

# Vitamin B12 Deficiency in Patients with Type-II Diabetes Mellitus Using Metformin

Vitamin B12  
Deficiency in  
Patients with  
Type-II Diabetes

Haseeb ul Hassan<sup>1</sup>, Idrees Zafar<sup>1</sup>, Hamza Azhar<sup>1</sup>, Noor-us-Sabahat<sup>2</sup>, Khizra Manzoor<sup>1</sup> and Maryum Saleem Raja<sup>1</sup>

## ABSTRACT

**Objective:** To find out the prevalence of vitamin B12 deficiency among the patients with type-II diabetes mellitus using metformin.

**Study Design:** Cross-sectional study

**Place and Duration of Study:** This study was conducted at the Abbasi Institute of Medical Sciences Muzaffarabad. Study was completed in six months duration from July 2021 to December 2021 for a period of six months.

**Materials and Methods:** All previously diagnosed cases with type-II diabetes mellitus using metformin for more than six months duration was included in this study. Blood level of vitamin B12 was measured in all cases. SPSS-17 software was used for data analysis. P-value <0.05 was taken statistically significant.

**Results:** Total 200 cases were studied including 127(63.5%) male and 73(36.5%) female cases. 23% diabetic patients using metformin were having vit-B12 deficiency with the blood level <150 pg/ml. age range of the patients was 30-75 years with mean age of  $45.7 \pm 5.8$  years. Smokers were having more incidence of vit-B12 deficiency than non-smokers. Use of multivitamins prevent B-12 deficiency.

**Conclusion:** Use of metformin in diabetes mellitus is strongly associated with B-12 deficiency, so endocrinologist and physician should evaluate diabetic patients for B-12 deficiency and treat it properly.

**Key Words:** Diabetes mellitus, Vitamin B12, Metformin

**Citation of article:** Hassan H, Zafar I, Azhar H, Sabahat N, Manzoor K, Raja MS. Vitamin B12 Deficiency in Patients with Type-II Diabetes Mellitus Using Metformin. Med Forum 2022;33(3):122-124.

## INTRODUCTION

Diabetes mellitus is defined as an endocrine disorder characterized by impaired metabolism of carbohydrates, fats and proteins.<sup>1</sup> 5-7% of united state population is affected from diabetes mellitus due to unhealthy eating practices and sedentary life style.<sup>2</sup> According to Al Saeed et al about 7.2 million Pakistanis are suffering from diabetes mellitus and its prevalence in urban population is 10.6% as compared to 7.7% in rural population.<sup>3</sup> Metformin from the group of biguanides is the most commonly used drug for type-II diabetes mellitus.<sup>4</sup> Its most common side effect is gastrointestinal disturbance that limit its compliance and efficacy.<sup>5</sup>

<sup>1</sup>. Doctor in Abbas Institute of Medical Sciences Muzaffarabad Azad Kashmir.

<sup>2</sup>. Doctor in CMH Muzaffarabad Azad Kashmir.

Correspondence: Haseeb ul Hassan, Doctor in Abbas Institute of Medical Sciences Muzaffarabad Azad Kashmir.

Contact No: 03469077771

Email: haseeb.0079@gmail.com

Received: January, 2022

Accepted: February, 2022

Printed: March, 2022

Mostly neglected side effect of this drug is vitamin B-12 deficiency which can cause subacute degeneration of spinal cord.<sup>6</sup> Vitamin B12 deficiency is defined as concentration <150 pmol/L.<sup>7</sup> According to a study conducted by Alvarez et al B12 deficiency was found in 67% of study population.<sup>8</sup> Metformin decreases serum level of B12 by 22-29% as compared to placebo and glyburide.<sup>9</sup> Metformin associated B12 deficiency depends on the dosage and duration of metformin use and age of the patient.<sup>10</sup> Purpose of conducting this study is to highlight the most important side effect of metformin use causing B12 deficiency in diabetic patients that is commonly neglected. This study will help the physicians and endocrinologist to estimate frequency of B12 deficiency in diabetic patients to treat them early and prevent their complications and to consider dosage and duration of metformin in relation to B12 deficiency.

## MATERIALS AND METHODS

This is a cross sectional study conducted in Abbasi Institute of Medical Sciences Muzaffarabad. Study was completed in six months duration from July 2021 to December 2021. Ethical approval was taken from the institutional review board and consent was also taken from all the patients for including them in this study. Sample size was calculated using WHO sample size calculator. Our sample size was 200 with 95% level of

significance. Using consecutive sampling technique all previously diagnosed cases with type-II diabetes mellitus using metformin for more than six months duration was included in this study. Blood level of vitamin B12 was measured in all cases. SPSS-17 software was used for data analysis. P-value <0.05 was taken statistically significant. All data was documented on a performa regarding age, gender, medical history, drug duration and dosage and history of peripheral neuropathy. Patients having B12 level <150 pg/ml were labelled as B12 deficiency, those having B12>220pg/ml labelled as having adequate level. Quantitative variables like age, disease duration, metformin dose, serum B12 level were expressed in means and standard deviation while qualitative variables were expressed in percentages and frequencies.

