analysis^{10,11}.

In one study, among T2DM patients not taking metformin, the prevalence of B₁₂ deficiency was 4.4% compared with 14.1% in metformin users¹². Vitamin B12 deficiency prevalence amongst diabetic patient on metformin remedy was 21.9% in another study¹³. In another study, the B₁₂ deficiency was present in 16.2% T2DM patients using metformin¹⁴.

Our study was planned to define occurrence of vitamin B₁₂ deficiency in type II diabetes patients with metformin therapy. Doing a systematic study search, we establish that very infrequent data exists concerning the occurrence of vitamin B₁₂ deficiency between T2DM patients with metformin therapy and literally no data exists from the population of Pakistan. This study was an effort to found the level of the problem in our local diabetic population with metformin use. Consequences of our research was guidelines for planning future research plan and policies and to identify the mechanism of vitamin B12 deficiency prevention in T2DM patients with metformin treatment.

MATERIAL AND METHODS

Our study was cross sectional study directed at the Department of Medicine Hayatabad Medical Complex Peshawar. After synopsis approval, duration of study was six months from 14-02-2019 to 14-08-2019. Sample Size was 183 (21.9%) proportion of vitamin B12 deficiency among DM patients on metformin, with 95% confidence level & 6% absolute precision. The technique of Sampling was Non-probability consecutive sampling. Enclosure Criteria include; All patients of type II DM with minimum of five years duration, Patients using Metformin for the last at least one year, Both genders (male & females) were included, patient having age between 30-70 years. while Exclusion Criteria include; Patients on lipid lowering drugs on history, Patients with renal failure on medical records, Patients with Hepatic failure on medical records and laboratory investigations, Patients using Multivitamins supplements, Patients with pernicious anemia was excluded, Patients with malabsorption disorders was also be omitted

PROCEDURE FOR DATA COLLECTION

The study was conducted after sanction from hospitals ethical and research team. All patients with DM with metformin use for the last at least one year was registered in the study through OPD. All the patients were clarified about the benefits and purpose of our study and we also got a written informed consent. All

patients were subjected to complete history and clinical examination followed by routine baseline examinations. After overnight fasting blood samples were obtained from the patients and then sent to the hospital laboratory for the measurement of the vitamin B12 concentration.

In a pre-designed proforma all the figures comprising age, sex, name were documented and omission standards was followed strictly to control prejudice in our study outcomes. A skilled microbiologist, having experience of five years, performed all these examinations in a hospital laboratory.

DATA ANALYSIS PROCEDURE

SPSS version 23 was used for the analysis of data. For quantitative variables like age, fasting blood glucose level, HbA_{1c}, BMI and vitamin B₁₂ levels, mean \pm standard deviation was calculated. For categorical variables like gender and vitamin B₁₂ deficiency, frequencies and percentages was calculated. Vitamin B₁₂ deficiency was divided among age, gender, fasting blood glucose, HbA_{1c}, BMI and duration of diabetes to understand the outcome of modifications using chi square test with p value considered as ≤ 0.05 as significant. The presentation of all the results were done in the form of tables and graphs.

RESULTS

This study was piloted at Department of Medicine Hayatabad medical Complex Peshawar in which a total of 183 patients were included to find the frequency of vitamin B₁₂ Deficiency in patients with type-II diabetes mellitus with Metformin therapy and the results were evaluated as: Age wise distribution amongst 183 patients was analyzed as n=1.5 years (29 %) 30-40 years (20.2%) 41-50 year (27.3%) 51-60 years (23.5%) 61-70 Mean age was 2.45 years with standard deviation ± 1.142 (table No 1). Gender distribution amongst 183 patients was examined as n= (37.7%) were male pa-

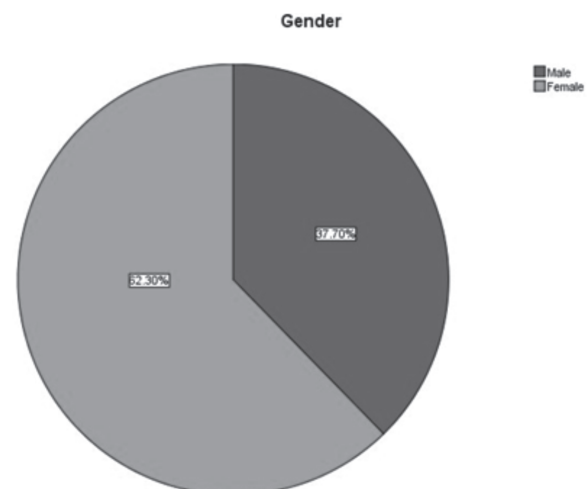


Figure 1: Gender Wise Distribution

Table 1: Age Wise Distribution of Sample Size (n=183)

Age groups	Frequency	Percent
30-40	53	29.0
41-50	37	20.2
51-60	50	27.3
61-70	43	23.5
Total	183	100.0

Table 2: Gender Wise Distribution of Sample Size (n=183)

	Gender	Frequency	Percent
Valid	Male	69	37.7
	Female	114	62.3
	Total	183	100.0

Table 3: Frequency of BMI (n=183)

