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METFORMIN VS NO METFORMIN DIABETES TREATMENT FOR PATIENTS WITH CLINICAL ANEMIA

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ABSTRACT. 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). This prospective study was performed in Arad County Clinical Emergency Hospital - Hematology Section over 131 patients (aged 18-75 years) diagnosed with type 2 diabetes (termed Lot DZ) admitted to the Arad Hematology Clinic from 2014 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.
KEY WORDS*: Diabetes, Metformin, therapy, anemia*

INTRODUCTION

In normal individuals, fasting plasma glucose levels range from about 60 to 100 mg/dL (3.3 to 5.6 mmol/L) [1]. In patients with diabetes mellitus, insulin deficiency or insulin resistance leads to a state of hyperglycemia. Galega officinalis (goat's rue or French lilac) was used to treat diabetes in medieval Europe. The active ingredient, guanidine, was used to synthesize other antidiabetic agents in the 1920s [2], and the biguanide hypoglycemic agents phenformin and metformin became available for clinical use in the 1950s.Two classes of oral hypoglycemic drugs directly improve insulin action: biguanides (only metformin is currently available) and thiazolidinediones (TZDs).

In the absence of contraindications, metformin is considered the first choice for oral treatment of type 2 diabetes (table 1). A 2006 consensus statement from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), updated regularly, proposed that metformin therapy (in the absence of contraindications) be initiated, concurrent with lifestyle intervention, at the time of diabetes diagnosis [1-6,20].

Metformin typically lowers fasting blood glucose concentrations by approximately 20 percent and A1C by 1.5 percent, a response similar to that achieved with a sulfonylurea [10,11,26-28]. The United States Multicenter Metformin Study Group, for example, randomly assigned obese patients with type 2 diabetes who were inadequately controlled on diet alone to either metformin or placebo [29]. After 29 weeks, the mean A1C concentration was 7.1 percent in the metformin group as compared with 8.6 percent in the placebo group.

Regarding combination therapy, combinations of drugs are often necessary to achieve optimal glycemic control. Metformin can be given in combination with sulfonylureas, insulin, glinides, alpha-glucosidase inhibitors, thiazolidinediones (TZDs), sodium-glucose cotransporter 2 (SGLT2) inhibitors, glucagon-like peptide-1 (GLP-1) agonists, and dipeptidyl peptidase-4 (DPP-4) inhibitors. In meta-analyses of placebo-controlled trials evaluating different drugs (sulfonylureas, TZDs, meglitinides, alpha-glucosidase inhibitors, GLP-1 agonists, DPP-4 inhibitors) as add-on therapy to metformin, reductions in A1C with different classes of drugs ranged from 0.42 to 1.0 percentage points [30,31]. Combination therapy is discussed in detail in separately.)

Macrocytosis is a descriptive term for red blood cell (RBC) size larger than the normal range. It may be caused by abnormalities of RBC production in the bone marrow, altered RBC membrane composition, or an increase in the percentage of reticulocytes, which are larger than mature RBCs. This topic discusses causes of macrocytosis and macrocytic anemia. Additional topics discuss the following:

- ●Microcytosis/microcytic anemia
- ●General anemia evaluation
  - •Child
  - •Adult
- ●Vitamin B12 and folate deficiency – (See "Clinical manifestations and diagnosis of vitamin B12 and folate deficiency".)
- ●Myelodysplastic syndromes

●Alcohol-induced anemia

Macrocytosis refers to red blood cells (RBCs) larger than usual. It is strictly a morphologic term and does not imply a specific pathophysiology. Macrocytosis can be documented using the mean corpuscular volume (MCV; also called mean cell volume) from an automated hematology instrument, measured in femtoliters (fL; 10-15 liter) or by observing larger-than-normal RBCs on the peripheral blood smear.

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.

Metformin reduces intestinal absorption of vitamin B12 in up to 30 percent of patients and lowers serum vitamin B12 concentrations in 5 to 10 percent but only rarely causes megaloblastic anemia [11,12]. In some patients with vitamin B12 deficiency, peripheral neuropathy may precede the development of megaloblastic anemia [13]. The dose and duration of use of metformin correlates with the risk of vitamin B12 deficiency [12,14]. In one study, this reduction appeared to be due to poor absorption of B12 in the ileum and was corrected by administration of oral calcium carbonate (1.2 g daily) [15]. In another study, supplementation with a daily multivitamin was associated with a lower prevalence of B12 deficiency [16]

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.

