Vitamin B12 deficiency and clinical neuropathy with metformin use in type 2 diabetes

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ABSTRACT

Type 2 diabetes, which is more prevalent (more than 90% of all diabetes cases) and the main driver of the diabetes epidemic, now affects 5.9% of the world's adult population with almost 80% of the total in developing countries. Currently, 422 million people worldwide are suffering from diabetes. In India, reports show that 69.2 million people are living with diabetes (8.7%) as per 2015 data. Long-term metformin treatment is a known pharmacological cause of vitamin B12 deficiency, as was evident within the first 10-12 years after it started to be used. This was a cross-sectional study conducted in the Postgraduate Department of Medicine at S.M.H.S. Hospital. A total of 700 consecutive patients with type 2 diabetes were taken for the study. Type 2 diabetic patients were divided into two groups: those taking metformin, and those who were not taking metformin. Cumulative metformin doses were recorded in patients taking metformin using their dose and duration of treatment history. Serum vitamin B12 levels were done in all patients. All the included patients were subjected to a vitamin B 12 assay. Based on the results of B12 levels, patients were classified into the normal level, possible B12 deficiency, and definite deficiency. In our study, we found that metformin use is associated with Vitamin B12 deficiency, dependent upon the cumulative dose of metformin. Importantly prolonged metformin use is also associated with an increase in the prevalence of clinical neuropathy.

Introduction

Diabetes is becoming the fast epidemic of the 21st century. Type 2 diabetes, which is more common in approximately more than 90% of all diabetes cases and the main source of the diabetes epidemic, now affects 5.9% of the world's adult population with almost 80% of the total in developing countries1. Presently, 422 million people worldwide are bearing diabetes 2. Nowhere is the diabetes epidemic more pronounced than in India as the World Health Organization (WHO) reports show that 69.2 million people are living with diabetes (8.7%) as per 2015 data. Of these, it remained undiagnosed in more than 36 million people3. The International Diabetes Federation (IDF) roughly calculates the total number of diabetic subjects to be around 40.9 million in India and this is further set to rise to 69.9 million by the year 20251.

Metformin is the most commonly prescribed oral anti-diabetic drug in patients with type 2 diabetes mellitus4. Metformin impedes hepatic gluconeogenesis and glycogenolysis and glucose uptake from the intestines and refines peripheral insulin sensitivity. Long-term metformin treatment is a known pharmacological cause of vitamin B12 deficiency, as was evident within the first 10-12 years5-9 after it started to be used [1]. This is clinically important because patients with diabetes often suffer from neurological symptoms, such as numbness, paraesthesia, and impaired vibration sensation and proprioception. It was as early as 1971 when researchers began to speculate that one of the side effects of metformin use was vitamin B12

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malabsorption. Current research points to the effect of metformin on the calcium-dependent B12-intrinsic factor complex and absorption in the terminal ileum as the primary mechanism for vitamin B12 depletion [2-5].

Methodology

This was a cross-sectional study conducted in the Postgraduate Department of Medicine at S.M.H.S. Hospital, an associated hospital of Government Medical College, Srinagar from September 2014 to November 2016. A total of 700 consecutive patients of Type 2 diabetes meeting inclusion/exclusion criteria were taken for the study. This sample size was based on an anticipated prevalence of vitamin B 12 deficiency in the non-metformin group of 2%, with C.I. of 95% and an anticipated Odds ratio of 4. Type 2 diabetic patients were divided into two groups:

Those taking metformin, and those who were not taking metformin. Cumulative metformin doses were recorded in patients taking metformin using their dose and duration of treatment history. In all the outpatients and admitted diabetes patients, a detailed history taking and clinical examination was performed. Blood pressure, body mass index (BMI), HbA1c and baseline investigations were recorded in every patient. Serum vitamin B12 levels were done in all patients. Serum samples were stored at room temperature (15-30°C) for not longer than 7 hours. All the included patients were subjected to vitamin B 12 assay which was done using the Roche E-170 Vitamin B12 ECLIA (electrochemiluminescence immuno assay or method). Based on the results of B12 levels, patients were classified into the normal level, possible B12 deficiency, and definite deficiency. The inclusion criteria in this study were: age group of 31-70 years, patients of type 2 diabetes according to WHO criteria and patients of type 2 diabetes on treatment for diabetes. Patients who were excluded from the study if they give a history of alcoholism, ongoing pregnancy, liver disease, renal disease, thyroid disorders, history suggestive of malabsorption disorders and history of proton pump inhibitors intake/vitamin B12 supplement intake. The study protocol was approved by the institutional review board and the institutional ethics committee of government medical college Srinagar J&K, India [6-10].

