RESEARCH ARTICLE

Therapeutic Modifications to Correct Megaloblastic Anemia in Patients with Long Term Use of Metformin

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ABSTRACT

Introduction: Metformin is the first drug of choice for type 2 diabetes mellitus unless it is contraindicated. Patients with maximum metformin dose and for longer duration may suffer from megaloblastic anemia.

Material and Methods: A prospective, interventional, comparative study was conducted at a tertiary care teaching hospital. Type 2 diabetic patients on maximum metformin dose patients were advised to stop metformin and start long-acting insulin + DPPP4 inhibitors and injection of vitamin B12 to correct megaloblastic anemia.

Result: The Mean ± SD hemoglobin, MCV, serum vitamin B12 level before and after the therapeutic modification were 9.1 ± 0.89 and 12.8 ± 1.02 gm/dl, 106.7 ± 1.23 and 93.12 ± 5.56 fL, respectively, 254.14 ± 58.12 and 468.13 ± 69.32 pg/mL,.

Conclusion: Improvement in the Hemoglobin, MCV and serum vitamin B12 level suggestive of the cause of megaloblastic anemia was metformin.

Keywords: Metformin, Megaloblastic anemia, Serum vitamin B12 level, Hemoglobin, Type 2 diabetes.

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INTRODUCTION

Diabetes affects a large number of people globally and is becoming more common. Its high incidence is mostly caused by a growingly sedentary lifestyle, poor eating habits, and lack of exercise. With an 11.4% prevalence of diabetes, India is regarded as the global center for diabetes. Nearly 90% of diabetic people have type 2 diabetes mellitus, which is the most prevalent kind of the disease.[1-3] Patients with type 2 diabetes utilize various oral antidiabetic drugs to regulate their blood sugar levels. Metformin is the primary pharmaceutical of choice unless it is contraindicated for the treatment of type 2 diabetes mellitus.[4,5] By decreasing hepatic gluconeogenesis and raising peripheral insulin sensitivity, metformin works. Nearly all individuals tolerate metformin extremely well, yet a small percentage experience moderate side effects such as nausea, diarrhea, and stomach discomfort.[6]

In a 2016 systematic review, it was discovered that 10 out of 17 observational studies indicated that patients with type 2 diabetes mellitus who took the maximal dose of metformin for a longer period of time had statistically significantly lower levels of vitamin B12.[7] In another study conducted M Shawan *et al.* and Beulens JWJ *et al.*[8] it was found that the deficiency of vitamin B12 deficiency is inversely related to the duration of type 2 DM with metformin therapy. On the other side, a study conducted by Elhadd T *et al.*,[9] suggests that the serum level of vitamin B12 in patients with type 2 DM with and without metformin therapy was less prevalent in group with metformin therapy. Metformin causes megaloblastic anemia is still a controversial topic. Some of the studies has mentioned the probable mechanism for metformin-induced vitamin B12 deficiency "(1) Interference with calcium-dependent binding of the IF-vitamin B12 complex to the cubilin receptor on enterocytes at the ileum level and/or interaction with the cubilin endocytic receptor; (2) Alteration in small intestine motility, leading to small intestinal bacterial overgrowth and subsequent inhibition of IF-vitamin B12 complex absorption in the distal ileum; (3) Alteration in bile acid metabolism and reabsorption, resulting in impaired enterohepatic circulation of vitamin B12; (4) Increased liver accumulation of vitamin B12, resulting in altered tissue distribution and metabolism of vitamin B12; and (5) Reduced IF secretion by gastric parietal cells. Of note, inhibition of calcium-dependent absorption of the IF-vitamin B12 complex at the terminal ileum has been increasingly recognized as the most plausible mechanism accounting for metformin-induced vitamin B12 deficiency".[10]

Vitamin B12 deficiency in early stages can be asymptomatic but in later stages it can be a serious disorder leading to severe neurological symptoms. The best way to manage this disorder

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is to prevent it by early diagnosing or by advising the patients with certain medications to carry out blood panel investigations on regular basis.

As of right now, to the best of our knowledge, no research has been published—aside from a case report—on the diagnosis of vitamin B12 deficiency in type 2 diabetes patients taking the maximum amount of metformin and modifying their treatment plans to assess response to therapy. For this reason, we carried out this study to provide solid evidence for metformin-induced megaloblastic anemia.

Aim

To find out does metformin causes megaloblastic anemia

Objective

To dechallenge the megaloblastic anemia induced by metformin maximum dose for longer duration in patients of type 2 diabetes mellitus".

MATERIAL AND METHODS

The study was conducted in tertiary care teaching hospital. It was a prospective, comparative, interventional study. After getting approval from ethics committee the study was conducted in the department of medicine.

