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ADVERSE DRUG REACTIONS BY METFORMIN: A SHORT REVIEW

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Abstract:

According to the most recent diabetic recommendations, metformin is the first-line treatment for type 2 diabetes. This article's goal is to provide clarification about metformin therapy and metformin associated drug adverse effect in the patients. When blood sugar levels are too high, metformin can help bring them down and let your body start using food as fuel again. Patients with type 2 diabetes have also demonstrated increased insulin binding after using metformin. Side effects with metformin are frequent but typically not fatal. The most typical complaints include stomach discomfort, bloating, exhaustion, and anorexia. About one-third of patients experience gastro-intestinal disturbances such as anorexia, nausea, abdominal pain, and diarrhoea as the most frequent side effects of metformin. In certain cases, severe diarrhoea may prevent a person from taking metformin. Long-term metformin use may interfere with vitamin B12 absorption. Lactic acidosis and vitamin B12 deficiency are the rare adverse effect associated with metformin therapy. Metformin production and buildup in saliva can have the unfavorable impact of taste disturbance. Metformin-related systemic allergic responses are rare. Although there are very few reports of cutaneous allergic responses, physicians should be aware that they do occur. metformin inhibits mitochondrial glycerophosphate dehydrogenase (mGPD), which raises the cytosolic redox state (cytosolic NADH/NAD+ ratio) and prevents lactate dehydrogenase from converting lactate to pyruvate. This leads to MALA (metformin associated lactic acidosis) in the patients. The mechanism of metformin induced vit B12 deficiency is well understood. Metformin antagonizes the calcium cation and prevents the IF-vitamin B12 complex from binding to the ileal cubilin receptor in a calcium-dependent manner, leading to malabsorption vitamin B12 absorption to the blood. In certain conditions, the precaution should be taken for metformin use. When a patient needs IV contrast agents for a diagnosis, metformin should be temporarily stopped and, in cases of severe infection, acute myocardial infarction, or an aggravation of congestive heart failure, it should be stopped.

Keywords: Metformin, Metformin adverse effect, Metformin risk, Metformin effect, Oral hypoglycemic drug.

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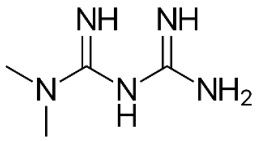
INTRODUCTION:

First-line medication for type II diabetes care is metformin, a biguanide antihyperglycemic drug. It is frequently referred to as a "insulin sensitizer" since it lowers insulin resistance and lowers plasma fasting insulin levels in a way that is clinically meaningful. First authorised in Canada in 1972, metformin was later approved by the FDA in the United States in 1995 [1]. When a person has type 2 diabetes, their body's insulin is unable to adequately transport sugar into their cells. Metformin can help lower blood sugar when it is too high and restore your body's ability to utilize food as fuel. Type 2 diabetic patients have also shown an increase in insulin binding following metformin treatment [5]. It can also be used in combination with insulin or another type of oral antidiabetic medication called a sulfonylurea [4]. It is also used in the treatment of polycystic ovary syndrome [8]. The risk of hypoglycemia associated with metformin is far less than that with sulfonyl urea. Metformin lowers FPG levels by 60 to 80 mg/dL and A1C levels by 1.5% to 2%. It also maintains its ability to lower FPG levels when they are extremely high (>300 mg/dL or >16.7 mmol/L). Metformin slightly raises high density lipoprotein (HDL) cholesterol by 2% while reducing plasma triglycerides and low-density lipoprotein (LDL) cholesterol by 8% to 15% in the body [9]. In overweight adults with type 2 diabetes, metformin dramatically decreased the incidence of stroke and all-cause mortality when compared to intensive therapy with insulin or sulfonylurea. Metformin side effects are common, although usually not life-threatening. The most common complaints are fatigue, bloating, anorexia, and abdominal pain [7]. The most common problems, which usually go away with time, are mild diarrhoea and fatigue.

Chemistry of metformin



As a biguanide with two methyl substituents at position 1, metformin belongs to the class of guanidines. Chemical name -1,1-Dimethylbiguanide.
Molecular weight-129.16 g/mol
Molecular formula- C4H11N5.
For a number of years, its structure was typically shown in an incorrect tautomeric form; however, this was fixed in 2005 [10].

Benefits of metformin.

