

Mini review Metformin toxicity Mezgebu Legesse Habte.

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Abstract

One of the widely used and frequently prescribed oral anti-hyperglycemic drugs is metformin. It is a family of biguanide and used to regulate hyperglycemic condition through inhibition of hepatic glycogenolysis and gluconeogenesis. In addition, metformin enhances glucose uptake by peripheral tissue in type 2 diabetes. Several studies showed that metformin is safe and well tolerated anti-hyperglycemic drug throughout the world. In contrast, there are reports that indicate metformin induces toxicity. One common and serious mechanism by which metformin induces toxicity is initiation of lactic acidosis. According to different studies, metformin induced acidosis become fatal especially when higher dose is taken and the patients have other health problem like kidney and lung diseases. Metformin also inhibits mitochondrial electron transport chain by blocking complex-I and leads to mitochondrial poisoning. Type 2 diabetic patients who use metformin for a long period of time have high chance to experience anemia and neurological damage due to metformin induced vitamin B12 deficiency. To reduce metformin induced poisoning there are guidelines, which all patients and physicians need to follow. Before starting metformin treatment, patients should have to perform vital organ function tests like kidney and liver function test, and measure serum vitamin B12 level. In addition, lower dose of metformin is recommended at the beginning with vitamin B12 supplement. Once intoxication happened, immediate management and treatment must be given to reduce severe complications and mortality rate.

Keywords: Anemia, lactic Acidosis, Metformin, Poisoning, Toxicity, Vitamin B12.

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Introduction

The Metformin is a family of biguanide and the first choice of anti-hyperglycaemic drug especially for treatment of type 2 diabetes mellitus. The effect of metformin is similar in all age groups and both sexes. It has glucose lowering and anti-inflammatory effects thereby significantly reduce the risk of cardiovascular disease and all cases of mortality. A number of studies confirmed that metformin is effective in regulating hyperglycaemic condition and have ant-oxidant properties with minimum side effects. Metformin significantly inhibits hepatic gluconeogenesis and glycogenolysis, appetite and of intestinal carbohydrate absorption. In addition, it increases glucose uptake by peripheral tissue cells. One of the special benefits of preferring metformin is that it is safe to combine with other hypoglycaemic drugs. Similarly, metformin can give augmented benefit with diet and exercise. Relatively low cost and minimum chance of getting weight gain gives additional benefit to the users [1-3].

Recent studies explained that metformin has profound effect in treating different types of cancer, obesity and other diseases like liver, brain and kidney problems. According to different studies and clinical trials, metformin plays a great role in regulating metabolic disorders and its effect is dose dependent [1]. Study done by Bostrom B. et al. found that metformin is safe and effective for treatments of metabolic disorder induced by hyperglycemia [4]. As any other drug, metformin has its own side effect and can induce toxicity. Heartburn, stomach pain, nausea or vomiting, bloating, gas production, diarrhea,

constipation, weight loss, headache, unpleasant metallic taste in mouth and others are the most common side effects of metformin especially at first use. According to several studies lactic acidosis, which is characterized by extreme tiredness, weakness, decreased appetite, nausea, vomiting, trouble breathing, dizziness, and lightheadedness is rare but serious metformin induced intoxications. In addition, metformin can induce serious anemia and hypoglycemia conditions, which could be fatal especially when taken at the first time [5, 6]. One important mechanism by which metformin induces toxicity is lactic acidosis. Metformin can downregulate mitochondrial respiration event that disrupts lactate production or clearance from the body. The disturbed blood pH as a result of lactate accumulation may lead to acute kidney injury, hepatic failure, respiratory failure and circulatory shock and finally death. These conditions are commonly seen among elderly patients [7, 8].

Biochemical mechanisms of metformin toxicity

Metformin is a family of biguanide oral hypoglycemic drugs mainly used for treatment of non-insulin dependent diabetes mellitus, and it gives best result when taken with life style modification. Metformin helps manage hyperglycemic condition and its primary target is mitochondria, in which it inhibits complex I and results in blockage of cAMP and protein kinase A signaling in response to glucagon secretion. Also, metformin activates 5' AMP activated protein kinase to lower blood glucose. According to different studies, energy stress as a result of metformin usage is used to control tumorigenesis.

With these function, metformin intoxications can cause fatal complications like severe lactic acidosis, haemolytic anemia, pancreatitis and other organ damage. To reduce the effect metformin induced intoxications, immediate biochemical diagnosis and follow-up is recommended [9-11].

Lactic acidosis

One of the common and serious challenges raised as results of metformin usage is lactate accumulation in the blood, which leads to acidosis. A number of studies showed that lactic acidosis from metformin treatments is most likely due to inhibition of gluconeogenesis by blocking pyruvate carboxylase enzyme. Pyruvate carboxylase catalyzes the first step of gluconeogenesis, which converts pyruvate to oxaloacetate. Metformin blocks this enzyme and leads to accumulation of lactic acid in the blood [12].

