

# Diabetes Mellitus and Metformin: Fatal Vitamin B12 Deficiency Associated with Anemia and Sepsis in a Young Adult

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## ABSTRACT

Metformin is recommended as the first-line therapy to treat type 2 diabetes mellitus with better efficacy. We present a young adult with severe fatigue and dyspnea along with difficulty during the walk and tingling sensation in both the lower limbs. He had T2DM for 9 years and continuing metformin 1 g daily for five years. He presented to the hospital with untreated wounds over lower limbs. His haematological reports showed the megaloblastic anemia and transfused with several pints of packed red blood cells (PRBCs). The patient developed sepsis during hospitalization and started on antibiotics. After several PRBC transfusions and aggressive treatment also patient did not improve and succumbed on 5<sup>th</sup> day of hospitalization.

## INTRODUCTION

Metformin is a most prescribed oral hypoglycaemic agent, used in the management of diabetes mellitus (T2DM). Metformin is compatible with a maximum number of drugs and conditions with fewer contraindications and lesser drug interaction profile. The drug is preferred with lifestyle modifications for the better therapeutic outcome. Few studies have reported the metformin-associated Vitamin B12 (VitB12) deficiency on extensive and long-term use (Kang *et al.*, 2014; Liu *et al.*, 2014). VitB12 deficiency leads to anemia and peripheral neuropathy in T2DM patients (Reinstatler *et al.*, 2012). Here we present a case of metformin-associated vitamin B12 deficiency that led to fatal anemia and sepsis in a young adult with T2DM.

## CASE REPORT

A 42 years old male presented to the AMCU (Acute Multi Care Unit) department of a tertiary care hospital at Karimnagar, a South Indian district, with the multiple small ulcers on the bilateral lower limbs till toe for four weeks with numbness, tingling sensation and leg pain. The patient also complained the severe fatigue, dyspnoea on exertion and difficulty in walking for 2 months. On physical examination he was pallor. He had a history of T2DM for 9 years and continuing a single drug metformin 500 mg twice daily for 5 years. In the family, his father also had T2DM and continued oral hypoglycemic agents. All possible causes of lower limb injuries were ruled out. Bilateral lower limb arterial and venous doppler showed normal flow without obstruction. He has provisionally diagnosed to have diabetes-related foot ulcers. At admission, his lab investigations showed borderline high sugar levels. At day 1 his fasting blood sugar (FBS), random blood sugar (RBS) and glycosylated haemoglobin (HbA1C) were near normal; 124 mg/dL, 148 mg/dL and 6.2 mmol/L respectively. Liver, thyroid and kidney function test were normal. Haematological studies showed the severe anemia. Hemoglobin level, haematocrit

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and total red blood cells (TRBC) were 6.2 g/dL, 28% and  $2.7 \times 10^3$  cells/microL respectively.

For foot ulcers, preliminary dressings were done with antiseptics. Serum procalcitonin (ProCT) and blood culture were sent for suspected wound infections/sepsis. ProCT was negative for bacterial infection with the value of 0.02 ng/mL and two out of three blood samples showed *staphylococcus* and beta-haemolytic *streptococci* species growth after 24 hours.

Surgery and gastroenterology opinions were sought to rule out the possible causes of anemia i.e. gastric ulcers. Ultrasound (USG) abdomen and oesophago-gastro duodenoscopy (OGD scopy) showed no gastrointestinal ulcer. As per the patient's note, there is no active bleeding from foot ulcers.

The iron profile was tested which shows degraded serum iron, ferritin and total iron binding capacity (TIBC) levels; 45 mcg/dL, 26 ng/mL and 470 mcg/dL respectively. Mean corpuscular volume (MCV) and Mean corpuscular hemoglobin (MCH) levels were increased; 176 fL/cell and 56 pg/cell respectively where mean corpuscular hemoglobin concentration (MCHC) was slight high (44 g/dL). A blood smear analysis showed senile neutrophils, poikilocytosis, the presence of macrocytes and anisocytosis. The VitB12 level was 55 pg/mL, which is much lesser than the standard and possible cause of anemia. Metformin-induced VitB12 deficiency was suspected because of long-term use of metformin. Coomb's test was negative. These all findings suggested the final diagnosis of 'Megaloblastic anemia' due to VitB12 deficiency.

As per the provisional diagnosis and lab investigations, metformin was discontinued and glimepiride 1 mg twice daily was started. Cefotaxime 1 g twice daily was started for bacterial infection. Acetaminophen and pantoprazole along with IV fluids were given as supportive measures.