Those without diabetes may also benefit from metformin's potential health benefits.

- Prediabetes: People with prediabetes may be able to avoid or postpone the onset of diabetes by taking metformin.
- Gestational diabetes: Blood sugar levels in pregnant women may rise, but they will return to normal after giving birth. For these women, metformin can help regulate blood sugar throughout pregnancy.
- Polycystic ovary syndrome: Women with PCOS have been administered metformin for years to aid with blood sugar elevation, menstrual management, and fertility [2].

Dosage

Table 1: Dosage of metformin [13].

Age category	Dosage form	Initial dose	Titration dose	Maximum dose
Adult	Immediate-release metformin	500 mg/daily or 850 mg/daily	500 mg/weekly or 850 mg/2 weeks	2550 mg/daily
	Extended-release metformin	500 mg/daily or 1000 mg/daily	500 mg/weekly	2000 mg/daily
Geriatrics	With caution; to start at the low end of the dosing range.			
Paediatric (>10 years old)	Immediate release	500 mg/daily	500mg/weekly	2000 mg/daily
	Extended release	Not yet established		

contraindicated in individuals with impaired kidney function; as age grows, use with caution and closely monitor renal function in the elderly [3].

Mechanism

Metformin is a multifaceted medication with several molecular mechanisms and sites of action. Metformin functions physiologically by decreasing glucose synthesis in the liver either directly or indirectly. It also increases glucose utilisation, increases GLP-1, and modifies the microbiome in the gut. Metformin works at the molecular level to inhibit the liver's mitochondrial respiratory chain, which activates AMPK and improves insulin sensitivity by affecting fat metabolism. It also lowers cAMP, which in turn decreases the production of gluconeogenic enzymes [11].

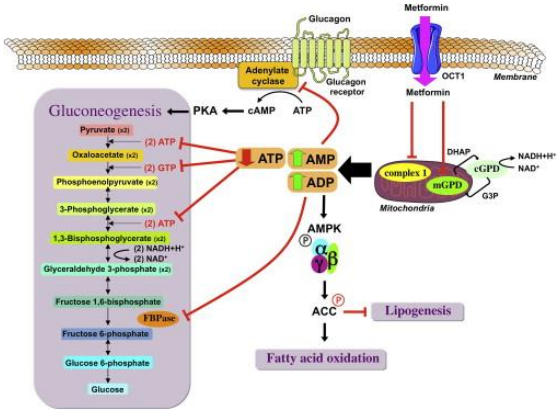


Figure 1: The molecular mechanisms underlying the inhibition of hepatic glucose output induced by metformin [12].

Reduced gluconeogenesis results from a number of factors, including decreased glycerol conversion to glucose, inhibition of mGPD contributing to an altered redox state, decreased activity of the key gluconeogenic enzyme FBPase, and an ATP deficit that limits glucose synthesis.

ADVERSE REACTIONS BY METFORMIN:

About one-third of patients experience gastro-intestinal disturbances such as anorexia, nausea, abdominal pain, and diarrhoea as the most frequent side effects of metformin [14]. Extreme diarrhoea in certain persons may make it impossible to take metformin. Prolonged usage may disrupt the absorption of vitamin B12 by the use of metformin [6]. A study shows substantial positive relationship between lactate and serum metformin levels. Blood metformin concentration and serum lactate level had a positive correlation [15].