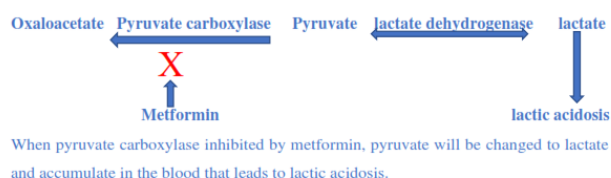


Figure 1. Biochemical mechanism how metformin induced lactic acidosis

Metformin induced lactic acidosis is highly associated with the higher dose and chronic diseases like kidney and liver problems. Several studies indicated that voluntary metformin intoxication resulting in the highest metformin concentration ever described was the most common cause of lactic acidosis [13]. According to the case report done by Silvestre J in 2007, incidence of metformin induced lactic acidosis was 0.05 per 1000 patients [14]. Other literatures that indicate metformin associated lactic acidosis reported more than 6 per 100000 patients who were on metformin drug [15]. According to a national 10-year survey and a systematic literature review done by F. RENDA in Italy in 2013, metformin is associated lactic acidosis as high as 18.2% of all drug adverse reactions with mortality rate of 25.4% [16].

Anemia

Anemia is defined as a low number or defective form of red blood cells circulating in the blood that result in tissue hypoxia. There are different types of anemia that have their own causes. Different risk factors play a great role in developments of anemia. For insurance, usage of drug like metformin is very important risk factor that induces anemia. Different studies showed that metformin use is associated with early risk of anemia in individuals with type 2 diabetes and the mechanism how it happens is not fully understood but interference with vitamin B12 metabolism is the one which is confirmed. Individual who had taken higher dose of metformin for longer period of time were highly affected with vitamin B12 deficiency [17]. A case report presented by Albai O et al in 2020 showed that type 2 diabetes mellitus patient treated with metformin was suffered from vitamin B12 deficiency and

suggested that regular supplement of vitamin B12 should be given in the case of patients with Type 2 diabetes mellitus treated with metformin [18]. Similarly, a cohort study done by Aroda VR. et al in 2016 explained that anemia resulted from vitamin B 12 deficiency was highly prevalent among patients taking metformin for a long period of time. Accordingly, periodical assessment of serum vitamin B12 levels in metformin-treated patients should be considered and it is really helpful to patients [19]. Vitamin B12 [cobalamin] is one of nutritionally important water-soluble vitamin mainly obtained from ingestion of fish, meat, dairy products, fortified cereals and fabricated supplements. Vitamin B12 plays crucial in neurologic function, red blood cell production and maturation, DNA synthesis and acts as cofactor for enzymes involved in essential reactions. As a result, deficiency of this vitamin affects all the above biological activity. Risk factor like gastric disorder, defect in intrinsic factor, unbalanced diet, prolonged use of drugs is highly associated vitamin B12 deficiency. A number of case control, cohort and other studies indicated that metformin used for more than one year cause vitamin B12 deficiency. Metformin affects intrinsic factors that are involved in vitamin B12 absorption from intestine; mainly metformin-induced alterations of calcium status which have effect on vitamin B12 and receptor interaction in the intestinal cell [18, 20]. In addition, metformin can affect gastric motility that leads to bacterial overgrowth, which in turn results in vitamin B12 consumption by the bacteria. Another idea about effect of metformin on vitamin B12 is its effect on bile salt activity that can chelate calcium and it can disturb the vitamin B12 absorption [21].

Hepatotoxicity

Liver is the important and vital organ, which plays a vital role in metabolism of endogenous and exogenous molecules and it regulates most biochemical levels in the blood. The enzymes in the liver cell metabolize exogenous drugs in a number of ways [22]. A drug induced liver toxicity is uncommon but fatal complication and it could be intrinsic and idiosyncratic. Drugs and their metabolites can affect the normal function and integrity of liver cell. According to some literatures, metformin does not undergo hepatic metabolism and metformin-induced hepatotoxicity is not common, rather it is given to treat different forms of liver diseases [23]. number of cases studies and clinical trials that reviled metformin is safe but, metformin can induce acute and chronic liver toxicity. A highly controlled case study reported by Miralles-Linares F. et al showed that patient who had taken metformin [1700 mg/day for 6 weeks] presented with symptom of liver disease and clinical laboratory result showed as hepatocellular injury happened [24]. A similar case report done by Kutoh E. in 2005 indicated that elderly type 2 diabetic patients taken metformin [500 mg/day for three week] presented with symptom of hepatotoxicity which could be hepatocellular and cholestatic [25]. Hepatotoxicity effect of metformin is also supported by another study done in 2013 that suggested regular and periodic physical and laboratory examination of liver is required for patients who are taking metformin [26].

The mechanism how metformin induces hepatotoxicity is not fully explained yet. According to different studies, lactic acidosis as a result of metformin may be one factor for hepatocellular death. In addition, metformin can inhibit fat oxidation that leads to fatty liver [27].