BMI		Frequency	Percent
Valid	18.4 or less(under-weight)	20	10.9
	18.5 to 24.9(Normal)	53	29.0
	25.0 to 29.9(Over-weight)	74	40.4
	40.0 to 49.9 (Morbidly Obese)	36	19.7
	Total	183	100.0

Table 4: Mean Serum of Vitamin B 12 (n=183)

	Mean	Standard Deviation
Vitamin B12 Deficiency	1.75	.435

Table 5: Mean of Serum B12 levels (n=183)

	Mean	Standard Deviation
Serum B12 levels	128.39	36.302

Table 6: Mean of HBA1C (n=183)

	Mean	Standard Deviation
HBA1C	7.96	.766

Table 7: Mean of Fasting Blood Glucose Level (n=183)

	Mean	Standard Deviation
Fasting Blood Glucose Level	159.90	26.481

tients and (52.30%) were female patients.(Figure No 1) 25% of Vitamin B12 Deficiency was observed amongst type II Diabetic Patients.

DISCUSSION

The vitamin B12 deficiency in the study group of patient having type II diabetes mellitus was determined by our cross-sectional study to be 29.66%. A comparison of our prevalence with the results of former researchers is not direct and straight forward, therefore there should be consideration of other factors. Former researchers obtained comparable results Previous researchers have come up with comparable results, however the mechanism by which this deficiency come-up has not been ^{18, 19}.

In this concern insufficient record is available. Correspondingly, in Pakistan there has been no study done for the evaluation of vitamin B12 deficiency that occur in diabetic patient who are on metformin remedy. An earlier study by Jager and colleagues ²⁰, after type II diabetes taking metformin 2550 mg / day for 4.3 years showed that metformin was associated with a normal decrease of 19% in vitamin B12 levels compared to placebo (95% confidence interval from -24% to -14%; P <0.001A

A factor was determined that was significantly associated with vitamin deficiency includes the simultaneous administration of metformin with inhibitors of proton pump or blockers of H2. The concept that the reduction of stomach acidity shows an important role in malabsorption of vitamin B12 strongly support the relationship of vitamin B12 deficiency and inhibitors of proton pump or H2 blockers. Reduction in acid secretion by parietal cells is caused by both of these drugs. For the breakdown of vitamin B12 from the nutritional sources, the release of gastric acid from these cells are essential ¹⁶. Such type of relationship is found rarely. No connection was found between the use of omeprazole and the level of vitamin B12 in the serum in a study done by Nervo, et al. ¹⁵ additionally we should keep in mind the possible outcome amongst metformin, inhibitors of proton pump and H2blockers comparative to vitamin B12 uptake. For combination therapy serious cautions are advised. Vitamin B12 deficiency risk is high in patient who use metformin continuously. Our study hence suggested that in type II diabetes patients on metformin the vitamin B12 deficiency should be find out. Our study also suggested the use of multivitamins in daily life as it has protective role in diabetic patient by preventing vitamin B12 deficiency. The serum vitamin B12 level increases by using a multivitamins suggested by Literature documentation. Increased level of vitamin B12 in the blood of adults was observed in a randomized controlled trial study, who take regularly use of vitamin B12 from 6 to 9 microgram.

Consistency of our prevalence with previous studies is not simple and easy with placebo ¹⁷. Similarly,

for the evaluation of the daily use of multivitamins for the prevention of vitamin B2 deficiency no studies have been done. Increased dosages of supplementations administered orally or parentally for the typical management of vitamin B12 deficiency is notable finding of our study. Though, multivitamin preparation that have 6 to 25 microgram of vitamin B12 are adequate for vitamin B12 deficiency. To avoid vitamin B12 deficiency, further research and study is the need of the day for supporting the idea of multivitamin usage. On the other hand other risk factors like age progression and usage of blocker of acid were not observed to have association with the vitamin B12 deficiency.

We consider that our this study is significant statistically and it should be used as valuable guide for physicians appraise the vitamin B12 as a main element for the patient specially when they are on high dose of metformin for longer period of time. Although the effect of inadequacy along with the precise medical importance is unknown. Former researchers suggested that vitamin B12 supplements should be prescribed for avoiding neuropathic pains.¹⁸

Our study faced many limitations. . First limitation of our study was that of external validity because study group in our study was in a single center. This can lead to different results and there may be considerable variation from the diabetic patients that are present all over the community. The second limitation of our study is the exclusion of the measurement of methyl malonic acid level in the blood which can recognize the deficiency of vitamin B12 in the primary non-symptomatic period. After replacement of vitamin B12 the outcome was not followed-up. For dosage outcome and vitamin B12 supplementation period, regular follow-up can be helpful^{19, 20}.

CONCLUSIONS

Greater probabilities of increasing biochemical vitamin B12 deficiency in the patients of type II diabetes mellitus, associated with the continuing cure with metformin and parallel usage of blocker of acid were confirmed from this cross-sectional study. Medical physician should keep this in mind and it should be distinguished from other factors. The diabetic patients on metformin treatment for secondary vitamin B12 deficiency and other patient who have any distressed neurologic symptoms should be screened. Additionally, by the regular intake of added multivitamins and supplements vitamin B12 deficiency can be prevented.

