



Administration of metformin in clinical medicine; an updated mini-review on current findings

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ABSTRACT

Metformin is in the biguanide class that has been considered as the treatment for insulin resistance diabetes and polycystic ovarian disease. Many mechanisms have been suggested for it such as inhibition of the mitochondrial respiratory chain and mitochondrial glycerophosphate dehydrogenase, activation of adenosine monophosphate-activated protein kinase, inhibition of glucagon-induced elevation of cyclic adenosine monophosphate with reduced activation of protein kinase A, an effect on gut microbiota and activation of adenosine monophosphate-activated protein kinase. Metformin is a suppressor for transforming growth factor- β 1 via directly binding and interact with transforming growth factor- β 1 receptor. Lactic acidosis is one of the adverse and noxious effects of metformin. Nowadays, metformin has an important role in inflammation pathways and antioxidant pathways that can prevent or decrease kidney fibrosis, cardiac remodeling in hypertensive heart disease, and cell death in cerebral ischemia, kidney crystal formation, immunological diseases and cancer. Although there has been strong evidence for the potential harm caused by metformin, several studies have shown beneficial effects for it. Hence, it is necessary to revision and modification in contraindications for prescription of this drug.

Implication for health policy/practice/research/medical education:

Metformin has an important role in inflammation and antioxidant pathways that can prevent or decrease kidney fibrosis, cardiac remodeling in hypertensive heart disease, and cell death in cerebral ischemia, kidney crystal formation, immunological diseases and cancer.

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Introduction

Metformin (1, 1-dimethylbiguanide hydrochloride) is in the biguanide class that was discovered in 1922 and introduced as a medication in 1957 (1). First, it was derived from the lilac *Gallegos officinalis* (2).

Metformin hydrochloride (Glucophage) is formed of a white to off-white crystalline compound with a molecular weight of 165.63. Metformin hydrochloride is soluble in water but is insoluble in acetone, ether and chloroform.

It has been considered as first-line therapy for insulin resistance diabetes (type 2 diabetes) as a monotherapy and combined with other medication such as pioglitazone, vildagliptin and sitagliptin (3). It does not induce hypoglycemia (4). It is also used in type 1 diabetes in conjunction with insulin therapy (5). In addition, metformin is used in the treatment of polycystic ovary syndrome (6).

Many physicians believe that metformin prescription should be stopped with the presentation of severe kidney

disease (7) or diabetic ketoacidosis state (8) but there is novel information about its beneficial effects.

There are recommendations that metformin is contraindicated in patients with renal dysfunction, abnormal creatinine clearance (9), conditions such as cardiovascular shock, septicemia and metabolic acidosis (10).

Materials and Methods

For this paper, we used a variety of sources including Web of Science, PubMed, EBSCO, Embase, Scopus and directory of open access journals (DOAJ). The search was performed by using combinations of the following key words and or their equivalents; chronic kidney disease, diabetes mellitus, hypertension, acute kidney injury, type 2 diabetes, end-stage renal disease, kidney, lactic acidosis, renal failure, metformin, nephrotoxicity, mitochondrial dysfunction, metformin-associated lactic acidosis, glucose transporter 4, adenosine monophosphate-activated

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protein kinase and antioxidants.

How does metformin act in the body?

The action mechanism of metformin is incompletely understood and many mechanisms have been suggested for it. Metformin prevents the production of glucose in the liver, reduces the amount of sugar absorbed by the intestines and improves the body's sensitivity towards insulin. Furthermore, the molecular mechanism of metformin is not fully understood (11). Researchers have been proposed the following potential mechanisms; inhibition of the mitochondrial respiratory chain and mitochondrial glycerophosphate dehydrogenase (12), activation of adenosine monophosphate-activated protein kinase (13), inhibition of glucagon-induced elevation of cyclic adenosine monophosphate with reduced activation of protein kinase A (14) and an effect on gut microbiota (15).

The drug has an inhibitory effect on the production of glucose by activation of adenosine monophosphate-activated protein kinase (AMPK) that plays an important role in the metabolism of glucose, insulin signaling, and whole body energy balance in liver cells (16). Moreover, metformin increases AMPK activity in skeletal muscle that causes glucose transporter 4 (GLUT4) placements to the plasma membrane, causing in insulin-independent glucose uptake (17).

Metformin may antagonize the action of glucagon through an effect on glucagon-like peptide-1 secretion and reduce fasting glucose levels (18).

