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Prevalence of Vitamin B12 deficiency in Type II diabetic patients using metformin.

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ABSTRACT… Objectives: To determine the prevalence of Vitamin B12 deficiency in type II diabetic patients using metformin. **Study Design:** Cross Sectional study. **Setting:** Endocrinology Unit Shalamar Hospital Lahore. **Period:** July to September 2017. **Material & Methods:** All of our patients were having previously diagnosed type II diabetes and using metformin for more than six months. Using strict exclusion criteria, vitamin B12 levels of patients were measured and analyzed. **Results:** It was evident from the present study that 27.33% of type II diabetic patients using metformin were having vitamin B12 levels less than 150pg/ml. Furthermore, our study showed that smokers are more liable to develop vitamin B12 deficiency than the nonsmokers. Also, use of multivitamins (containing vitamin B12) had a protective role against vitamin B12 deficiency. **Conclusion:** Long term use of metformin in type II diabetic patients is strongly associated with Vitamin B12 deficiency, therefore endocrinologists and physicians should take into consideration this significant adverse effect of metformin and screen for vitamin B12 deficiency in diabetic population before starting metformin therapy.

Key words: Metformin, Type II Diabetes Mellitus, Vitamin B12 Deficiency.

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INTRODUCTION

Diabetes mellitus is a common endocrine disorder characterized by persistent hyperglycemic state secondary to impaired metabolism of carbohydrates, proteins and fats. About 5 to 7% of US population is affected by diabetes and majority of them are having type II diabetes mellitus, mainly due to sedentary lifestyle and unhealthy eating practices.[1]

According to a data collected by Ramachandran and his team in 2012, more than 7.2 million Pakistanis are suffering from diabetes mellitus and its prevalence in urban population (10.6%) is more than in rural (7.7%) areas.[2]

Among all the oral hypoglycemic drugs used in type 2 diabetes mellitus, biguanides e.g. metformin are most commonly prescribed. For years, metformin has been known to cause gastrointestinal upset greatly limiting its efficacy and patient compliance, but the often neglected and least discussed side effect of this prototype dug is vitamin B12 deficiency, which can lead to subacute combined degeneration of spinal cord in some cases.[3,4]

The purpose of the study was to determine prevalence of vitamin B12 deficiency in type 2 diabetic patients on long term metformin therapy.

MATERIAL & METHODS

This cross sectional study was conducted at endocrinology and diabetes unit Shalamar Hospital Lahore from 1ST July to 30TH September 2017. The study was approved by ethical committee (SMDC-IRB/AL/114/2021). Our Sample size was 150 with 95% confidence interval. Patients included in the study were those who had previously diagnosed type II diabetes, aged more than 35 years and using metformin for more than six months. Patients excluded from the study were those who had chronic renal failure as evident from persistently elevated serum creatinine >2.0mg/dl, patients who previously had gastric bypass procedure,

ileal resection or gastrectomy, those using other drugs causing vitamin B12 deficiency e.g. proton pump inhibitors, history of ethanol use, having prior history of autoimmune pernicious anemia or thyroid illness.

After obtaining a written informed consent, patients' data was collected as per our designed Performa which included patient name, age, sex, duration of diabetes, complete drug history including metformin (dosage and duration) and symptoms of peripheral neuropathy. Ensuring complete aseptic measures, patients' venous samples were obtained and using DXI automated analyzer, vitamin B12 level was measured. Patients having vitamin B12 level less than 150pg/ml were labeled as vitamin B12 deficient while those having vitamin B12 levels more than 220pg/ml were labeled as having adequate levels. All the data obtained was analyzed using SPSS version 23. Quantitative variables like age, duration of diabetes and metformin use, serum vitamin b12 level, were expressed as standard deviation, while qualitative variables e.g. gender were expressed as frequencies and percentages. P value of 0.05 or less was chosen as statistically significant.

RESULTS

A total of 150 patients were enrolled in our study with age group of 35 to 75 years, mean age of the patients being 56.49± 6.35 years. Male gender was dominant (83 patients, 55.33%) (Figure-1). Other baseline characteristics are shown in Table-I.

There was a wide range in serum vitamin B12 values, from 110 to 2100pg/ml. About 41 (27.33%) patients had serum vitamin B12 level less than 150pg/ml while 19(12.66%) patients had vitamin B12 level in intermediate range. The remaining 90 (60.00%) patients had vitamin b12 level in the normal range i.e. more than 220pg/ml (Figure-2). Regarding metformin dosage, 43 (28.66%) were using 2500mg /24hr or more, 9(6.00%) were using less than 850mg/day, and the remaining 98(65.33%) were using a dose between 850mg and 2500mg per day (Figure-3). Additional findings in our study were that smokers are more liable to vitamin b12 deficiency than nonsmokers (P<0.001) and multivitamins have a protective role against vitamin B12 deficiency (P<0.05). Of those who did not develop vitamin b12 deficiency, about 40 (26.66%) were using multivitamins (containing Vitamin B12) and only 3 patients developed vitamin B12 deficiency (7.5%). The study also showed that longer the duration of diabetes, more are the chances of vitamin b12 deficiency (p value 0.04). Additionally, longer the period of metformin use, more are chances of vitamin b12 deficiency (p value0.001). There was no significant impact of body mass index on Vitamin B12 in both groups.

Variable	Mean Value
Age (Years)	66.49±13.35
Duration of diabetes mellitus (Mean, Years)	9.16±5.59
BMI (Mean, SD)	29.43±5.01
Smoking	41(27.33%)
B12 level (Mean, SD)	432±240
Metformin use	150(100%)
Multivitamin use (containing vitamin B12)	3/40(7.5%)

Table-I. Baseline characteristics and mean Vitamin B12.