## RESULTS

Total 200 cases were enrolled into this study including 127(63.5%) male and 73(36.5%) female cases. 23% diabetic patients using metformin were having vit-B12 deficiency with the blood level <150 pg/ml, 20(10%) cases with 150-220 pg/ml and 134(67%) cases had B12 level >220 pg/ml (Figure-I). age range of the patients was 30-75 years with mean age of  $45.7 \pm 5.8$  years. Smokers were having more incidence of vit-B12 deficiency (19%) than non-smokers. This study showed that longer the disease duration more deficiency of B12 ( $p < 0.001$ ), similarly increased dose of metformin is associated with more deficiency of B12 ( $p < 0.001$ ) (Table-I).

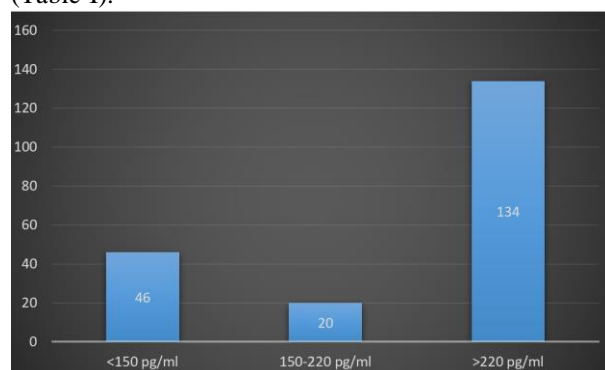


Figure No.1: Vit-B12 values

Table No.1: Baseline characteristics of study group (n=200)

| Variables                             | Mean value        |
|---------------------------------------|-------------------|
| Age (years)                           | $56.52 \pm 12.87$ |
| Duration of Diabetes mellitus (years) | $8.55 \pm 4.76$   |
| Smoking                               | 38 (19%)          |
| BMI (Mean $\pm$ SD)                   | $28.61 \pm 3.88$  |
| B12 level (Mean $\pm$ SD)             | $457 \pm 220$     |
| Metformin use                         | 200 (100%)        |

## DISCUSSION

Metformin is a first line of drug therapy in the treatment of type-2 diabetes mellitus.<sup>11</sup> It is taken orally. Its main side effect under study is deficiency of vit-B12. Mechanism by which metformin causes B12 deficiency is not known completely.<sup>12</sup> According to one theory metformin affect intrinsic factor-B12 complex formation hence inhibiting its absorption, but other mechanisms may be involved that are not clear yet.<sup>13</sup> Total 200 cases were enrolled into this study including 127(63.5%) male and 73(36.5%) female cases. 23% diabetic patients using metformin were having vit-B12 deficiency with the blood level <150 pg/ml, 20(10%) cases with 150-220 pg/ml and 134(67%) cases had B12 level >220 pg/ml. A previously conducted study by Lata Kanyal et al reported 31% cases using oral metformin were having B12 deficiency.<sup>14</sup> Elhadd et al stated that metformin dose is inversely proportional to the serum level of B12 with statistical significant p value <0.001.<sup>15</sup> Kim et stated that prevalence of B12 deficiency among the diabetic patients using metformin for more than 12 months was 25.4%. It is close to our study result of 23%.<sup>16</sup> A cross sectional study conducted by Hasan et al in Pakistan stated that B12 deficiency was more among type-2 diabetics using metformin (22.5%) than those not using metformin (7.4%).<sup>17</sup> Zalaket et al concluded that there is strong relation of duration of metformin use and B12 deficiency, hence increased duration more deficiency of B12.<sup>18</sup> Tesega et al reported that Type-2 diabetic patients using metformin for prolong period were having B12 deficiency in 43.7% cases.<sup>19</sup> Dietary habits can also influence serum B12 level which was not considered in this study so that is limitation of our study.<sup>20</sup>

## CONCLUSION

This study concluded that prolong use of metformin causes B12 deficiency in significant number of type-2 diabetic patients. It is very important for physicians and endocrinologists to know strong relation of metformin dosage and duration of therapy to predict b12 deficiency and to manage it properly and it is also important for them to differentiate between diabetic neuropathy and B12 deficiency induced neuropathy.

