

Diabetes mellitus (DM) is a metabolic disease characterized by high plasma glucose, which if not controlled effectively in time, will result in multiple micro-and macrovascular complications. The prevalence of diabetes is increasing world wide affecting 382 million people in 2013 and is expected to rise to 592 million by 2035. Diabetes is now recognized as the 8th leading cause of death and in 2012 and 2013, diabetes had resulted in 1.5 to 5.1 million deaths. Also, if not treated effectively in time, it is now recognized as the leading cause of end-stage kidney disease (ESRD), non-traumatic lower-limb amputations, blindness, and a major cause of cardio vascular disease and strokes in the individuals. With the availability of various oral drugs and insulin, DM can be treated and its complications can be minimized through appropriate glycemia control. For every 1% drop in HbA1C, there is a 40% reduction in the risk of microvascular complication (e.g. retinopathy, nephropathy, and neuropathy).

Metformin, a biguanide, is well known treatment for type 2 diabetes mellitus that has diverse mechanism of actions. Various studies have elucidated the role of this drug in different pathologies. Data has been conclusive that Metformin also has beneficial role in lipid disorders as it improves the markers of metabolic syndrome. Evidence is accumulating that metformin also improves the fertility in females with polycystic ovarian syndrome (PCOS). It also delays aging and is effective in aging-related disorders and is equally effective inflammation-related disorders atleast in different rodent studies. Researchers are working to reveal more benefits of this magic drug, but it remains an unexplored territory for the medical community.

Metformin was clinically developed in 1957 by the French physician Jean Sterne, who gave it its first trade name, glucophage (“Glucose eater”). Phenformin was quite popular in the 1960s, but was withdrawn in the early 1970s due to the emergence of frequent lactic acidosis and increased cardiac mortality. Metformin, a less lipophilic biguanide, proved safer and has replaced phenformin.

After 20 years of use in Europe, metformin was approved for use in the USA in 1995. In 2002, metformin became available as a generic medication, making it one of the least expensive diabetes treatments.

PHARMACOKINETICS OF METFORMIN

After oral administration, metformin is slowly absorbed from the proximal small intestine and absorption is apparently complete within 6 hours of ingestion. Metformin is rapidly distributed following absorption and does not bind to plasma proteins. The mean plasma elimination half-life after oral administration is between 4.0 and 8.7 hours. The clearance of metformin is dependent on renal elimination as metformin does not undergo relevant biotransformation in the liver or biliary excretion.

Factors how Metformin Scores over other Oral Hypoglycemic Agents (OHAs)

- Weight loss: favorable weight profile
- Glycemic durability higher
- Antihyperglycemic effect: freedom from hypoglycemia
- Submaximal dosing for therapeutic effects
- “Vascular drug”: favorable cardiovascular effects, microvascular and macrovascular benefits
- Lipid friendly: favorable modulation of deranged lipid parameters
- Equivalent benefits demonstrated in obese and non-obese diabetics
- Gestational DM: Trials underway show therapeutic role

CLINICAL EFFECTS OF METFORMIN (FIGURE 1)

Metformin, a biguanide, has been available for the treatment of type 2 diabetes mellitus for nearly 20 years. Its mechanism of action involves the suppression of endogenous glucose production, primarily by the liver. Because insulin levels decline with the metformin use, it has been termed an ‘insulin sensitizer’. Metformin has also been shown to have several beneficial effects on cardio vascular risk factors and it is the only oral Antihyperglycemic agent thus far associated with decreased macrovascular outcomes in patients with diabetes. It has potential role for a variety of insulin resistant and pre diabetic states, including impaired glucose tolerance, obesity, polycystic ovary syndrome and

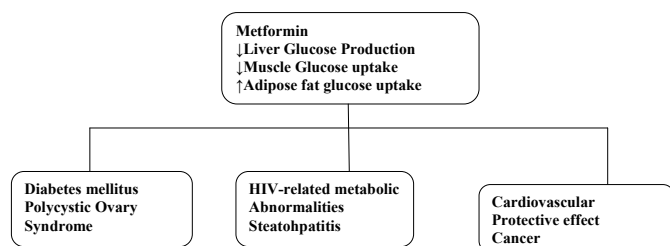


Fig. 1: Clinical Effects of Metformin

the metabolic abnormalities associated with HIV disease. Metformin is transported into hepatocytes mainly through organic cation transporters (OCTs). OCT1 and partially inhibits mitochondrial respiratory-chain complex 1, resulting in reduced adenosine triphosphate (ATP) levels and accumulation of adenosine monophosphate (AMP). Gluconeogenesis is reduced as a result of ATP deficit limiting glucose synthesis. Inhibition of mitochondrial glycerol phosphate dehydrogenase (mGPD) contributes to altered redox state and reduce conversion of glycerol to glucose. Metformin-induced change in AMP/ATP ratio also activates AMPK, which suppresses lipid synthesis and exerts insulin-sensitizing effects.

Cardioprotective Effects of Metformin

Animal and in vitro studies proposed a protective action of metformin against several cardiovascular diseases linked to T2D, including myocardial infarction, hypertrophy, and diabetic cardiomyopathy, which lead to cardiac dysfunction that could evolve to heart failure. The molecular mechanisms involved in this protection are multifaceted, targeting endothelial, cardiomyocyte, and fibroblast dysfunctions.

