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Original Research Paper

Pathology

STUDY OF VITAMIN B12 DEFICIENCY IN TYPE- 2 DIABETIC PATIENTS USING METFORMIN AT RIMS RAIPUR CHHATTISGARH

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ABSTRACT The prevalence of vitamin B12 deficiency varies from 5.8% to 30% among patients undergoing long-term treatment with metformin.Our study aimed to determine the frequency of B12 deficiency and related factors among patients with type 2 diabetes mellitus (T2DM) using metformin.Patients with T2DM and a control group of non-diabetics were included. Serum B12 levels were measured and biochemical B12 deficiency was defined as serum levels < 180 pg/ml. Associations between B12 deficiency and age, duration of T2DM, duration of use and dosage of metformin, and use of proton pump inhibitors (PPIs) or histamine H2 antagonists were determined.300 T2DM patients using metformin (T2DM-met) and 300 controls were included. No difference in the frequency of PPI or H2-antagonist use was seen between the groups. B12 deficiency was more frequent in the T2DM-met group (22.5% *versus* 7.4%) and this difference persisted after excluding PPI/H2-antagonist users (17.9% *versus* 5.6%). The factors that interfered with serum B12 levels were PPI/H2-antagonist use and duration of metformin use ≥ 10 years. Use of PPI/H2-antagonists was associated with B12 deficiency, with an odds ratio of 2.60 (95% confidence interval, 1.34-5.04).Among T2DM patients, treatment with metformin and concomitant use of PPI/H2-antagonists are associated with a higher chance of developing B12 deficiency than among non-diabetics.

KEYWORDS : Diabetes mellitus; Vitamin B 12 deficiency; Metformin; Proton pump inhibitors; Histamine H2 antagonists.

INTRODUCTION

Vitamin B12, or cyanocobalamin, is found in foods of animal origin and has an important role in deoxyribonucleic acid (DNA) synthesis and in many biochemical reactions. The prevalence of B12 deficiency varies from 5.8% to 30% among patients undergoing long-term treatment with metformin.Identifying B12 deficiency is clinically relevant since several conditions may be associated with this, such as megaloblastic anemia, neuropathy, cognitive dysfunction, memory loss, irritability, dementia, extrapyramidal signs and increased risk of osteoporosis.Because of the reported association between metformin use and B12 deficiency,the present study aimed to determine the frequency of biochemical B12 deficiency and its related factors among T2DM patients using metformin who were followed up at RIMS RAIPUR CHHATTISGARH.Study population T2DM patients were recruited from the OPD,over a 24-month period. A substantial proportion of these patients are referred to our hospital by primary care centers in the same municipality. The control group consisted of non-diabetic individuals, who were matched for sex and age and were recruited in the same outpatient clinic and at the Blood Donation Center of this hospital. The inclusion criteria for the patients' group were that they needed to have T2DM, be older than 18 years of age and have been using metformin for at least three years. Patients and controls were excluded from the study if they had a history of partial or total gastrectomy, malabsorptive diseases, B12 supplementation during the three months prior to enrollment in the study or documented pernicious anemia, or if they were vegetarians or pregnant women. Demographic data such as age and sex were noted, as well as the following parameters: T2DM duration, metformin use (duration and dose), use of proton pump inhibitors (PPIs) or type 2 histamine receptor blockers (H2-antagonists), smoking habits and alcohol consumption. Smoking habits were divided into current and non-smokers. Patients were defined as "alcohol consumers" if their average consumption was one to two drinks per day. Laboratory data included serum B12 levels, hemoglobin (Hb) and mean corpuscular volume (MCV). We did not obtain dietary histories, nor did we document the prevalence of neuropathy. The reference values were 180-914 pg/ ml, with an analytical sensitivity of 50 pg/ml. Biochemical B12 deficiency was defined as serum levels < 180 pg/ml. Anemia was defined as Hb < 13 g/dl for males and < 12 g/dl for females, based on WHO guidelines. Associations between B12 deficiency and categorical variables were determined using the chi-square test. Associations between continuous variables and B12 deficiency were determined by means of the Mann-Whitney U test.