In addition to increasing insulin sensitivity, metformin decreases insulin-induced suppression of fatty acid oxidation (19) and diminutions absorption of glucose from the gastrointestinal tract (20).

Metformin may be mediated by protein kinase C and mitogen-activated protein kinase that is a signaling molecule to involve in multiple cellular processes such as cell proliferation and cell growth (21).

Metformin is recently known as a suppressor for transforming growth factor- β_1 via directly binding and interact with transforming growth factor- β_1 receptor (22). Transforming growth factor- β_1 is involved in the progression of numerous diseases such as cardiovascular, fibrotic and immunological diseases and cancer (22).

Absorption and bioavailability

Oral metformin bioavailability is 50%–60% under fasting conditions. Peak plasma concentrations are reached within 1-3 hours of ingestion immediate-release the drug and 4-8 hours with extended-release formulations. The plasma protein binding of metformin is very small, but its volume of distribution is very high (654 ± 358 L after a single dose) and distributed to red blood cells. The steady state plasma concentrations of metformin are usually reached less than 1 $\mu\text{g/mL}$ within 24 to 48 hours. Metformin is not metabolized and cleared by tubular secretion and excreted unchanged in the urine.

The adverse and noxious effects

The adverse effect of metformin consumption is gastrointestinal irritation such as dyspepsia, nausea, vomiting, diarrhea, cramps, and increased flatulence diarrhea that occurs in up to 30% of patients (23). Symptoms of metformin overdose may be nonspecific and include malaise, abdominal pain, nausea, vomiting, myalgia and dizziness (23). The severe clinical manifestation of this poisoning is metformin-associated metabolic acidosis (MALA) with hyperlactatemia (24). Although hypoglycemia is not common event in metformin toxicity process, there are some cases that reported previously (25).

The studies have reported a reduced serum thyroid-stimulating hormone (TSH) levels at the initiation of metformin administration (26). According to another study metformin-induced TSH suppression was not associated with cardiac effects (27). However other researchers have not found significant changes in thyroid function tests and serum levels of TSH in euthyroid patients with receiving metformin (28).

Metformin-associated lactic acidosis

The overdose of this medication is commonly known to cause MALA (29). The frequency of MALA occurrence has been reported to be 0.7% in poly-pharmacy overdoses to 9.1% in mono-overdose (30).

The mortality rate of the condition has been reported to be between 3.5%-22.7% in accidental and 25%-83% in intentional overdoses in different studies. However, MALA may be considered as a very rare complication of chronic metformin therapy, with an incidence of around 5 cases per 100 000 patient-years (24).

A systematic review showed that MALA is not common (31). It is mainly caused due to suppression of the pyruvate decarboxylase enzyme (32), inhibition of gluconeogenesis in hepatic cells (33) and inhibition of plasma cell differentiation antigen (34,35).

Hyperlactatemia occurs in various diseases, but in this condition, it can be present in the absence of acidosis. Lactic acid does not produce a net increase in hydrogen ion concentration unless there is associated impairment of oxidative metabolism. Impaired oxidative metabolism leads to an increase in hydrogen ion production through the hydrolysis of adenosine triphosphate. In an animal model research, mitochondrial dysfunction and inhibition of oxygen consumption occurred due to metformin overdose. Additionally in another study, metformin inhibits both hepatic lactate uptake and conversion of lactate to glucose in isolated perfused rat liver.

Symptoms may be nonspecific and include confusion, mental status depression, hypothermia, respiratory insufficiency, hypotension and blindness. Patients may be developing renal failure or other serious comorbid conditions and need to the administration of sodium bicarbonate and further management with hemodialysis or other techniques of extracorporeal removal.

Fatalities following poisoning are rare, but may occur. A

review study did not find deaths in cases with a serum pH greater than 6.9, a peak serum lactate concentration less than 25 mmol/L or a peak serum metformin concentration less than 50 µg/mL. Moreover, serum metformin concentrations could be obtained as a diagnostic aid, but these did not correlate with the clinical condition in both the acute overdose setting and the setting of therapeutic metformin administration.

Notably, there have been millions of metformin user for many years, numerous of them with serum creatinine values nearly 1.5 mg/dL with estimated glomerular filtration rates lesser than 60 mL/min/1.73 m² who have not developed lactic acidosis.