Metformin's and Cancer

Metformin's anticancer mechanisms of action focus on both the systemic effects of the drug and the direct effects on cancer cells. Systemically, insulin and insulin-like growth factors (IGF) stimulate cancer cell proliferation through activation of PI3K-AKT signaling, leading to tumor growth by improving peripheral insulin sensitivity and increasing insulin growth factor-binding proteins (IGFBP), metformin treatment results in a net reduction in systemic glucose, insulin and IGFs, ultimately leading to inhibition of tumor growth. The current hypothesis for metformin's direct action in cancer cells points to AMPK activation as primarily mediating metformin's effects. In addition, reports indicate that metformin inhibits mitochondrial glycerophosphate dehydrogenase, a redox shuttle enzyme that reduces the conversion of lactate and glycerol to glucose and impairs hepatic gluconeogenesis. Metformin also has novel anticancer effects that are independent of its impact on metabolism. Metformin may protect against cancer through modulation of small non-coding RNA segments (miRNA) that inhibit gene expression at the post-translational level. Evidence currently available suggests Metformin therapy is associated with estimated 29% reduction in lung cancer and 15% in cancer of the respiratory system. Metformin therapy was associated with significantly lower risks of cancers of the lung and respiratory system.

Metformin: Pancreatic Cancer in Patients with Type 2 Diabetes Mellitus

Recent epidemiological studies indicated that use of metformin might decrease the risk of various cancers among patients with type 2 diabetes mellitus (T2DM). The analysis included 11 articles (13 studies) comprising 10 cohort studies and 3 case-control studies. Use of metformin was associated with a significant lower risk of pancreatic cancer. Metformin associated with a 37%

reduction of pancreatic cancer risk compared with other treatments for diabetes.

Metformin and Insulin Resistance

Insulin resistance and beta-cell dysfunction, especially loss of first-phase insulin secretion, the early events in the pathogenesis of type 2 diabetes, also occur in first-degree relatives of type 2 diabetic patients. Metformin reduces hepatic glucose output, partly via reduced gluconeogenesis, ameliorates insulin resistance, particularly in liver and muscle, and may inhibit glucose absorption. Numerous studies have shown that metformin improves glycemia by suppressing hepatic glucose production and enhancing insulin-mediated glucose uptake, often accompanied by reduced insulin levels.

Metformin in Polycystic Ovary Syndrome

The benefits of metformin on insulin sensitivity have been demonstrated in non-DM women with PCOS. The use of metformin is associated with increased menstrual cyclicality, improved ovulation, and a reduction in circulating androgen levels. Metabolic benefits are enhanced in the presence of weight loss, and weight loss itself may be enhanced in the presence of metformin.

- Women who lose even 5-10% of their total body weight can reduce central fat up to 30%, improve insulin sensitivity, and restore ovulation. Lifestyle intervention should be the cornerstone of therapy.
- The initiation of metformin may be considered in women with PCOS who exhibit abnormal results on the 75g load oral glucose tolerance test (OGTT), but do not meet the criteria for DM.
- In a subset of patients with oligomenorrheic PCOS, the initiation of metformin will instigate regular menstrual cycles.

Metformin and Gestational Diabetes Mellitus

Type 2 diabetes and gestational diabetes mellitus (GDM) are closely related disorders characterized by increased insulin resistance. Metformin, a biguanide compound, exerts its clinical effect by both reducing hepatic glucose output and by increasing insulin sensitivity. The result is a decreased glucose level without an associated high risk of either hypoglycemia or weight gain. These characteristics have established metformin as an ideal first-line treatment for people with type 2 diabetes; and hypothetically, a particularly attractive drug for use in pregnancy. However, metformin is known to cross the placenta, and its use in pregnancy has been limited by concerns regarding potential adverse effects on both the mother and the fetus.

In women with established T2DM, insulin usually replaces oral agents during pregnancy; however, metformin has been continued during the pregnancy in some cases. In women with PCOS, metformin may initially be used to facilitate ovulation and promote conception and is then continued throughout the pregnancy. Metformin is currently listed as a category B drug for using pregnancy.

Table 1: Improved cardiovascular outcomes with metformin in T2DM

Study	Main Findings
UKPDS34	Reduced risk of macrovascular diabetic complications
Kooy, et al.	Reduced risk of composite of macrovascular events
PRESTO	Reduced risk of any clinical outcome, MI, Death
Johnson, et al.	40% reduction in risk of death. Reduced risk of mortality, Hospitalization, cardiovascular death
Eurich, et al.	30% reduction in risk of death, 70% reduction in risk of death or Hospitalization
Evans, et al.	3.7-fold lower risk of cardiovascular mortality

The metformin in Gestational Diabetes (MIG) trial demonstrated that there were no differences in neonatal outcomes when metformin was compared to subcutaneous insulin therapy for the management of GDM. A recent systematic review and meta-analysis by Dhuklotia et al. concluded that there were no differences in glycemia control of pregnancy outcomes when oral hypoglycemic agents were compared with insulin.

Effects on Thyroid Function

Metformin decreases serum levels of thyrotropin (TSH) to subnormal levels in hypothyroid patients that use levothyroxine (L-T4) on a regular basis. A significant decrease in TSH ($P < 0.001$) without reciprocal changes in any thyroid function parameter in diabetic patients had also been reported but only in hypothyroid subjects, not in euthyroid ones. The mechanism of the drop in TSH is unclear at this time.

Metformin Use in Renal Dysfunction (Chronic Kidney Disease)

NICE guidelines state the review of clinical circumstance when serum creatinine exceeds 130mmol/L (1.5mg/dl) or eGFR falls below 45ml/min per 1.73m². Discontinue if serum creatinine exceeds 150mmol/L (1.7mg/dL) or eGFR is below 30ml/min per 1.73 m².

The Canadian Diabetes Association practice guidelines based solely on eGFR, caution with eGFR <60ml/min per 1.73m². