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# Metformin and kidney; overview on current concepts

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**Abstract**
Type 2 diabetes (T2DM) is a chronic disorder categorized by hyperglycemia due to insulin resistance of cells. T2DM can cause many micro or macrovascular complications. Metformin, a biguanides derivative, has multiple benefits except anti-hyperglycemia effect, comprising amelioration blood cholesterol levels, blood pressure and depressing vascular complications accompanied with T2DM. It is proposed that metformin act via adenosine monophosphate-activated protein kinase (AMPK) -dependent or -independent approaches. The mechanisms by which metformin regulates glycemic level in T2DM are complex. In addition to its peripheral effects on insulin resistance and glycogenesis, metformin has direct beneficial effect on the beta-cell secretion. A large part of the metabolic advantages of metformin can be related to effects on gastrointestinal glucose uptake and the interaction of metformin with numerous new objects for glucose depressing in the gastrointestinal tract, including the incretin receptors, bile salt transporters and the gut microbiota.
**Keywords:** Type 2 diabetes, Hyperglycemia, Metformin, Biguanides, Gut microbiota, Diabetic nephropathy, Glycogenesis, Glycolysis
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## Introduction

Galega officinalis has been consumed as a natural treatment in contrast to diabetes, since middle ages. Galega officinalis comprises the phytochemicals, galegine and guanidine, which both have anti-hyperglycemic effects, but lead to side effects. The study of galegine, guanidine and correlated molecules (such as biguanide) caused growth of oral antidiabetic medicines including metformin. Biguanides for example metformin are constituted of two guanidine molecules combined together with the losing of ammonia molecule. Unlike other biguanides (phenformin and buformin), metformin is a moderately harmless drug, with known pharmacokinetics and controllable toxicities (1).

## Search strategy

For this review, we searched Web of Science, EBSCO, Scopus, PubMed/Medline, DOAJ (Directory of Open Access Journals), Embase, and Google Scholar, using various keywords including; type 2 diabetes, hyperglycemia, Metformin, biguanides, gut microbiota, diabetic nephropathy, glycogenesis and glycolysis.

## Diabetes

Insulin resistance and beta-cell dysfunction are two mechanistic essential elements for diabetes. Type 1 diabetes (T1DM) happens when the pancreas disables to generate sufficient insulin for glucose metabolism. Type 2 diabetes (T2DM) is a chronic disorder categorized by hyperglycemia due to insulin resistance of cells. T2DM can cause many micro or macrovascular complications. Metformin, a biguanides derivative, has multiple benefits except anti-hyperglycemia effect, comprising amelioration blood cholesterol levels, blood pressure and depressing vascular complications accompanied with T2DM.

## Diabetic nephropathy

The main pathway of metformin removal is transfer of metformin from peritubular capillaries to the renal tubular lumen in the kidney. Renal illness is very common in T2DM, since moderate renal functional damage (estimated glomerular filtration rate [eGFR] <60 mL/min) happens almost in one quarter of T2DM patients. The patients with advanced renal damage are at bigger risk for hypoglycemia. Insulin and some the incretin hormones (anti-hyperglycemic drugs) are removed more gradually, with renal elimination. Thus, dose reduction and careful assessment of consequences (glucose level and edema) may be essential (2). It is suggested that metformin could inhibit from suffering fibrosis, which has important role in the advancement of diabetic nephropathy (3). In some recommendations, 30<eGFR< 45 mL/min (serum creatinine around 2 mg/dL) could be regarded as a stop stage for metformin administration in patients with recognized renal damage. In spite of old worries about the danger of lactic acidosis in patients with kidney

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

Lowing blood sugar effect of metformin is carefully associated with its abilities in reduction of hepatic glycogenesis, insulin sensitivity, improvement of beta-cell functions, and gastrointestinal glucose absorption.

damage, the United States Food and Drug Administration (FDA) agency has lately loosened its approvals about administrating metformin. The latest recommendations from the FDA will further help encourage the administration of metformin at 30<eGFR< 45 mL/min by dose reduction and with caution to decrease glucose levels in diabetic nephropathy patients.

## Pharmacokinetics and pharmaceutics of metformin

Metformin hydrochloride (dimethylbiguanide) is usually prepared from the reaction between dimethylamine hydrochloride and dicyandiamide through a simple cyano addition reaction at high temperature about 130°C (4). Metformin has acid dissociation constant (pKa) value about 11.5, thus occurs as the hydrophilic cationic species with high water solubility at physiological pH values and cannot pass through the cell membranes quickly due to low lipophilicity. Currently, investigators in diverse studies try to formulate more lipophilic derivatives of metformin with improved bioavailability (5).

Metformin is broadly delivered into body tissues by transporters include organic cation transporters (OCTs), multidrug and toxin extrusion transporters and plasma membrane monoamine transporter (5).