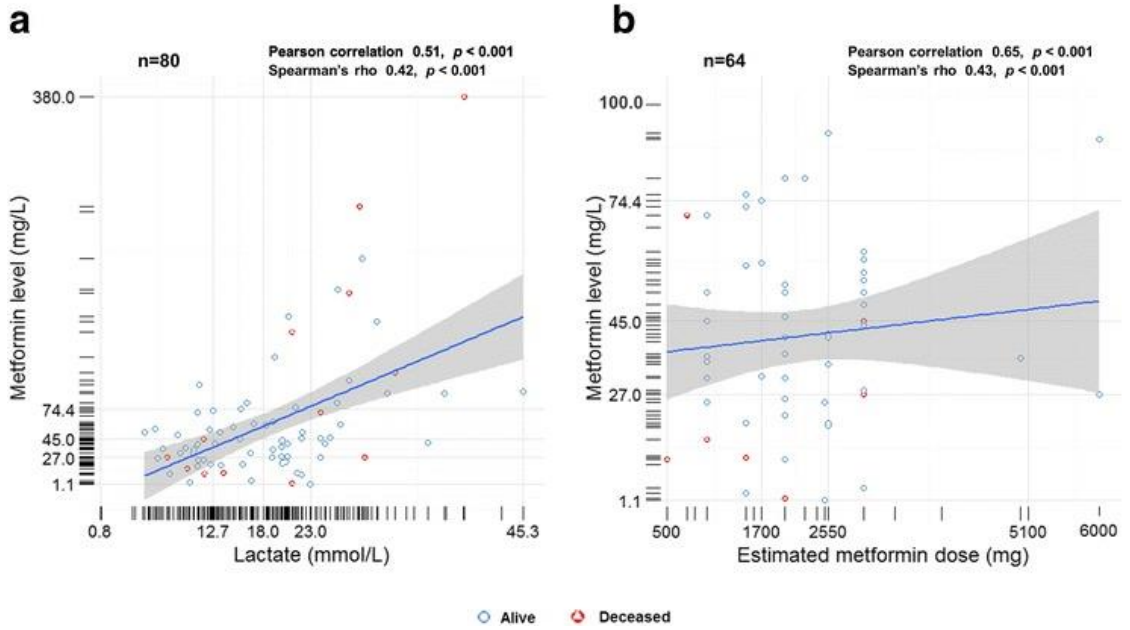


Figure 2: Serum lactate levels (a) and the anticipated metformin dosage (b) are plotted against the levels of serum metformin.

Multiple logistic regression showed that there was an associated 9% (95% CI, 2–17, p-value = 0.01) increase in MALA (metformin-associated lactic acidosis) related mortality for every unit rise in serum lactate. Studies discovered a linear correlation between serum lactate level and MALA-related mortality in the dose-response analysis, especially in the range of more than 20 mmol/L [15].

According to a recent study, metformin inhibits mitochondrial glycerophosphate dehydrogenase (mGPD), which raises the cytosolic redox state (cytosolic NADH/NAD+ ratio) and prevents lactate dehydrogenase from converting lactate to pyruvate [16]. Although, the major adverse effect associated with the metformin therapy are;

- Gastrointestinal intolerance
- Altered taste
- Fatigue
- Anorexia
- Allergic reaction
- Bloating
- Lactic acidosis
- Vitamin B12 deficiency

Lactic acidosis and vitamin B12 deficiency are the rare adverse effect associated with metformin therapy.

a) Gastrointestinal intolerance:
About 20% of individuals experience gastrointestinal side effects, which include nausea, diarrhoea, meteorism, and constipation [17][18]. Metformin boosts the anaerobic cycle's utilisation of glucose and the enterocyte's synthesis of lactate. Adverse responses may be linked to a localised increase in lactate production [19]. Scarpello et al. showed that metformin causes osmotic diarrhoea via slowing the absorption of bile acids [20].
A study by Razavi N et al. comparing individuals with Type 2 diabetes mellitus's baseline and after switching to metformin capsules, information on fasting blood glucose, haemoglobin A1c, and gastrointestinal symptoms [26].

Characteristics*	Baseline value	After receiving metformin capsule	P value
HbA1c (mg/dl)	7.0 (6.7-7.6)	6.8 (6.5-7.4)	<0.0001§
GI side effects (%)	40 (53.3)	16 (21.3)	0.001†

Table 2: Comparison of gastrointestinal symptoms, haemoglobin A1c, and fasting blood glucose in patients with Type 2 diabetes mellitus before and after switching to metformin capsules (n=75) [26].

***Data are presented as median (IQR), or n (%), where applicable, P values calculated by § Wilcoxon-signed ranks and † McNemar's test.**

b) Altered taste:
Metformin production and buildup in saliva can have the unfavourable impact of taste disturbance. According to Lee N et al., the organic cation transporter-3 (OCT3), which is in charge of metformin carriage, is highly expressed in the salivary glands and may play a role in the mechanism underlying this side effect [21].

c) Allergic reactions:
Metformin-related systemic allergic responses are rare [22] [23]. Although there are very few reports of cutaneous allergic responses, physicians should be aware that they do occur.

