Case Report

Metformin Associated B12 Deficiency

Anand Ajit Kumthekar*, Hitesh Vinod Gidwani**, Ajit Bhaskar Kumthekar***

Abstract

According to the ADA guidelines, metformin and lifestyle modifications are the first line therapies in the treatment of type 2 diabetes mellitus. Metformin does, however, cause vitamin B-12 malabsorption, which may increase the risk of developing vitamin B-12 deficiency — a clinically important and treatable condition. Here we report a case of 60 year old diabetic male presenting with clinical features of Vitamin B-12 deficiency on long term metformin therapy, which was confirmed on investigations. Patient showed symptomatic improvement with change in treatment.

A 60 yr old male patient was brought to the OPD by his son (who was abroad for 18 months) who noticed few changes in the behaviour of his father like:

1. Tendency to postpone intellectual work.
2. Delay important business decisions and
3. Slowness of higher functions.

On direct questioning the patient, said that he has been having these complaints since last 2-3 months, felt lethargic and experienced tingling numbness of both hands and feet, but he did not report it to his physician. The symptoms were gradual in onset and progressively worsened over a period of time and were not noticed by his wife too. Dietary history revealed that he was consuming a mixed diet with intake of meat at least 4 times a week. The meat is usually chicken with occasional addition of goat meat and rarely fish. Alcohol intake was once a week in a quantity of 60-90ml. There is no history of smoking or any other addictions. No history of alteration of bowel habits or any abdominal surgery.

He is a known case of diabetes and hypertension for the last 5 years. He was on a regular therapy with Gliclazide (80mg) and Metformin (850mg-1.5g) depending on his blood glucose level control. Appropriate anti-hypertensive drugs were added to control his hypertension.

O/E, Ht: 189cms, Wt: 119kg, BMI: 33.31. B.P was 140/100mmHg and other vital parameters were normal. There was no pallor.

Significant findings in neurological examination were:

1. Loss of sensations of touch and vibrations in both feet
2. Ankle jerk was present bilaterally

Cardiovascular, Respiratory and P/A examination were normal.

Investigations

Laboratory data at initial visit revealed a haemoglobin of 12.1gm/dl and HbA1C of 8.5 %. Vibration Perception Threshold (VPT) done with a Bio-Thesiometer demonstrated moderate grade peripheral neuropathy in both lower limbs (Between 21-25 Volts). A B12 level was ordered which came back as 60pg/ml (Normal=>140pg/ml). Patient was asked to discontinue metformin, his anti-diabetic medications were adjusted for better glycemic control and was given injectable B12 1 week apart for 4 weeks. B12 level after completion of injectable therapy was 888.60pg/ml and VPT testing still demonstrated moderate neuropathy. B12 level repeated after 8 months following discontinuation of metformin therapy was 424.0 pg/ml and VPT testing showed no neuropathy(< 15 volts), which was a marked improvement (Table 1-5).

Management

Metformin was discontinued with immediate effect and he was given hydroxycobalamin injections 1 week apart for 1 month. Patient was also advised to have liver soup in his diet.

After one month with this new treatment, he is feeling better. His is more energetic and was prompt in taking business decisions as he was before.

Tingling numbness has improved in both the legs. Serum B12 level is 888pg/ml. Metformin was not reintroduced in the management of diabetes. Gliclazide and voglibose were used for glycemic control. Serum B12 levels assayed 8 months after stopping metformin is 424 pg/ml.

Discussion

Metformin, a biguanide is an oral hypoglycaemic agent, which has been in clinical practice for last 40 years. The UK Prospective Diabetes Study Group 34 showed metformin to be an effective hypoglycaemic agent with less weight gain, and decreased glycosylated haemoglobin, myocardial infarction, stroke and death. According to the new ADA/EASD guidelines, lifestyle intervention and metformin are the first lines of treatment in the management of hyperglycemia in type 2 DM.

Metformin use gives an excellent metabolic control and it also has beneficial effects on the advanced glycation end product formation in peripheral nerves and may prevent apoptosis involved in diabetes-associated neurodegenerative processes.1,2

Metformin acts by decreasing the hepatic glucose output in the fasting state. Initiation of metformin therapy can cause GI disturbances, which can be reduced by starting low dose therapy and gradually increasing. Lactic acidosis is rare if metformin is used judiciously.

Metformin is also reported as a pharmacological cause of B12 deficiency. It is estimated that 10% to 30% of patients undergoing metformin therapy develops evidence of vitamin B12 deficiency.3 Another study showed a 22% prevalence of B12 deficiency in type 2 DM on metformin therapy.4

The responsible mechanism for B12 deficiency in metformin users has been controversial; proposed contributors have included competitive inhibition or inactivation of Cbl

*Resident Medical Officer, Sumati Diabetes Clinic, Nashik 422002; **Resident Medical Officer, Sunshine Diagnostic Centre, Mumbai 400050; ***Consultant Diabetologist, Sumati Diabetes Clinic, Nashik 422002
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absorption, alterations in intrinsic factor levels, bacterial flora, gastrointestinal motility, and interaction with the cubulin endocytic receptor. Patients on metformin have low B12 levels because of a calcium dependent ileal membrane antagonism. Low B12 levels due to prolonged metformin use can cause or exacerbate diabetic peripheral neuropathy (DPN).

Low B12 levels due to prolonged metformin use can cause or exacerbate diabetic peripheral neuropathy (DPN). Low serum B12 levels also alter cerebral functions like memory, cognition, alertness etc.

DPN is a common disorder and estimates show that 20% of the adult diabetic population suffer from it. One important point is that all cases of tingling numbness in a diabetic are not due to DPN. Other causes (B12 deficiency, Hansen’s disease) should be kept in mind. Currently there are no definitive guidelines for B12 level screening for patients on metformin but annual screening may be worthwhile. Careful examination and appropriate laboratory investigations can detect side effects associated with

### References