Data analysis was done using SPSS 20.0 Statistical software (Statistical Package for the Social Sciences) Continuous data were summarized as mean and standard deviation. Categorical data were summarised as frequency and percentage. The difference in the prevalence of vitamin B12 deficiency and clinical neuropathy between metformin and non-metformin groups was analysed using the chi-square test. The association between cumulative metformin dose and vitamin B12 levels was analysed using Pearson's correlation coefficient and regression analysis. Moreover, Student's Independent t-test and ANOVA with Post hoc, Bonferroni test were also employed for analysis of data. Graphically the data was presented by bar, pie and scatter diagrams. A p-value of <0.05 was taken as statistically significant.

Results

Out of 700 types 2 diabetic patients in the age group of 30 to 70 years in this study done at SMHS hospital of Government Medical College, Srinagar. We found that 366 patients (52.29%) were males and 334 (47.71%) were females. The minimum age among patients taken in this study was 31 years and the maximum age of 70 years. The mean age of males was 50 years and that of females was 52.56 years. There were 373 (53.29%) patients in our study living in urban and 327 (46.71%) in rural areas. 98% were married and only 2% were unmarried, 320 (45.71%) were literate and 380 (54.29%) were illiterate (TABLE 1).

TABLE 1: Relationship between Cumulative dose of metformin and Vitamin B 12 deficiency.

B12 de ficiency	No. of patients	Mean	SD	Min.	Max.	P value
Vitamin BI2 deficient	205	4663.02	1506.8	720	8640	
Borderline Vitamin BI2 deficient	42	3637.89	776.71	720	4320	ROS
Vitamin BI2 sufficient	204	2230.32	1051.79	180	5040	ROS
Total	451	2999.79	1606.32	180	8640	ROS

Out of 700 t2 diabetic patients, 451 (64.4%) were on metformin and 249 (35.6%) patients were on insulin, sulfonylureas and gliptins. We divided these patients into two groups: those taking metformin (metformin group) and those not taking metformin (non-metformin group). In the metformin group, 307 patients were on metformin alone, 116 patients were on metformin and sulfonylureas and 28 patients were on metformin as well as insulin. In the non-metformin group out of 249 patients, 203 were on insulin and 46 patients were on sulfonylureas and/or voglibose. The mean BMI of the study population was 27.15 ± 2.2, for males it was 26 ± 2.31 kg/m^2 and for females was 28.4 ± 2.16 kg/m^2 with a minimum value of 19.6 kg/m^2 and it maximum value of 36.8 kg/m^2.

Based on Vitamin B 12 levels, the patients were grouped into three groups: Vitamin B 12 sufficient group, borderline deficient group and B12 deficient group.

Discussion

We defined definite and possible (borderline) deficiency as serum vitamin B12 levels of<150 and<220 pmol/L, respectively17-21. In adults, a vitamin B12 level of 150 pmol/L is considered the lowest level for an adequate state. In a developing deficiency, serum concentrations are maintained by depleting body storage. Therefore, a concentration of 150 pmol/L might not reflect a sufficient vitamin B12 status, and a cut-off value of<220 pmol/L is proposed by some.21 Anaemia tends to occur only when metabolic deficiency is moderately severe or the deficiency is severe enough to affect the haematological indices. In addition, macrocytosis can be masked by coexisting microcytic processes including thalassaemia and iron deficiency. Estimation of vitamin B12 deficiency in type 2 DM patients taking metformin will help in the formulation of guidelines regarding vitamin B12 monitoring and supplementation in such patients. Our study was conducted to identify the prevalence of vitamin B12 deficiency in type 2 diabetic patients, to see the effect of metformin on vitamin B12 levels and the effect of vitamin B12 deficiency on neuropathy, as vitamin B12 induced neuropathy is a treatable disease that may be confused with diabetic neuropathy and hence leading to inappropriate management. Seventy hundred patients were enrolled in this study who fulfilled the criteria for type 2 diabetes framed by American Diabetic Association (ADA).