Inclusion Criteria

- Age between 25 to 50 years
- NIDDM patients
- Patients with metformin dose 2000 mg
- Patients with diabetes with minimum history of 5 years

Exclusion Criteria

- Elderly patients
- IDDM
- Patients with compromised liver and kidney functions
- Heart diseases
- Pregnancy
- Gastric surgeries
- Inflammatory bowel disease
- Malignancy
- Acute complications of diabetes
  i) Hyperglycaemic hyperosmolar state
  ii) Diabetic ketoacidosis

MATERIALS AND METHODS

Already diagnosed diabetic patients attending the medicine OPD who are taking metformin 2000 mg daily for at least minimum 3 years were advised for hemogram and peripheral smear. Patients with megaloblastic anemia diagnosed depending on the MCV values and peripheral smear were included in the study as per the inclusion and exclusion criteria and serum vitamin B12 level was assessed for all the patients to confirm the megaloblastic anemia (normal vitamin B12 level 300 – 900 pg/mL).[11] Detail history taking and clinical examination has been carried out for all the patients.

Other causes of vitamin B12 deficiency like -

- TSH level
- Detail dietary history
- Chronic alcoholic
- Lead toxicity
- Syphilis
- HIV myelopathy
- Multiple sclerosis"

Were ruled out by respective investigations and detailed history taking and clinical examinations.

Therapeutic Modification

Metformin was stopped in all the patients and a combination of insulin and DPP4 inhibitors was used to control the blood sugar level.

The vitamin B12 injection was administered to all patients at a therapeutic dose of 1-mg intramuscularly (IM) for two weeks, and then the maintenance dose was given once a month for three months.

Outcome

All the patients were asked to report to OPD after three months and blood hematogram and serum vitamin B12 level were repeated. All the parameters were recorded on a proforma.

After the therapeutic modifications was done, before and after comparison of all the parameters was done to assess the improvement with modified therapy.

Statistical Analysis

All the data was recorded in the Microsoft excel 2019 and the data analysis was done using Microsoft excel and SPSS version 26. The mean ± standard deviation was calculated for all the quantifiable variables; paired t test was used to calculate the significant difference between before and after treatment modifications.

RESULT

About 54 patients with type 2 diabetes mellitus who were on metformin maximum dose of 2000 mg were enrolled in the study and were investigated for complete blood count, and peripheral smear. Out of the 54 patients 45 patients were having hemoglobin level less than 11 gm/dl and macrocytic - hyperchromic presentation in the peripheral smear. The rest of the patients were either having microcytic – hypochromic (n = 5) presentation or normal haemoglobin level (n = 4). Total 45 patients were screened for the study out of which 30 patients fulfilled the inclusion and exclusion criteria for enrolment and had followed completed therapeutic modification as advised.

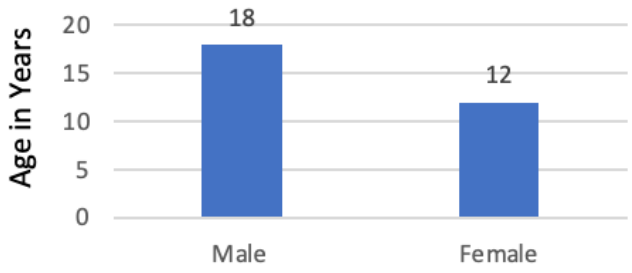

Figure 1: Gender wise distribution of patients in the study

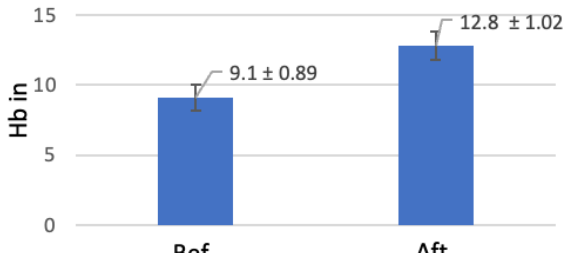

Figure 2: Haemoglobin level before and after therapeutic modifications in all the patients

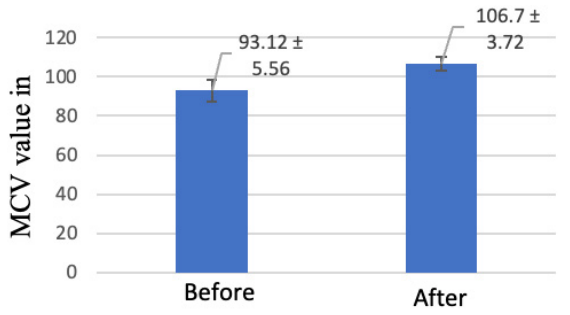

Figure 3: MCV level before and after therapeutic modifications in all the patients

Of the 45 patients, 15 could not be included in the trial; three had a deficiency in both serum vitamin B12 and folic acid; six had a history of persistent alcoholism; and six were lost to follow-up.

The mean ± SD of age of the patients in the study was 55.48 ± 12.12 years. Out of 30 patients 60 % (n = 18) were male and 40 % (n = 12) were female patients as shown in Figure 1.