**Table 1:** Showing laboratory investigations during hospitalization.

| Parameters                         | At admission (Day 1) | Day 2 | Day 3             | Day 4 | Day 5             |
|------------------------------------|----------------------|-------|-------------------|-------|-------------------|
| Temperature (degree F)             | 98.4                 | 100.2 | 98.8              | 99.0  | 98.7              |
| Hemoglobin (gm/dl)                 | 6.2                  | 6.8   | 5.8               | 5.2   | 5.0               |
| Hematocrit (%)                     | 28                   | 26    | 26                | 22    | 25                |
| TRBC ( $\times 10^3$ cells/microL) | 2.7                  | -     | 2.2               | -     | 2.0               |
| Platelet counts (cells/mL)         | $1.7 \times 10^3$    | -     | $1.6 \times 10^3$ | -     | $1.4 \times 10^3$ |
| TWBC (cells/cumm)                  | 9700                 | -     | 17000             | 13000 | 14000             |
| Neutrophils (%)                    | 67                   | -     | 68                | -     | 56                |
| Lymphocytes (%)                    | 30                   | -     | 27                | -     | 32                |
| Esinophils (%)                     | 3                    | -     | 5                 | -     | 2                 |
| RBS (mg/dl)                        | 148                  | 86    | 137               | 128   | 102               |
| FBS (mg/dl)                        | 124                  | 98    | 96                | 109   | 97                |
| HbA1c (%)                          | 6.2                  | -     | -                 | -     | -                 |
| Blood urea (mgs%)                  | 18                   | -     | 20                | -     | 26                |
| Serum Creatinine (mg/dL)           | 0.9                  | -     | 1.1               | -     | 1.3               |
| Serum Procalcitonin (ProCT) ng/mL  | 0.02                 | -     | -                 | 25.54 | -                 |

Treatment was given based on the symptoms, severity of the condition and laboratory investigations. For first three days 2-pint PRBC/day were transfused and 1 pint on the 4<sup>th</sup> day but hemoglobin levels were not improved. Repeat ProCT was highly positive on the 4<sup>th</sup> day of admission for suspected sepsis. The antibiotic-resistant test was done and intravenous meropenem 500 mg twice daily has started as per the resistance reports. At fifth day afternoon, patient's dyspnoea has worsened suddenly and while shifting to Intensive care unit, he succumbed.

## DISCUSSION

Metformin is the drug widely used to treat T2DM and found to be safe as first-line therapy with lifestyle modifications (Kumthekar and Gidwani, 2012). It is also useful in polycystic ovary syndrome (PCOS) and insulin resistance conditions with the positive effect on vascular protection, weight loss and carbohydrate metabolism. Vitamin B12 deficiency is the detrimental effect of metformin processed by malabsorption of vitamin B12 (Liu *et al.*, 2014).

Almost 30% patients develop vitamin B12 deficiency on long-term metformin therapy. Longer duration of metformin therapy and dose are the factors associated with metformin-induced vitamin B12 deficiency. Increasing the dose of metformin to 1 g/day increases the twofold higher risk of VitB12 deficiency where dose increment to 2 g/day increases the risk fourfold. Long-term use of metformin (3–5 years) can decrease the VitB12 levels by 30–50% (Kang *et al.*, 2014; Singh and Baheti, 2016; Aroda *et al.*, 2016). It leads to metformin-induced neuropathy (Ting *et al.*, 2006).

The exact mechanism of VitB12 deficiency is controversial. Adopted mechanism shows the slow gut mobility, stimulation of bacterial overgrowth and the increased consumption of VitB12 by bacteria. It can alter the level of intrinsic factor which could affect vitamin B12 absorption adversely. The metformin may also inhibit Calcium-dependent absorption of the vitamin B12. Metformin also inhibits the intrinsic factor complex at the terminal ileum (Kumthekar and Gidwani, 2012; Jager *et al.*, 2010). Metformin also contributes to glucose-6-phosphate dehydrogenase (G6PD) mediated hemolysis (Kirkiz *et al.*, 2013; Meir *et al.*, 2003).

The National Health and Nutrition Examination Survey 1999–2006, noticed that the 6% patients had developed VitB12 in T2DM patients taking metformin. This survey and Institute of Medicine recommended the administration of VitB12 at 2.4 micrograms/day for continuation; general multivitamins are not sufficient to prevent the crisis (Reinstatler *et al.*, 2012). There are no specific guidelines about the screening of metformin-induced VitB12 deficiency, but few studies and health organizations recommend the VitB12 routine screening before and after metformin use. Serum methylmalonic acid (MMA) and homocysteine levels screening also considerable in T2DM patients with borderline VitB12 (Singh and Baheti, 2016; Kibirige and Mwebaze, 2013).

Sepsis can change the mechanical and functional properties of red blood cells (RBCs). It alters the oxygen-carrying capacity of RBCs and rheology of microcirculation. Other blood components including platelets can also lose their functional capabilities by an alteration in erythron. It prevents the

improvement in Hb and PRBCs levels inspite transfusion (Goyette *et al.*, 2004). Transfusion-related acute lung injury (TRALI), haemolytic transfusion reactions and transfusion-associated circulatory overload (TACO) are the transfusion complications occurs acutely within 6 h to 72 h. In this case, delayed reactions or transfusion-related worsening of infection is suspected (Sadaka, 2013).

## CONCLUSION

Long-term use of metformin can cause the severe VitB12 and anemia. Sepsis or infections can even worsen the condition by transfusion failure mechanism. This case is not criticising the efficacy and better safety profile of metformin, but the clinicians and patients should be aware of the screening, duration of therapy and complications related to metformin use which can be life-threatening or fatal. Proper care of wounds, diabetic foot and an early visit to clinician can prevent that kind of situations.

## INFORMED CONSENT

Written Informed consent was taken from the patient before examination and publication.

## CONFLICT OF INTEREST

There are no conflicts of interest.

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