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ASSOCIATION OF VITAMIN B12 AND METFORMIN IN TYPE 2 DIABETES PATIENTS IN PATIENTS TREATED AT TERTIARY CARE CENTRE.

Medicine

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ABSTRACT

Objective: As oral hypoglycemic agent Metformin therapy is the gold standard treatment for type 2 diabetic patients. Long term use of metformin has been associated with vitamin B12 deficiency. We aimed to study the level of vitamin B12 in type 2 diabetic patients on metformin, and to determine other factors affecting the level of vitamin B12.

Methodology: In tertiary care institute 300 patients with type 2 diabetes that were interviewed from January to December 2017 & investigated for vitamin B12 levels deficiency.

Result: Most of the patients, 56.4% had a normal vitamin B12 level. Dyslipidemia and hypertension were significantly more (p=0.007 and 0.012 respectively) in patients with normal vitamin B12 level. Percentage of normal B12 level patients was higher (p=0.001) even in more than 20 years of metformin use; 37.2% of more than 20 years Metformin users had vitamin B12 level within 301-450 pg/mL and 23.2% had more than 450 pg/mL.

Conclusion: We recommend routine screening for basal vitamin B12 level for all patients with type 2 diabetes mellitus (T2DM) at the initiation of metformin therapy with subsequent annual follow up of the level.

KEYWORDS

Metformin, Type 2 diabetes, Obesity, Vitamin B12,Peripheral Neuropathy.

INTRODUCTION

Metformin is considered as the first-line antidiabetic agent in the treatment of type 2 diabetes mellitus (T2DM) due to its effect on glucose and lipid metabolism, simultaneously with the major protective role it plays against life threatening complications. It acts as an insulin sensitizer on insulin-targeted tissues; liver, muscle, and adipose tissues and reduces insulin resistance. Additionally it offers protection from cardiovascular diseases and heart failure[1]. Given its safety and efficacy record, it is routinely prescribed to approximately 120 million type 2 diabetes patients world-wide [2,3].

Diabetic neuropathy, affecting more than 90% of the patients is the commonest complication of diabetes[4]. The fact that vitamin B_{12} deficient neuropathy and diabetic neuropathy cannot be distinguished clinically[5] renders it difficult to determine which of the two pathology is actually responsible for the neuropathy in a diabetic patient with a coexisting vitamin B_{12} deficiency. Long term treatment with metformin therefore increases the chance of vitamin B_{12} neuropathy be misdiagnosed as diabetic neuropathy or it may contribute in worsening the diabetic neuropathy.

In addition to neuropathy long term metformin therapy has been linked also to the development of anaemia[6]. Once again the mechanism of this could be the metformin induced vitamin B_{12} deficiency as it is a well-recognized cause of megaloblastic anemia.

As vitamin B_{12} deficient neuropathy and diabetic neuropathy both present with similar indistinguishable clinical manifestations, the objectives of this study were: 1) to determine the level of Vitamin B_{12} in T2DM patients on metformin; 2) to identify additional factors that may affect the Vitamin B_{12} level in T2DM patients on metformin; 3) the effect of metformin use in the level of vitamin B_{12} in type 2 diabetic patients.

MATERIAL AND METHODS

Type 2 diabetic adult patients attending the tertiary care centre were randomly recruited between January 2017 to December 2017. Each participant was interviewed with a structured questionnaire and was asked about: personal data, duration of T2DM, duration and dose of metformin, other risk factors (dyslipidemia, hypertenstion, cerebrovascular diseases, Coronary Vascular Disease, smoking, hypothyrodsim, use of insulin and nephropathy) and symptoms of peripheral neuropathy. The interview consisted of a verbal consent followed by direct questions by the treating physician who recorded the answers manually. To evaluate cerebrovascular diseases, patients were questioned about past history of cerebrovascular accident, transient ischemic attack or stroke. Peripheral neuropathy was assessed by asking the patient about presence of tingling sensation, heat sensation or paresthesia of the lower limb.

A total of 300 patients who were above the age of 30 years, who are being treated by metformin were interviewed. Serum Vitamin B_{12} Assay was ordered by the treating physician. Nor were the T2DM below 30 years of age, not receiving metformin, or suffering from chronic renal insufficiency defined by serum creatinine level less than 3. Patients with a prior history of gastrostomy, bariatric surgery, ileum resection or Crohn's disease were also excluded.

Level of vitamin B_{12}, HbA1C, hemoglobin were recorded. Patients were considered low Vitamin B_{12}level if it were less than 300 pg/ml. Ethics Board approval was obtained.

Statistical Analysis

Data were collected and stored in a spreadsheet using Microsoft Excel 2010® software. Data management and coding were then done in Excel. Data were analyzed using SPSS® version 20.0. Descriptive analysis was done, where categorical variables were presented in the form of frequencies and percentages. Chi2 test was used to test for differences between the groups and test for associations.

RESULT

The highest number of participants, (46.1%) was from 50 to 60 years old. Most of the patients (56.4%) had a normal vitamin B_{12} level (p=0.023). The majority of patients, (57.8%) were male. Greater percentage (59.3%) of the patients were obese with a BMI higher than 30. About 32% of patients had T2DM duration of 1-5 years and 6-10yrs. Similarly longest period of time treated with metformin is 1-5 years 36.2% and 6-10yrs 33.2%. Majority of the patients, 65.9% were receiving total daily dose above 2000 mg. A good number of patients, 49.7% reported symptoms of peripheral neuropathy. In spite of laboratory result revealing Hb level below 12 mg/dl in 18% of the participants, only 12% of the patient presented with clinically apparent anaemia. The level of last HbA1c was between 6 to 7% in (31.4%) participants.