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 prospective study using data from 131 patients admitted to the Arad County Emergency Clinical Hospital, hematology, during 2014-2016. All studied patients admitted to the hematology department were previous diagnosed with anemia.

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 or no metformin treatment 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 (53.09%), and in over 45% of patients the dose was 1000-2000 mg / day (48.21%) .

Metformin was administered in the majority of patients as monotherapy (59.30%), with triple therapy being given only 4.36%.

The 131 cases were structured in 3 sublots:

- DZMet Lot - includes type 2 diabetic patients who received only Metformin treatment - 78 cases

- DZFMet Lot - includes type 2 diabetic patients who received oral antidiabetic therapy, including Metformin - 32 cases

- Lot DZIns - includes type 2 diabetic patients who did not receive Metformin treatment - 21 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.

RESULTS

Women (58.13%, 61.23% and 58.12% 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 ($p = 0.401$).

There are no significant differences between the three age groups ($p = 0.833$), the median age being 53.24 years in the Metformin group, 51.12 years in the group without Metformin and 57.35 years in the group with diabetic insulinoneceptors.

Most patients in the 3 sub-classes came from urban areas (50.80%, 51.23% and 52.00% 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 ($p = 0.783$).

Daily consumption of alcohol is recognized by a relatively small percentage of patients (between 9.12% in the Metformin group and 14.44% in the insulin group). Also, smokers represent 9.91% of the Metformin group and 4.12% in the insulin group, the differences being insignificant.

In both the batch and the 3 subgroups, about 11% of patients work or worked in a toxic environment (10.11%, 9.83% and 9.54% respectively).

Normoponderal patients are also the majority in all three sublots (53.18%, 52.28% and 53.08% respectively) ($p = 0.534$). However, overweight and obesity accounts for approximately 46% of the total of the three groups (46.23%, 44.41% and 39.28% respectively).

In the 3 sub-classes, the heredo-collateral history was mainly in the form of cardiovascular disease (21.16%, 25.78% and 26.34%, respectively). Diabetes mellitus was found in AHC in percent between 7.14% in the ADO group and 9.19% in the Metformin group.

In the three subgroups, the most common conditions were cardiovascular (78.21%, 71.21% and 52.31%, 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 sublot, where the duration of diabetes evolution was 1-5 years, the mean was 3.2 years in the Metformin group and 3.8 years in the non-metformin group, while in the group with mean insulin was 8.7 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 78.28% of patients, in the non-metformin group at 79.80% and 76.53% in the insulin group ($p = 0.289$).

Over 50% of patients had a metformin treatment duration of 2-3 years (51.17%).

Over 45% of diabetic patients treated with Metformin received a dose of 1000-2000 mg / day (47.24%) and 37.10% daily dose was 37.19%.

Unbalanced / very unbalanced metabolic balance was encountered particularly in patients with respiratory diseases (32.13%), cardiovascular (27.51%) and hepatic (22.45%).

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.

Initial treatment of patients with type 2 diabetes mellitus includes education, with emphasis on lifestyle changes including diet, exercise, and weight reduction when appropriate. In the absence of specific contraindications, metformin is considered initial pharmacologic therapy for most patients with type 2 diabetes because of glycemic efficacy, absence of weight gain and hypoglycemia, general tolerability, and favorable cost [2,3,23-25]. It can be initiated at the time of diabetes diagnosis, along with consultation for lifestyle intervention. For highly motivated patients with glycated hemoglobin (A1C) near target (<7.5 percent), a three- to six-month trial of lifestyle modification before initiating metformin is reasonable.

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..

For patients taking metformin, we need measure A1C every three to six months, serum creatinine annually, and hemoglobin, hematocrit, and red cell indices at diagnosis and at other times if the patient develops symptoms suggestive of anemia, neuropathy, or deteriorating renal function.

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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