

## THE ONSET OF BIERMER ANEMIA IN PATIENTS WITH TYPE II DIABETES MELLITUS TREATED WITH METFORMIN

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**ABSTRACT.** Management of type 2 diabetes mellitus (DZ2) requires aggressive treatment to achieve the proposed glycemic and cardiovascular goals and to reduce the incidence of risk factors. Metformin, an old and widely accepted first-line agent, stands out not only for its anti-hyperglycaemic properties, but also for its effects outside glycemic control, such as improving endothelial dysfunction, hemostasis and oxidative stress, insulin resistance, redistribution of adipose tissue and the very important role in the vitamin B12 economy and balance within the human body. This retrospective study was performed in Arad County Clinical Emergency Hospital - Hematology Section over 351 patients (aged 18-75 years) diagnosed with type 2 diabetes (termed Lot DZ) admitted to the Arad Hematology Clinic from 2013 to 2015, with a duration of diabetes mellitus of about 1-15 years. The study found that treatment with metformin in patients diagnosed with type II diabetes in combination with cyanobalamin treatment resulted in favorable outcomes, reducing the symptoms of Biermer anemia.

**KEYWORDS:** *Diabetes, Metformin, vitamin B12, therapy, biermer anemia*

### INTRODUCTION

Metformin, which belongs to the biguanide class, is one of the most generally used oral hypoglycemic agents. Metformin is the only oral anti-diabetic agent associated with improvements in cardiovascular morbidity and mortality and is the cornerstone of medical therapy with lifestyle modification in most patients with diabetes. B12 deficiency has been recognized many years ago as an important side effect in diabetic patients who take metformin for more than 5-10 years [1]. Vitamin B-12 and folate coenzymes are required for thymidylate and purine synthesis; their deficiency results in altered DNA (Deoxyribonucleic acid) synthesis. In vitamin B-12 deficiency and folic acid deficiency, the defect in DNA synthesis affects other rapidly dividing cells as well, which may be manifested as glossitis, skin changes, and flattening of intestinal villi.

The World Health Organization defines anemia as a hemoglobin concentration of <13 g/dl in men and 12 g/dl in women. If we add an average cell volume (MCV) greater than 100 fL, we can address the discussion on macrocytic anemia.

The most widely recognized cause of macrocytic anemia is considered to be megaloblastic anemia, which is the result of an impaired synthesis of DNA. Although DNA synthesis is impaired, RNA synthesis is unaffected. This aspect is leading to a buildup of cytoplasmic components in a slowly dividing cell. This results in a larger-than-normal cell. The nuclear chromatin of these cells also has an altered appearance. [1-5]

The etiology of red blood cells frailty in diabetes patients is multifactorial and incorporates aggravation, different insufficiencies, accompanying immune system illnesses, drugs, and hormonal changes notwithstanding renal dysfunction.

The clinical presentation symptoms of macrocytosis to diabetes patients are attributable either to the anemia itself or to the underlying condition causing the anemia. They may include the following:

- Dyspnea – This is a consequence of anemia; in acute or severe anemia, the volume of hemoglobin in the blood is inadequate to provide appropriate oxygenation of the tissues
- Headache – This is a symptom of anemia due to decreased oxygenation of the tissues
- Fatigue – This may be attributed to underlying disease, if present, or to inadequate blood volume
- Sore tongue – This may reflect glossitis or atrophy of the tongue, which are common findings in folate and vitamin B-12 deficiencies[15]
- Diarrhea or other gastrointestinal symptoms – These may be present in patients with tropical or celiac sprue; sprue may cause folate or vitamin B-12 deficiencies[16]
- Paresthesia or gait disturbances – These suggest vitamin B-12 deficiency

Vitamin B12 deficiency has been recognized since the past as an important side effect in patients with diabetes who are receiving metformin over a period of 5-10 years [18]. Vitamin B12 and folate

coenzymes are required for the synthesis of purines and thymidylate; their deficiency leads to a faulty synthesis of DNA. In the deficiency of vitamin B12 and folic acid, the defect in DNA synthesis affects rapidly dividing cells; Clinically, it can also manifest with glossitis, skin changes and flatulence of intestinal villitis.[20-23]

A significant number of diabetic patients are not treated with metformin alone for glycemic control; there have however been few studies on the effect of hypoglycaemic agents with metformin on vitamin B12 deficiency. [23]

Metformin is the most prescribed medicine used to treat diabetes in the world (usually type 2 diabetes). Its efficacy is equal to or greater than many other available medicines and has an excellent safety profile for most individuals. However, over the last ten to fifteen years, the question arises as to whether metformin causes a vitamin B12 deficiency in those taking this drug for long periods of time.

It should be borne in mind that vitamin B12 deficiency leads not only to megaloblastic anemia and neuropsychiatric disorders, but also has deleterious effects on the health of the cardiovascular system due to iatrogenic hyperhomocysteinemia. [25-31]

## MATERIALS AND METHOD

We conducted a retrospective study using data from patients admitted to the Arad County Emergency Clinical Hospital, hematology, during 2013-2015.

Patients were clinically and paraclinically examined by blood counts (erythrocyte count, hemoglobin count), serum cobalamin, Hb A1c, fasting blood glucose, body mass index (BMI), and anamnestic personal history (other associated diseases), duration of treatment with metformin, duration of type II diabetes (1-5 years), diagnosis with berry anemia or other type, age, sex, consumption of toxic substances.