Low vitamin B_{12} was observed in 43.6% of the total number. In comparing the patients with low vitamin B_{12} and the normal, normal vitamin B_{12} was significantly more frequent in age 41 and above (p=0.044), females (60.3%) (p<0.001). None of the risk factors we investigated-dyslipidemia, hypertension, insulin treatment, smoking, CVD, hypothyroidism, nephropathy showed any statistically significant association with vitamin B_{12}deficiency .On the other hand dyslipidemia, hypertension was found significantly more with a p-value of 0.007 and 0.012 respectively, in patients with normal vitamin B_{12} level.

The correlation between serum B_{12} levels and the duration of metformin was determined in two different ways. Firstly we compared the patients who were using metformin for the same duration. There was significant difference in the 1to 5 years users and above 20 years users. At the same time in both these groups the percentage of participants with normal B_{12}level was significantly higher. Most of the patients, 59.8% (p=0.003) using metformin for the last 1-5 years had normal B_{12}level. Similarly, 15 patients were receiving metformin for more than 20 years 80% showed normal vitamin B_{12} level (p=0.001) Moreover 37.2% of this group had vitamin B_{12} level within 301-450 pg/mL and 23.2% had more than 450 pg/mL Anemia and hemoglobin level did not have any statistically significant difference between low and normal vitamin B_{12}.

DISCUSSION

In our study we found that low vitamin B_{12} level was prevalent in 43.6% of T2DM patients on metformin. Higher current daily dose and duration of metformin use have positive association with low vitamin B_{12} level. The present study could not establish any association between the low vitamin B_{12} level and BMI, symptoms of peripheral neuropathy, anemia and hemoglobin level. The normal vitamin B_{12} level patients had higher HbA1c level. Also this study found that more than 90% of patients were already checked for vitamin B_{12} deficiency.

Prevalence of vitamin B_{12} deficiency among diabetic patients shows a wide range of variation from 5.8% to 52%. This discrepancy between different studies may be due to the fact that, each of the studies followed their own reference ranges for normal value of vitamin B_{12}, along with difference in age, study settings, and dose and duration of use of metformin. De Jager et al. [5,8,9] studied patients from Netherlands, United States and Sweden. Their prevalence was much lower than the present study; 5.8 to 9.9%. Another recent study conducted in South Africa found a moderately higher prevalence of 28.1%[7]. The difference might not reflect the difference in geographical distribution. Rather this might be explained by their cut off point ranging between 145-150 pmol/L compared to our 300 pmol/L. We chose this cutoff point following a recent study that was conducted in a large sample of 700 patients in Korea, chose serum level ≤ 300 pg/mL, their cut off point for vitamin B_{12} deficiency [19] Even with this high cutoff point their prevalence was 9.5%. The high prevalence in the current study might be explained by both the early detection of vitamin B_{12} deficiency and high number of deficient patients. More than ninety one percent of the participants were already investigated for vitamin B_{12} deficiency by their treating physicians.

In this study we did not find statistically significant difference in presence of cerebrovascular diseases between the participants with normal and low vitamin B_{12} levels. When compared with total study population, in both deficient and normal vitamin D group, 48% was positive for peripheral neuropathy (p=0.987). In view of the fact that peripheral neuropathy is by itself is a complication of the T2DM, we further analyzed the data of the patients showing symptoms of peripheral neuropathy independently. That analysis revealed that significantly larger portion (56.1%) of the patients with peripheral neuropathy infact had normal vitamin B_{12} level (p=0.036). Similar to our study the result of another study published in 2016 could not establish any association with the presence of diabetic peripheral neuropathy in T2DM patients and use of metformin[16] Similar observation was reported from a study comparing metformin user and nonuser diabetic patients[17] There was no difference in neurological function between both the groups.

The present study found that larger daily dose of metformin has a positive correlation with vitamin B_{12} deficiency [18] Several previous studies have already reported this inverse effect of dose of metformin on serum vitamin B_{12} level [7,12,15]

In our study we found weak association of duration of metformin use with low vitamin B_{12} level. All the patients who had below 100 vitamin B_{12} level were receiving metformin for 11-20 years. On the other hand almost half of the patients who were receiving metformin for more than 20 years had a serum vitamin B_{12} level between 300 to 450 pg/mL Level of HbA1c in relation to serum vitamin B_{12} levels was also calculated. We demonstrated that high HbA1c level is found more frequently in T2DM patients with a normal vitamin B_{12} level. Previously two other studies[7,14] supported a similar association. Ahmed et al[7] tried to explain this association from the perspective of patient compliance. The gastrointestinal adverse effects of metformin may promote poor compliance in patients, especially with high dose of the drug. The poor or noncompliance may consequently lead to poor glycaemic control and higher HbA1c.

One major limitation of this study is that we did not look for the number of patients already on vitamin B_{12}supplementation (some of the patient may take vitamin B_{12} supplementation from other hospitals) there is a possibility that a good number of patients are receiving it. And that might be the reason for our study result not showing much significant difference between the variables of both the groups.

CONCLUSION

Our result indicates that vitamin B_{12} deficiency is prevalent among type 2 diabetic patients treated with metformin, especially those on high dose of medication and longer duration. There is no association of vitamin B_{12} deficiency with diabetic neuropathy. Also this study revealed that the majority of the patients are being investigated for Vitamin B_{12}deficiency, which is a very positive sign for the health care system. So we recommend routine screening for basal vitamin B_{12} level for all patients with T2DM at the initiation of metformin therapy with subsequent annual follow up of the level. Although we could not establish any association between diabetic neuropathy and Vitamin B_{12} deficiency, further studies are needed to identify symptoms that will help to distinguish these two separate entities.

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