The role of metformin in the development of MALA in the setting of acute renal failure is debated. Several experiments suggested that this drug can be nephrotoxic. A systematic review of controlled trials suggested metformin is not associated with any measurable harm in people and it may reduce mortality in comparison with other antidiabetic agents. However, according to other studies, the risks of MALA increase in patients with some conditions including kidney disorders, liver disease (for example; alcoholic fatty liver disease), lung disease and heart failure (particularly; acute congestive heart failure). A review of intentional and accidental metformin overdoses described that MALA was rare although the elderly seemed to be at greater risk. In a cohort study including cases with diabetes that developed acute renal failure, the administration of metformin was associated with MALA and worsening of renal function. When impaired kidney function is present, clearance of lactate and metformin is reduced. Hence, renal function is recommended to assess before administration of metformin and to temporarily intercept before any radiographic study with iodinated contrast agents. Moreover, it is better to measure lactate levels for patients presenting under critical conditions in an emergency department or even in a clinic to be able to recognize and treat MALA in a timely manner.

The novel beneficial effects

Although there have been a number of surveys on the potential harm caused by metformin, some studies have investigated its beneficial effects.

In addition to treatment of diabetes mellitus (36) and polycystic ovarian disease (6), metformin may prevent kidney fibrosis (37). Tubulointerstitial fibrosis is the unavoidable sequel to chronic kidney disease regardless of the primary underlying causes (38). Tubular epithelial cells, myofibroblasts and endothelial cells play important roles in this process (38). Injured tubular epithelial cells suppress fatty acid oxidation with effect on the regeneration capacity and fibrogenesis during metabolic rearrangements (39). Immune cells in kidney such as macrophages, lymphocytes, mast cells and dendritic cells mediate inflammation and immune response (40). The in-vitro and in-vivo model study showed that metformin exerts anti-fibrotic effects in aldosterone on the heart (41).

In description, metformin might be inhibited aldosterone which induced activation, migration and proliferation of cardiac fibroblasts and inhibited AMPK phosphorylation as well as induced protein phosphatase magnesium dependent 1A (PPM1A) activation and collagen expression (41). As a further matter, Mummidi and Das highlighted that metformin inhibited pro-inflammatory cytokine expression and potentially inhibited effects of spironolactone on aldosterone-induced collagen expressions (41). Thus, metformin can potentially reduce adverse cardiac remodeling in hypertensive heart disease (41). Saedi et al also demonstrated that metformin inhibited inflammatory cytokines, oxidative stress and necrosis by acetaminophen-induced hepatotoxicity in mice through hepatocytes protection and an anti-inflammation and antioxidative mechanism (42). There is clear evidence that metformin can decrease cell death in cerebral ischemia (43). In recent studies metformin was able to conduct AMPK in the experimental cerebral ischemia, suppress inflammation pathways, protect cells through antioxidant pathways through increased the level of catalase activities and glutathione (43). Moreover, the drug may increase lipid peroxidation, DNA degradation and monoamine oxidase activity. Additionally, metformin can stabilize and normalize the membrane functions via reduction in membrane fluidity, sodium-potassium pump, antioxidant enzymes activities (44).

Other beneficial effect of metformin, according to a rat study, is the prevention of renal tubular epithelium cell injury associated to oxalate and stone by inhibition of kidney crystal formation via renal tubular cell protection and anti-oxidative effects (45).

Researchers showed that metformin may rescue neurons from Huntington's disease by acting on cell metabolism at multiple levels through activation of AMPK, prevention of mitochondrial membrane depolarization and modulation of the disturbed mitochondrial dynamics in brain (46). Lin et al also showed that activation of AMPK via metformin has been associated with reducing the oxidative stress and neurodegeneration in human neural stem cells (47). Likewise, Bibi et al demonstrated that metformin treated subjects has beneficial effects against apoptotic neurodegeneration in HCN-2 neuronal cells and seizures (48).

Metformin may protect auditory hair cells from apoptotic cell death by reduction of intracellular reactive oxygen species (49).

Metformin also has inhibitory effects on various cancer types in mouse models (50). In addition, cancer incidence and cancer-related mortality decreased in patients with type 2 diabetes treated with metformin in epidemiological studies (51).

Conclusion

Although there has been strong evidence for the potential harm caused by metformin, some studies have showed beneficial effects for it. Hence, it is necessary to revision

and modification in contraindication for prescription of this drug.

Authors' contribution

MH is the single author of the paper.

Conflicts of interest

The author declares no conflict of interest.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the author.

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