Exclusion criteria were: pregnant women, neoplastic patients, patients with hepatic, renal or cardiac insufficiency, patients with vitamin B12 deficiency anemia known prior to Metformin.

The diagnosis of anemia was highlighted with the help of blood counts and other adjacent functional explorations. [15-18]. To determine the influence of Metformin on the prevalence of Biermer anemia, a study was conducted on 139 diabetic patients who received Metformin alone or in combination with other oral antidiabetic agents.

Over 50% of patients had a metformin duration of 2-3 years (51.08%), and in over 45% of patients the dose was 1000-2000 mg / day (45.32%) .

Metformin was administered in the majority of patients as monotherapy (55.40%), with triple therapy being given only 5.76%.

The 351 cases were structured in 3 sublots:

- DZMet Lot - includes type 2 diabetic patients who received Metformin treatment - 139 cases
- DZFMet Lot - includes type 2 diabetic patients who received oral antidiabetic therapy, including Metformin - 114 cases

- Lot DZIns - includes type 2 diabetic patients who did not receive Metformin treatment - 98 cases

We compared the three groups according to BMI: underweight, normoponderal and obesity. They have also been subdivided into subgroups according to gender, age, duration of treatment with Metformin, metabolic control, and associated pathologies.

According to laboratory data, patients with good metabolic control were overweight and obese, whereas those underweight and over 60 years of age had metabolic imbalances.

These were patients requiring emergency treatment with a low degree of absorption at the intestinal level due to age.

## RESULTS

Women (61.15%, 60.53% and 57.14% respectively) predominate in all three subgroups, women / men ratio being 1.6: 1, 1.5: 1 and 1.3 :1. There are no significant differences between the three groups in terms of sex distribution ( $p = 0.445$ ).

There are no significant differences between the three age groups ( $p = 0.943$ ), the median age being 54.63 years in the Metformin group, 54.95 years in the group without Metformin and 56.65 years in the group with diabetic insulinoneceptors.

Most patients in the 3 sub-classes came from urban areas (51.80%, 52.63% and 50.00% respectively), with the urban / rural ratio being approximately 1.1: 1. There are no significant differences between the three groups in terms of environmental distribution ( $p = 0.816$ ).

Daily consumption of alcohol is recognized by a relatively small percentage of patients (between 10.07% in the Metformin group and 12.24% in the insulin group). Also, smokers represent only 7.91% of the Metformin group and 6.12% in the insulin group, the differences being insignificant.

In both the batch and the 3 subgroups, about 8% of patients work or worked in a toxic environment (7.91%, 7.89% and 8.16% respectively).

Normoponderal patients are also the majority in all three sublots (51.08%, 50.88% and 54.08% respectively) ( $p = 0.646$ ). However, overweight and obesity accounts for approximately 40% of the total of the three groups (41.73%, 42.11% and 38.78% respectively).

In the 3 sub-classes, the heredo-collateral history was mainly in the form of cardiovascular disease (24.46%, 23.68% and 24.49%, respectively). Diabetes mellitus was found in AHC in percent between 6.14% in the ADO group and 7.19% in the Metformin group.

In the three subgroups, the most common conditions were cardiovascular (61.87%, 64.91% and 56.12%, respectively). In the group of other conditions were found diseases of the osteoarticular apparatus, thyroid and psychiatric disorders (especially depression of low or medium intensity).

In the two oral hypoglycemic subplot, where the duration of diabetes evolution was 1-5 years, the mean was 3.08 years in the Metformin group and 3.39

years in the non-metformin group, while in the group with mean insulin was 8.46 years, with the duration being between 6-15 years.

Metabolic control, assessed with HbA1c, performed in all patients in the three groups.

In the Metformin group, good and very good metabolic control was recorded in 73.38% of patients, in the non-metformin group at 77.20% and 75.51% in the insulin group ( $p = 0.363$ ).

Over 50% of patients had a metformin treatment duration of 2-3 years (51.08%).

Over 45% of diabetic patients treated with Metformin received a dose of 1000-2000 mg / day (45.32%) and 33.09% daily dose was 33.09%.

Unbalanced / very unbalanced metabolic balance was encountered particularly in patients with respiratory diseases (31.03%), cardiovascular (26.51%) and hepatic (21.95%).

## DISCUSSIONS AND CONCLUSIONS

The present study had three main objectives: to determine the onset of Biermer anemia in patients with diabetes who have been treated with metformin.

A clinically more practical approach would be to administer each patient treated with metformin with an annual injection of 1000 micrograms of vitamin B12. This is sufficient to cover the needs of vitamin B12 for at least one year. An alternative therapy would be the prophylactic administration of calcium carbonate (1.2 grams per day), which could correct the enteral deficiency associated with metformin therapy [1,3,4,18-20,26-28].

There were no significant differences between the three age groups ( $p = 0.943$ ), the mean age being 54.63 years in the Metformin group, 54.95 years in the group without Metformin and 56.65 years in the batch with diabetic insulin requiring patients..

Patients with increased BMI, obesity or overweight, according to laboratory data had better metabolic control, whereas those underweight and over 60 years of age had metabolic imbalances.

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