RESULT

A total of 600 subjects were included from Jan 2015 to Jan 2017, comprising 300 T2DM patients who were using metformin (T2DM-met) and 300 controls.The median serum B12 level was lower in the T2DM group.Considering the T2DM-met patients, B12 levels were significantly lower in PPI or H2-antagonist users compared with T2DM-met patients that did not use PPI or H2-antagonist. After excluding PPI or H2-antagonist users among the patients and controls, the serum B12 levels were still significantly lower in the T2DM-met group.Frequency of vitamin B12 deficiency Biochemical B12 deficiency was more frequent in the T2DM-met group than in the control group (22.5% versus 7.4%; P < 0.001). After excluding PPI or H2-antagonist users among the patients and controls, the frequency of B12 deficiency continued to be significantly higher in the T2DM-met group (17.9% versus 5.6%; P = 0.001).Comparing patients with and without B12 deficiency, there were no differences with regard to age, sex, T2DM duration or metformin use (duration and dose). PPI or H2-antagonist use was more frequent among the B12-deficient patients (40.4% versus 20.7%; P = 0.004). A weak negative correlation between serum B12 levels and the duration of metformin use (r = -0.18; P = 0.006) was seen. However, no correlation was found between serum B12 levels and the daily dose of metformin.Among the T2DM-met patients with B12 deficiency, anemia was seen in 23.1% (n = 12). The prevalence of anemia did not differ between T2DM-met patients with and without B12 deficiency (23.1% versus 31.3%; P = 0.378). Considering all the T2DM-met patients with anemia 4.4% had macrocytic,88.2% had normocytic and 7.4% had microcytic anemia. Macrocytosis was significantly more frequent in the B12- deficient group (9.6% versus 0.6%; P < 0.001). However, the MCV did not differ between T2DM-met patients with and without B12 deficiency (89.4 versus 89.0; P = 0.153). In analyzing only the T2DM-met patients with B12 deficiency, macrocytic anemia was only found in two patients, while three others had macrocytosis with normal red blood cell counts.

DISCUSSION

The serum levels of vitamin B12 were significantly lower in the T2DM-met group than in the control group, even after excluding PPI and H2-antagonist users. Similarly, the PPI and H2-antagonist users (T2DM-met and control groups) had lower serum B12 levels than patients who did not use these medications. These findings suggest that PPI/H2-antagonists and metformin have an additive effect with regard to promoting vitamin B12 malabsorption. Both of these categories of medications are widely used by patients, sometimes

without medical prescription, and their use should not be overlooked. When clinically indicated, their use should be monitored because of the possibility of vitamin B12 malabsorption and its consequences. The prevalence of B12 deficiency among T2DM-met patients was significantly higher than in the control group matched for to sex and age (22.5% versus 7.4%). Previous studies have found similar results, but the mechanisms involved in this deficiency are not well established.Some evidence has supported the hypothesis that metformin-induced B12 malabsorption is due to enhanced bacterial overgrowth or to modification of the intestinal microbiota.In addition, metformin interferes with calcium-dependent membrane action and with the secretion of B12-intrinsic factor. Since the B12-intrinsic factor complex uptake by the ileal cell surface receptor is a calcium-dependent process, both mechanisms possibly cause a decrease in B12 absorption.One factor significantly associated with B12 deficiency was found was simultaneous use of metformin with PPI or H2-antagonists. The association between B12 deficiency and PPI or H2-antagonist use supports the notion that reduced gastric acidity has a role as a predisposing factor for B12 malabsorption. Both of these drugs decrease acid secretion by the parietal cells, and gastric acid produced by these cells is required for cleavage of vitamin B12 from dietary sources.Nervo et al. did not find any association between serum B12 levels and use of omeprazole. Nevertheless, considering the possible additive effect between metformin and PPI or H2-antagonists in relation to B12 absorption, caution should be used when these drug classes are combined.Concerning the duration of metformin use, there was a non-significant trend towards an association between B12 deficiency and longer duration of metformin use (≥ 10 years).Vitamin B12 deficiency is related to a number of comorbidities, such as peripheral neuropathy and megaloblastic anemia.The prevalence of anemia and mean corpuscular volume did not differ between T2DM-met patients with and without B12 deficiency (23.1% versus 31.3% and 89.4 fl versus 89.0 fl, respectively). The high rates of anemia in this particular sample might be related to several factors. The older age of our patients is one possible explanation, since it has been reported that the prevalence of anemia is higher in older age groups. Also, normocytic anemia was the most common presentation (83.3% and 89.2%, respectively) in both groups of patients, with and without B12 deficiency. Considering normocytic anemia, chronic inflammation must be highlighted as a possible cause, since it is associated with the release of proinflammatory cytokines.A population based cohort study carried out in São Paulo, Brazil, that only included individuals older than 65 years showed that 35.1% of the cases of persistent anemia could be attributed to chronic inflammation. Although chronic kidney disease is known to be a cause of anemia, we did not include patients with estimated glomerular filtration rate less than 60 ml/min. However, other coexisting conditions, such as thalassemic or sickle cell trait and iron deficiency may explain not only anemia but also the lack of correlation between B12 deficiency and MCV.Finally, because of the difficulty in excluding potential causes of peripheral neuropathy other than diabetes and B12 deficiency, the prevalence of neuropathy and its possible association with B12 deficiency were not evaluated.

CONCLUSION

Our study confirms that in patients with T2DM, long-term treatment with metformin and concomitant use of PPI/H2-antagonists are associated with higher chances of developing biochemical vitamin B12, in comparison with non-diabetics.

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