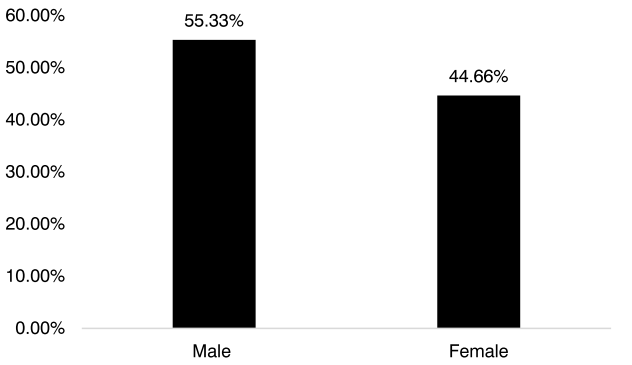

Figure-1. Gender distribution

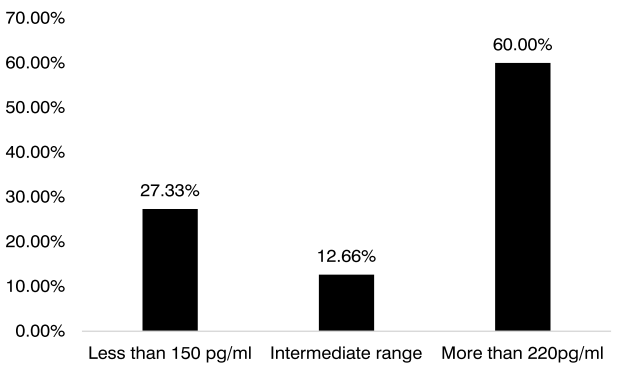

Figure-2. Vitamin B12 values.

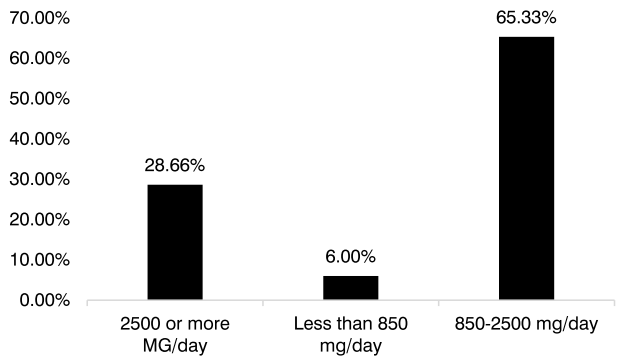

Figure-3. Different groups of Metformin dosage.

DISCUSSION

Metformin is the first line of all the oral hypoglycemic drugs prescribed in type 2 diabetics but the exact mechanisms responsible for vitamin B12 deficiency are poorly understood and need further exploration.[3,4] Metformin was thought to be causing vitamin B12 deficiency by affecting intrinsic factor-vitamin B12 complex formation via its calcium dependent ileal cell membrane action, but more complex mechanisms may be involved and are yet to be discovered.[5,6]

In our study, 27.33% diabetic patients using metformin for more than six months were having low (<150pg/ml) vitamin B12 levels. Data available on this topic is limited one, but a few studies conducted so far have shown almost similar results with some variations. A study conducted at medicine department Combined Military Hospital Kharian in 2012 by Raheel Iftikhar and his team showed that 31% of patients using metformin had vitamin B12 deficiency as compared to controls (8.6%). Dose of metformin was inversely proportional to vitamin B12 levels with statistically significant p value less than 0.001.[7] Another study conducted by Adnan and his colleagues at endocrinology unit, Hayat Abad medical complex Peshawar in 2016 showed that prevalence of vitamin B12 deficiency in non-insulin dependent diabetics using metformin for more than 12 months was about 25.4% which was near to our results.[8] In addition, they adopted a more comprehensive way by classifying vitamin B12 deficiency as mild, moderate and severe. A cross sectional study conducted by damiao CP and his colleagues in 2016[9] pointed out that vitamin B12 deficiency was more prevalent in type 2 diabetics using metformin (22.5%) than those not using metformin(7.4%).The factors which interfered with vitamin B12 levels were proton pump inhibitors and H2 receptor antagonists. Chapman LE and his colleagues conducted a similar study at department of nutritional sciences, university of surrey UK, in 2016 which concluded that there is a strong association between vitamin B12 deficiency and long term use of metformin.[10] A similar study was carried out in Brazil in 2010 showed that 43.7% of type 2 diabetic patients on long term metformin were vitamin B12 deficient.[11] There were two major limitations to our study. First, it was conducted without measuring methylmalonic acid level in serum which could have allowed us to identify vitamin B12 deficient patients in their asymptomatic phase.[12] Secondly, dietary predilections of our study population were not taken into consideration which could alter serum vitamin B12 level in the long run.[13]

CONCLUSION

This study led to the confirmation that long term use of metformin in non-insulin dependent diabetes patients had a strong link with vitamin B12 deficiency. Therefore, it is vital for endocrinologists and physicians to be not only aware of this strong documented association between metformin and vitamin B12 deficiency but also screen for vitamin B12 deficiency. It is also vital for endocrinologists to differentiate between diabetic neuropathy and peripheral neuropathy due to vitamin B12 deficiency. Moreover, use of multivitamins containing vitamin B 12 had a protective role against vitamin B12 deficiency.

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AUTHORSHIP AND CONTRIBUTION DECLARATION

Sr. #	Author(s) Full Name	Contribution to the paper	Author(s) Signature
1	Tahir Ullah Khan	Manuscript design and writing, Data collection.	14/7/2019
2	Rozina Arshad	Statistical analysis, Assisted in data collection.	16/7/19
3	Saleem Uz Zaman Adhami	Manuscript review, Proof reading.	