Metformin has been usually supposed to operate in the liver to reduce hepatic glucose generation. The absorption of metformin in liver is interceded chiefly by OCT1 (gene SLC22A1) and maybe by OCT3 (gene SLC22A3). Thus, decreased transport by OCT can decrease metformin efficiency. In OCT1-impaired persons such as native South American Indians, due to deficit some polymorphisms in OCT1 gene, the metformin level in the liver was meaningfully lesser in contrast with most East Asian and Oceanian individuals. Consequently, it is assumed that OCTs is vital for the hepatic uptake of metformin (5,6).

## Mechanisms of action of metformin versus hyperglycemia

Lowing blood sugar effect of metformin is carefully associated with its abilities in reduction of hepatic glycogenesis, insulin sensitivity, improvement of beta-cell functions, and gastrointestinal glucose absorption (7).

### *1-Glycogenesis and glycolysis by mitochondrial action*

Mitochondrial complex I is addressed as an important drug target to produce desired therapeutic effect of diabetes. Mitochondrial complex I inhibition is capable to lessen hyperglycemia in diabetic experimental samples through stimulating glycolysis, glucose consumption and reducing hepatic glycogenesis. It is proposed which metformin can act on liver via adenosine monophosphate-activated protein kinase (AMPK) dependent or -independent approaches (7). In AMPK dependent approach, metformin by increase in adenosine triphosphate (ATP) consumption leads to increase adenosine monophosphate (AMP) to ATP ratio. This increase in the AMP:ATP ratio prompts the activation of AMPK, which has a variation of effects including enhancing insulin sensitivity (via fat and glucose metabolism), reducing 3'-5'-cyclic adenosine monophosphate (cAMP), and thus reducing the expression of gluconeogenic genes. Additionally, analog of AMP, 5-aminoimidazole-4-carboxamide ribonucleoside increases AMPK-dependent glucose absorption through glucose transporter type 4 (GLUT-4) translocation mediated by phosphatidylinositol 3-kinase pathway that, mimicking the effects of extensive exercise practice (8).

AMPK-independent effects of metformin on the liver is summarized at a report (9) that some those include inhibition of mitochondrial respiration, inhibition of gluconeogenesis (through reduction glucagon secretion and inhibition of fructose-1,6-bisphosphatase generation by AMP), inhibition of inflammation (9,10). Suppression of complex I via AMPK independent-approach by metformin may attribute to the shift of the cellular nicotinamide adenine dinucleotide to NADH ratio by a new target, mitochondrial glycerol-3-phosphate dehydrogenase (mGPD) (11, 12).

### *2-Insulin sensitivity*

Metformin is broadly demanded as an insulin sensitizer for anti-diabetic properties, via the simulation of glucose uptake by peripheral tissues. The improvement in insulin sensitivity by metformin could be attributed to its helpful effects on insulin receptor expression and tyrosine kinase activity inhibited glycogen synthesis, phosphorylation of the acetyl-CoA carboxylase and an increase in the activity of GLUT4 glucose transporters (13). Tyrosine kinase activity in the cells includes cell-cycle regulation and characteristics of gene transcription. Phosphorylation of the acetyl-CoA carboxylase isoforms prevent fat synthesis and elevate of fat oxidation, thus decrease fat stocks and increase insulin sensitivity in liver (7).

### *3-Effect on beta cells and insulin secretion*

In 2005, Diabetes Prevention Program (DPP) study presented that metformin enhances the insulin secretion a little accompanied by the development of insulin sensitivity. Some popular trials using metformin are shown in Table 1. It is obtained currently metformin influences on essential functions of the pancreatic beta cell is categorized as insulin release, proliferation, transcriptional regulation and protective effects against toxicity and apoptosis (viability). It also can regulate transcriptional expression by increasing of glucagon-