The Mean ± Standard deviation for the haemoglobin for all the patients before and after the therapeutic modifications was 9.1 ± 0.89 gm/dL and 12.8 ± 1.02 gm/dL respectively as shown in Figure 2. A significant improvement in haemoglobin was seen after therapeutic modifications ($p < 0.05$).

Peripheral smear was assessed for all the enrolled patients before therapeutic modifications and after therapeutic modifications was macrocytic and hyperchromic and normocytic normochromic.

The Mean ± Standard deviation for the Mean corpuscular volume for all the patients before and after the therapeutic modifications was 106.7 ± 1.23 f L and 93.12 ± 5.56 f L, respectively as shown in Figure 3. A significant improvement in mean corpuscular volume was seen after therapeutic modifications ($p < 0.05$).

The Mean ± Standard deviation for the Serum vitamin B12 level for all the patients before and after the therapeutic modifications was 254.14 ± 58.12 pg/mL and 468.13 ± 69.32 pg/mL respectively as shown in Figure 4. A significant improvement in serum vitamin B12 level was seen after therapeutic modifications ($p < 0.05$)

For all the patients participated in the study the folic acid level was within the range of 3.1 – 17.5 ng/mL. The Mean ± SD for folic acid of all the patients in the study was 6.41 ± 1.32 ng/mL.

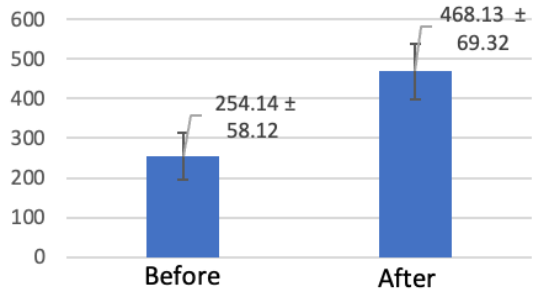

Figure 4 : Sr Vitamin B12 level before and after therapeutic modifications in all the patients

DISCUSSION

The prevalence of vitamin B12 deficiency after metformin use has been reported to be 6 to 30%, varying with race, standard values of vitamin B12, and metformin usage.[12-18] A large prospective study reported a 20.3% prevalence of vitamin B12 deficiency after 9.5 years of metformin use,[19] and a large dataset provided by the National Health and Nutrition Examination Survey showed a 22% prevalence when vitamin B12 deficiency was defined as levels below 300 pg/mL.[12] We modified the course of treatment for participants in our research who had metformin-induced megaloblastic anemia (2000 mg/day). Patients were recommended to cease taking metformin and switch to long-acting insulin and DPP4 inhibitors as alternative drugs to regulate blood sugar. Vitamin B12 injections were also started. In our study, participants took metformin for an average of three years. Following 9.5 years of metformin treatment, a major prospective study found that a 20.3% prevalence of vitamin B12 insufficiency.[19] The frequency of vitamin B12 insufficiency will increase with the length of time a metformin prescription is used. We enlisted 45 patients in total for our trial, of whom 30 finished the investigation. There were 40% female participants and 60% male participants in our study. The age range impacted in one study by Almatraffin S7 *et al.* was primarily between 51 and 64 years old, while the mean ± SD of the patients in our study was 55.48 ± 12.12 years. The above study's findings align with those of our own. There was a significant improvement in the patient's haemoglobin level ($p < 0.05$), with the mean ± SD levels before and after therapeutic changes being 9.1 ± 0.89 and 12.8 ± 1.02 gm/dL, respectively. Following treatment changes, the MCV level showed a considerable improvement, with values before and after the alterations being 93.12 ± 5.56 and 106.7 ± 1.23 fL, respectively. The levels of serum vitamin B12 were 254.14 ± 58.12 pg/ml and 468.13 ± 69.32 pg/mL, respectively, before and after treatment adjustments in our investigation. Unfortunately, very few studies are available on the similar topic in public domain so we have considered "a case report published by the Albai O[20] *et al.*, the author has claimed that the patient was taking 1-gm metformin twice daily for more than 3 years. After blood investigations it was

seen that the patient was having Hb= 8.7 g/dl, MCV= 119.6 fL, serum vitamin B12 level of 113 pmol/l, the patient was put on the alternative therapy, Glargine + Sitagliptin along with serum vitamin B12 injection, improved the serum vitamin B12 level and hemoglobin level after 3 months. The finding of the case coincides with result of our study.

CONCLUSION

Patients with type 2 diabetes mellitus who had been taking a 2 gm dose of metformin for more than three years were found to have megaloblastic anemia after all other possible causes had been ruled out. These patients were then started on therapeutic modifications to address the metformin-induced low serum vitamin B12 levels. With normal serum vitamin B12 levels, all patients fully recovered from megaloblastic anemia. This validates the experiment conducted to demonstrate that megaloblastic anemia was the reason for the extended use of the maximal dose of metformin.

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