### Author's Contribution:

Concept & Design of Study: Haseeb ul Hassan  
 Drafting: Idrees Zafar, Hamza Azhar  
 Data Analysis: Noor-us-Sabhat, Khizra Manzoor, Maryum Saleem Raja  
 Revisiting Critically: Haseeb ul Hassan, Idrees Zafar  
 Final Approval of version: Haseeb ul Hassan

**Conflict of Interest:** The study has no conflict of interest to declare by any author.

## REFERENCES

1. Wolffenbittel BH, Wouters HJ, Heiner-Fokkema MR, van der Klauw MM. The many faces of cobalamin (vitamin B12) deficiency. *Mayo Clin Proc: innovations, quality outcomes* 2019;3(2): 200-14.
2. Wang H, Li L, Qin LL, Song Y, Vidal-Alaball J, Liu TH. Oral vitamin B 12 versus intramuscular vitamin B 12 for vitamin B 12 deficiency. *Cochrane Database Syst Rev* 2018(3).
3. Al Saeed RR, Baraja MA. Vitamin B12 deficiency in patients with type 2 diabetes mellitus using metformin and the associated factors in Saudi Arabia. *Saud Med J* 2021;42(2):161.
4. Pavlov CS, Damulin IV, Shulpekova YO, Andreev EA. Neurological disorders in vitamin B12 deficiency. *Ter Arkh* 2019;91(4):122-9.
5. Kim J, Ahn CW, Fang S, Lee HS, Park JS. Association between metformin dose and vitamin B12 deficiency in patients with type 2 diabetes. *Med* 2019;98(46).
6. Singla R, Garg A, Surana V, Aggarwal S, Gupta G, Singla S. Vitamin B12 deficiency is endemic in Indian population: a perspective from North India. *Ind J Endocr Metabol* 2019;23(2):211.
7. Alvarez M, Sierra OR, Saavedra G, Moreno S. Vitamin B12 deficiency and diabetic neuropathy in patients taking metformin: a cross-sectional study. *Endocr connect* 2019;8(10):1324-9.
8. Jarquin Campos A, Risch L, Nydegger U, Wiesner J, Vazquez Van Dyck M, et al. Diagnostic accuracy of holotranscobalamin, vitamin B12, methylmalonic acid, and homocysteine in detecting B12 deficiency in a large, mixed patient population. *Dis Mark* 2020;2020. <https://doi.org/10.1155/2020/7468506>
9. Sukumar N, Saravanan P. Investigating vitamin B12 deficiency. *BMJ* 2019;365. <https://doi.org/10.1136/bmj.11865>
10. Wee AK. COVID-19's toll on the elderly and those with diabetes mellitus—Is vitamin B12 deficiency an accomplice? *Med Hypo* 2021 Jan 1;146:110374. <https://doi.org/10.1016/j.mehy.2020.110374>
11. Alharbi TJ, Tourkmani AM, Abdelhay O, Alkhashan HI, Al-Asmari AK, Bin Rsheed AM. The association of metformin use with vitamin B12 deficiency and peripheral neuropathy in Saudi individuals with type 2 diabetes mellitus. *PloS one* 2018;13(10):e0204420.
12. Shivaprasad C, Gautham K, Ramdas B, Gopaldatta KS, Nishchitha K. Metformin Usage Index and assessment of vitamin B12 deficiency among metformin and non-metformin users with type 2 diabetes mellitus. *Acta Diabetol* 2020;57(9): 1073-80.
13. Owhin SO, Adaja TM, Fasipe OJ, Akhideno PE, Kalejaiye OO, Kehinde MO. Prevalence of vitamin B12 deficiency among metformin-treated type 2 diabetic patients in a tertiary institution, South-South Nigeria. *SAGE Open Med* 2019;7: 2050312119853433.
14. Lata Kanyal MT, Mujawar A. Status of vitamin b12 in type 2 diabetes mellitus patients taking metformin based oral hypoglycemic agent—a cross sectional study. *Ind J Bas App Med Res* 2019; 1(9):18-26.
15. Elhadd T, Ponirakis G, Dabbous Z, Siddique M, Chinnaiyan S, Malik RA. Metformin use is not associated with B12 deficiency or neuropathy in patients with type 2 diabetes mellitus in Qatar. *Front Endocrinol* 2018;9:248.
16. Kim J, Ahn CW, Fang S, Lee HS, Park JS. Association between metformin dose and vitamin B12 deficiency in patients with type 2 diabetes. *Med* 2019 Nov;98(46).
17. Hasan NU, Makki MU, Abid I, Abid Butt MU. Association of vitamin B12 deficiency with intake of oral metformin in diabetic patients. *J Ayub Med Coll Abbottabad* 2019;31(1):72-5.
18. Zalaket J, Wehbe T, Abou Jaoude E. Vitamin B12 deficiency in diabetic subjects taking metformin: a cross sectional study in a Lebanese cohort. *J Nutr Intermed Metabol* 2018;11:9-13.
19. Tesega WW, Genet S, Natesan G, Tarekegn G, Girma F, Chalchisa D, et al. Assessment of Serum Vitamin B12 and Folate Levels and Macrocytosis in Patients with Type 2 Diabetes Mellitus on Metformin Attending Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia: A Cross-Sectional Study. *Diabetes, Metabol Syndr Obes: Targets and Therapy* 2021;14:2011. <https://dx.doi.org/10.2147%2FDMSO.S306433>
20. Infante M, Leoni M, Caprio M, Fabbri A. Long-term metformin therapy and vitamin B12 deficiency: An association to bear in mind. *World J Diabetes* 2021;12(7):916.