Nephropathy

Kidney is a vital organ that excretes drug and maintains the whole-body biochemical homeostasis. Kidney diseases which could be acute or chronic are conditions where kidneys are damaged and can't filter blood in the way they should. The risk factors like diabetes, hypertension, chronic alcohol consumption, etc. are highly associated with kidney diseases. In addition, different drugs induce kidney diseases, which can increase morbidity and healthcare utilization. According to some studies, some drugs seriously affect kidney function and can cause nephropathy [28]. Direct initiations of toxicity or immunological reactions are the most common mechanisms by which drugs induce kidney disease [29]. Metformin is one of the most frequently prescribed anti-hyperglycemic drugs throughout the world population, and is not metabolized and is excreted in the urine. The principal route of metformin elimination is active tubular secretion in the kidney [30]. Heaps of studies explained that metformin is safe for kidney function, even some studies showed that metformin is helpful for better improvements of chronic kidney disease patients [31]. In contrast, there are different studies that showed as metformin induce kidney disease. A prospective observational study of metformin-associated acute kidney injury cases for four years done by Arroyo D et al. showed that acute kidney injury is common and serious complication among type 2 diabetes patients who were on metformin drug [32]. Another study done by Hsu WH. et al in 2018 showed that discontinuation of metformin improves estimated glomerular filtration rate than continuously metformin used groups and concluded that metformin adversely affects kidney function [33]. Metformin induced acute kidney injury become serious with higher dose and happens concomitantly with lactic acidosis [34].

Neuropathy

One important system that has great role in regulating and coordinating normal biological activity is nervous system. A neurological disease is any disorder of the nervous system which could be structural, biochemical or electrical abnormalities. Now a day, there are number of nerve diseases and damages are identified with different signs and symptoms. Risk factors like compression/trauma, cancer, autoimmune diseases, drug side effects, toxic substances and others are responsible causes for different types of nerve diseases [35, 36]. Drug side effect is one of the common risk factors for different types of neurodegenerative disorders [37]. According to literature, metformin is first choice drug for type 2 diabetes and it is safe [38]. But resent and updated studies tried to explain encountered toxic effect of metformin on different organs and systems. According to report done by Bell DS in 2010, vitamin B12 deficiency as a result of prolonged metformin consumption leads to different types of neuropathies [39]. Another study done by Hashem MM et al in

2020 showed that diabetic patients who were using higher dose of metformin for longer period of time suffered from cobalamin deficiency and higher level of homocysteine and methylmalonic acid which are a leading cause of diabetic peripheral neuropathy [40]. Accordingly, up to 40% of type 2 diabetic patients who are using metformin suffered from peripheral neuropathies and its route cause is assumed to be vitamin B12 deficiency.

Suggested strategies to reduce metformin toxicity

Metformin is one of the most frequently prescribed and used oral anti-hyperglycemic for type 2 diabetes patients. Even though the safety of metformin is supported by a number of studies, there are literatures that showed metformin can induce severe and fatal toxicity. Lactic acidosis, neurological toxicity, anemia and others are the most commonly occurred metformin related toxicities and now a day need special concern [15, 18, 39]. Different guidelines put strategies to reduce metformin induced toxicity before and during consumption. According to the guidelines, before starting metformin the following need to be performed; fasting glucose, hemoglobin A

C [HbA1C], kidney function, complete blood count [CBC], blood ketones bodies, liver function tests and other health information have to be performed [41]. Based on these patients' information, physician will decide who can use metformin. Accordingly, patients with stage 4 or 5 kidney disease, type 1 diabetes, prediabetes over the age of 60 and currently experiencing diabetic ketoacidosis are not allowed to take metformin [42, 43]. In addition, beginners need to start with lower dose of metformin and strictly follow the guidelines to minimize its toxicity. To reduce metformin induced neurological toxicity, patients are advised to take vitamin B12 supplements. Patients who are on long term metformin treatments need to have regular organ function tests and counsel about risk and side effect of metformin [44-46]. According to a literature, metformin induced toxicity needs immediate management and treatment. For instance, metformin induced lactic acidosis can be treated with intravenous sodium bicarbonate and decreasing the blood levels of metformin. A report done by Leonaviciute D, et al in 2018 indicated that metformin induced lactic acidosis needs prolonged intermittent hemodialysis for full recover [47]. This finding is supported by case report done by Rifkin SI et al in 2011 [48]. Several literatures confirmed that long-term usage of metformin can result in B12 deficiency and megaloblastic anemia. Based on serum level of vitamin B12, patients who are on metformin treatment have to have sufficient vitamin B12 supplement [49]. In addition, vitamin B12 supplement is used to treat metformin induced neurological disorder [50].

Conclusion

Metformin is old and still it is the best and most frequently prescribed and used oral anti-hyperglycemic drug. Metformin effectively treats hyperglycemic condition through inhibition of intestinal absorption of glucose and hepatic glycogenolysis and gluconeogenesis. In addition, metformin downregulates

blood glucose by increasing glucose uptake by peripheral tissue and insulin sensitivity. Beyond that, metformin has anti-inflammatory and anti-microbial effect. Studies clearly explained that metformin can induce serious intoxication especially when higher dose is taken. Lactic acidosis, anemia and neurological disorders are the most commonly occurred metformin related side effects. In addition, metformin can cause hepatocellular damage and nephropathy.

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