REFERENCES

1. Dunstan DW, Zimmet PZ, Welborn TA, de Courten MP, Cameron AJ, Sicree RA. The rising prevalence of diabetes and impaired glucose tolerance. *Diabetes Care* 2012; 25(5):829-834.
2. Leong A, Porneala B, Dupuis J, Florez JC, Meigs JB. Type 2 diabetes genetic predisposition, obesity,

and all-cause mortality risk in the US: a multiethnic analysis. *Diabetes care*. 2016; 39(4):539-46.

3. Zimmet PZ, Alberti KG. Epidemiology of diabetes—status of a pandemic and issues around metabolic surgery. *Diabetes care*. 2016; 39(6):878-83.
4. Moradi-Lakeh M, Forouzanfar MH, El Bcheraoui C, Daoud F, Afshin A, Hanson SW, et al. High fasting plasma glucose, diabetes, and its risk factors in the eastern Mediterranean region, 1990–2013: Findings From the Global Burden of Disease Study 2013. *Diabetes care*. 2017; 40(1):22-9.
5. World Health Organization. The World Health Report. Geneva World Health Organization; 2011
6. Rydén L, Grant PJ, Anker SD. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: the Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). *Eur Heart J* 2013; 34:3035–87.
7. Rydén L, Grant PJ, Anker SD. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: the Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). *Eur Heart J* 2014; 35:1824.
8. Turner LW, Nartey D, Stafford RS. Ambulatory treatment of type 2 diabetes in the U.S., 1997–2012. *Diabetes Care* 2014; 37:985–92.
9. Beulens JW, Hart HE, Kuijs R. Influence of duration and dose of metformin on cobalamin deficiency in type 2 diabetes patients using metformin. *Acta Diabetol* 2014; 52:47–53.
10. Sato Y, Ouchi K, Funase Y. Relationship between metformin uses, vitamin B12 deficiency, hyperhomocysteinemia and vascular complications in patients with type 2 diabetes. *Endocrinol J* 2013;60:1275–80
11. Niafar M, Hai F, Porhomayon J. The role of metformin on vitamin B12 deficiency: a meta-analysis review. *Int Emerg Med* 2015; 10:93–102.
12. de Groot-Kamphuis DM, van Dijk PR, Groenier KH, Houweling ST, Bilo HJ, Kleefstra N. Vitamin B12 deficiency and the lack of its consequences in type 2 diabetes patients using metformin. *Neth J Me* 2013; 71(7):386-90.
13. Long AN, Atwell CL, Yoo W, Solomon SS. Vitamin B12 Deficiency associated with concomitant metformin and proton pump inhibitor use. *Diab Car* 2012; 35(12):e84-e84.
14. Reinstatler L, Qi YP, Williamson RS, Garn JV, Oakley GP Jr. Association of biochemical B₁₂ deficiency with metformin therapy and vitamin B₁₂ supplements: the National Health and Nutrition Examination Survey, 1999-2006. *Diab Car* 2012; 35:327–33.

15. Increased intake of calcium reverses vitamin B12 malabsorption induced by metformin. Bauman WA, Shaw S, Jayatilleke E, et al. *Diabetes Care*. 2000; 23:1227–1231. [PubMed] [Google Scholar]
16. A case-control study on adverse effects: H2 blocker or proton pump inhibitor use and risk of vitamin B12 deficiency in older adults. Valuck RJ, Ruscini JM. *J Clin Epidemiol*. 2004; 57:422–428. [PubMed] [Google Scholar]
17. Vitamin B12 deficiency associated with histamine 2-receptor antagonists and a proton-pump inhibitor. Ruscini JM, Page RL, Valuck RJ. *Ann Pharmacother*. 2002; 36:812–816. [PubMed] [Google Scholar]
18. The prevalence of vitamin B (12) deficiency in patients with type 2 diabetes: A cross-sectional study. Pflipsen MC, Oh RC, Saguil A, et al. *J Am Board Fam Med*. 2009; 22:528–534. [PubMed] [Google Scholar]
19. Association of vitamin B12 deficiency and metformin use in patients with type 2 diabetes. Ko SH, Ko SH, Ahn YB, et al. *J Korean Med Sci*. 2014; 29:965–972. [PMC free article] [PubMed] [Google Scholar]
20. Vitamin B12 in metformin-treated diabetic patients: A cross-sectional study in Brazil. Nervo ME. *Rev Assoc Med*. 2011; 57:46–49. [PubMed] [Google Scholar]

ONLINE SUBMISSION OF MANUSCRIPT

It is mandatory to submit the manuscripts at the following website of KJMS. It is quick, convenient, cheap, requirement of HEC and Paperless.

Website: www.kjms.com.pk

The intending writers are expected to first register themselves on the website and follow the instructions on the website. Author agreement can be easily downloaded from our website. A duly signed author agreement must accompany initial submission of the manuscript.