d) Lactic acidosis:
In a 2006 Cochrane meta-analysis examining data from 206 trials and cohort studies, no cases of lactic acidosis were discovered in either the control group or patients on metformin. Additionally, the metformin group did not have a significant increase in lactate levels, while there was a slight variation in individuals receiving biguanide versus phenformin [24]. Metformin inhibits mitochondrial glycerophosphate dehydrogenase (mGPD), which raises the cytosolic redox state (cytosolic NADH/NAD+ ratio) and stops lactate dehydrogenase from converting lactate to pyruvate, as per a recent study [16[.

e) Vitamin B12 deficiency:
In 1971, Tomkin et al. were the first to report vitamin B12 malabsorption linked to metformin [28]. According to the American Diabetes Association Guidelines, individuals with type 2 diabetes who have been using high-dose metformin (more than 2 g/day) for a prolonged period of time should have any potential vitamin B12 insufficiency evaluated [25]. Vitamin B12 levels were considerably lower in the metformin-treated group, according to a meta-analysis of 29 trials [27].

Mechanism of metformin induced vitamin B12 deficiency

Numerous theories have been put forth to explain why metformin prevents vitamin B12 from being absorbed. An early proposed mechanism involved an excess of intestinal bacteria, which caused the IF-vitamin B12 combination to attach to the bacteria instead of being

absorbed [29]. It has also been suggested that metformin decreases digestive motility, which lowers vitamin absorption [30].

According to the currently understood mechanism, metformin antagonises the calcium cation and prevents the IF-vitamin B12 complex from binding to the ileal cubilin receptor in a calcium-dependent manner [31]. The latter mechanism was strongly supported by the correction of metformin-associated vitamin B12 malabsorption by calcium supplementation. A study by Ahmed M.A et al. suggested that the hydrocarbon core of the ileal cell membrane is the target of the protonated metformin molecule, which positively charges the membrane surface and pushes the divalent calcium cations out of the way through repulsive forces. A malabsorption of the vitamin results from this displacement, which also affects the calcium-dependent binding of the IF-vitamin B12 complex to the ileal cubilin receptor [32]. This is shown in figure 3.

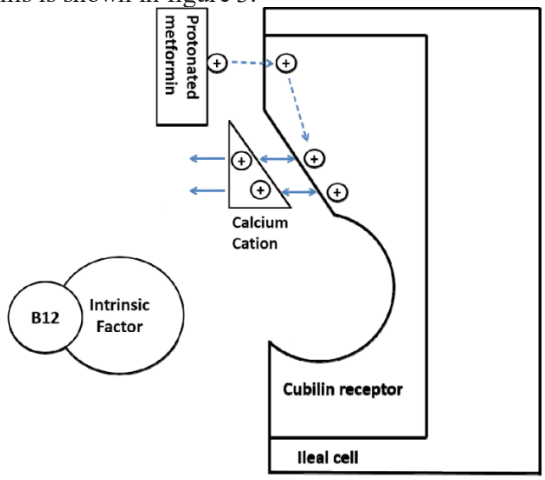


Figure 3: Mechanism of inhibition of vitamin B12 absorption by metformin [32].

Precautions of metformin use

- In cases of severe infection, acute myocardial infarction, or an aggravation of congestive heart failure, it should be stopped.
- When a patient needs IV contrast agents for a diagnosis, metformin should be temporarily stopped.
- Rarely, potentially fatal lactic acidosis has occurred [6].

CONCLUSION:

In conclusion, Metformin is a biguanide antihyperglycemic medicine used as the first line of treatment for type II diabetes. When compared to intensive therapy with insulin or sulfonylurea therapy, metformin significantly reduced the risk of stroke and all-cause mortality in overweight persons with type 2 diabetes. The most common adverse effects of metformin are gastro-intestinal disturbances, which include anorexia, nausea, abdominal pain, and diarrhoea in about one-third of patients. In certain cases, severe diarrhoea may prevent a person from taking metformin. Extended use of metformin may cause problems with vitamin B12 absorption. The metformin associated lactic acidosis (MALA) and vitamin B12 deficiency are rare in patients. Metformin boosts the anaerobic cycle's utilisation of glucose and the enterocyte's synthesis of lactate, causes lactic acidosis. Metformin-related systemic allergic responses are rare. Although there are very few reports of cutaneous allergic responses, physicians should be aware that they do occur. Also, taste disturbance is an adverse effect of metformin synthesis and accumulation in saliva.

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