**Table 1.** Some clinical trials using metformin (22)

| Trial name | |
|---|---|
| Diabetes Prevention Program (DPP)<br>China Diabetes Prevention Program （China DPP)<br>Indian Diabetes Prevention Program (IDPP) | Biggest and extended follow up of metformin for the inhibition of diabetes |
| DPP Outcomes Study (DPPOS) | The DPPOS is the long-term, continuing trial of the original DPP and to evaluate the effects of the mediations on the more progress of diabetes and diabetes complications, including cardiovascular, renal and retinal diseases |
| REducing with MetfOrmin Vascular Adverse Lesions (REMOVAL) | REMOVAL is the main clinical trial of additional metformin treatment in T1DM |
| UK Prospective Diabetes Study (UKPDS) | Reduction risk of cardiovascular disease by metformin in compare with other anti-diabetes drugs |
| TAME (Targeting Aging with Metformin) trial | This trial will examine whether metformin, can postpone the start of age-related diseases |
| Metformin and longevity (METAL) | To investigate the biological mechanism of metformin in prostate cancer |
| Metformin in Longevity Study (MILES) | To investigate metformin's potential protective effect against cancer |
| Metformin Add-on Study in Patients With T2DM | To study the efficiency and tolerability of empagliflozin, Sitagliptin, Pioglitazone as an supplementary to metformin treatment in patients with T2DM |
| Copenhagen Insulin and Metformin Therapy (CIMT) trial | To evaluate the effect of metformin treatment on variations in carotid intima-media thickness (IMT) in patients with T2DM |
| A Diabetes Outcome Progression Trial (ADOPT) | An worldwide study of the comparative efficacy of rosiglitazone, glyburide, and metformin in newly identified type 2 diabetes |

like peptide-1 receptor (GLP-1R) specially, while it did not increase plasma levels of the other incretin hormone (such as glucose-dependent insulinotropic polypeptide or peptide YY). Metformin can avoid the functional, biochemical and structural irregularities and glucose-stimulated insulin secretion in human islets from chronic exposure to high glucose. Moreover, metformin protects beta cells against lipotoxicity, glucotoxicity and palmitic acid (PA)-induced apoptosis (14,15). It is showed that metformin exposure in pregnancy modifies initial steps of beta cell growth to increase the total of pancreatic progenitors and these variations finally conclude in a greater beta cell heritage portion for child (16).

### *4-Gut tract of metformin*

The liver has been regarded as the key site of action for metformin through several hepatic pathways for reduction serum glucose including inhibition of mitochondrial complex I via activation of AMPK, weaken glucagon signaling and more recently, prevention of mGPD (17). However the liver is regarded the key site for metformin actions, new experimental investigations also show the gut as a main place of activity, because of oral administration of metformin is more efficient than intravenous administration. Several actions of metformin within the gut include increase glucose absorption, generation of lactate; secretion of the GLP-1, effects on the biochemical signaling between the gut and the central nervous system, bile acid metabolism and gut microorganisms. Bile acid metabolism causes reduction serum cholesterol concentrations by increasing bile acid synthesis from cholesterol (18). The primary effect of metformin aims to stimulate levels of certain bacteria to enrich the microbiota milieu. It is shown mucin-degrading *Akkermansia muciniphila* and several butyrate-producing bacteria were positively associated with metformin administration. The prescription of metformin in people with diabetes appears to favorably alter their gut microbiome, resulting in an improved glucose metabolism. It is tested how to restore balance in the gut microbiota to avoid disease beginning (19).

Lately, novel metformin formulations have been advanced for likely improvements in adeptness and tolerance. Besides the common formulation, extended-release (ER) metformin based time extent of digesting is now prepared. Metformin ER may be more tolerable for diabetic nephropathy patients with higher risk of lactic acidosis due to fewer side effects (20). An ER tablet of metformin is prepared by engineering a composition comprising metformin, using a mixture of hydrophobic and hydrophilic polymers (21).

## Advantages and adverse effects

The most prevalent beneficial and side effects of metformin are listed in Table 2. One of important side effects of metformin is gastrointestinal effects: diarrhea, vomiting and stomach irritation that can occur in up to half of patients using metformin. Diabetes Prevention Program Outcomes Study (DPPOS) trial described an amplified danger of deficient vitamin B12 amounts with long-standing therapy of metformin (23).

## Conclusion

Lowing blood sugar effect of metformin is carefully associated with its abilities in reduction of hepatic glycogenesis, insulin sensitivity, improvement of beta-

**Table 2.** Some advantage and adverse effects associated to and use of metformin (4,6,24)

| Adverse effects | Advantage effects |
|---|---|
| Gastrointestinal effects | Vascular protection (cardiovascular) |
| Lactic acidosis and pancreatitis | Anti-inflammation |
| B12 deficiency | Anti-cancer |
| Genotoxicity | Anti-aging |
| Folic acid deficiencies | Weight loss |
| Cytotoxicity | Glucose and lipid metabolism |
| Mutagenicity | Anti-hypertension |
| Embryotoxicity | TSH-lowering effect |
| Hypoglycemia | Neuroprotection, nephroprotection, renoprotection |
| Hormonal dearangment | Anti-fibrosis and treatment of polycystic ovary syndrome (PCOS) |

cell functions and gastrointestinal glucose absorption. It is suggested that gut-based pharmacology of metformin provide fresh remedial methods to mediate diabetes and related complications.

## Author's contribution

HN is the single author of the manuscript.

## Conflicts of interest

This author is a researcher in Nickan Research Institute. However, the process of peer-review was no affected by his job.

## Ethical issues

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

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