Out of 700 type2 diabetes patients, 451 (64.4%) and 249 (35.6%) patients belonged to the metformin and non-metformin group, respectively. The mean duration of diabetes of the study population from the time of diagnosis was 63.21 ± 29.23 months which was 62.5 ± 28.6 months for males and 64.01 ± 27.9 months for females. These parameters matched with a study.

The mean vitamin B 12 levels in this study was 370.82 ± 193.95 pmol/dL with a maximum level of 980 pmol/dL and a minimum value of 128 pmol/dL. Based on vitamin B 12 levels, the patients were divided into three groups: Vitamin B12 deficient, Vitamin B12 level <150 pmol/dl; possible vitamin B12 deficiency; Vitamin B12 level>150-220 pmol/dl and vitamin B 12 sufficient, Vitamin B12 level >220 pmol/dl observed in 29.29% of patients, 16% and 54.71% of patients, respectively.

The prevalence of vitamin B12 deficiency in the metformin and non-metformin group observed was 33.26% and 22.1% respectively. This shows that patients on prolonged metformin therapy have increased vitamin B12 deficiency by 11.16%. A study conducted by Singh showed almost similar results.

The mean cumulative dose of patients on metformin was 2999.8 ± 1606.3 grams with a maximum dose of 8640 grams and a minimum dose of 180 grams. In our study, it was seen that with an increase in the cumulative dose of metformin, vitamin B12 levels decreased linearly. The cumulative dose of metformin in vitamin B12 deficient patients was 4663.2 ± 1506.8 whereas in the borderline vitamin B12 deficient group, it is 3637.89 ± 776.71, and in patients with normal vitamin B12 levels the cumulative dose is 2230.32 ± 1051.79 (P-value<.001). Pearson's correlation coefficient for a cumulative dose of metformin and vitamin B12 levels observed was-0.662 which is statistically significant (P value<0.001). This clearly shows that with an increase in the cumulative dose of metformin, the levels of vitamin B12 decrease. These observations are supported by previous following studies done by Joline.

The prevalence of clinical neuropathy in the metformin exposed group was 45% whereas the prevalence of 31.8% was found in the non-metformin group. The evident discrepancy of the prevalence of neuropathy by the above two methods is due to differences in sensitivity, specificity between the two tools. TCSS score 6 when compared with the electrophysiological

method has 77.2% and 75.6% of sensitivity and specificity with an accuracy of 76.6%, hence explaining the difference in the results 30.

The mean age of patients with neuropathy was higher than those without neuropathy (59.01 ± 7.14 *vs* 49.95 ± 7.47) (p-value <.514, statistically insignificant). These results are consistent with studies done by Shihong.

The data from our study showed that with an increase in the dose of metformin, the neuropathy scores done by TCSS in our study increased which suggests that neuropathy worsens as the cumulative dose of metformin increases. The mean TCSS score of the whole study population, metformin exposed and non-metformin groups were 5.91 ± 2.997, 6.36 ± 3.43 and 5.1 ± 3.88, respectively. By linear regression analysis, it was observed that metformin use worsened the clinical score of neuropathy (coeff.=-2.947, P-value<.001). The HbA1c levels in patients with and without clinical neuropathy were 8.7 ± 1.27 and 7.92 ± 0.88 respectively (P-value<.001) showing that HbA1c levels in the clinical neuropathy group were higher by a mean of 0.78% than in patients without neuropathy suggesting that poor glycemic control is associated worse status of diabetic neuropathy. Similar results were obtained in a study conducted by Yacoub.

Conclusion

In our study, we found that metformin use is associated with Vitamin B12 deficiency, dependent upon the cumulative dose of metformin. Prolonged metformin use is associated with an increase in the prevalence of clinical neuropathy, possibly due to vitamin B12 deficiency caused by metformin use. Poor glycaemic control is also associated with an increased prevalence of clinical neuropathy. So its rationale is to screen the patients who are to be put on metformin therapy for vitamin B12 deficiency and monitor for B12 deficiency once the patient is started on metformin.

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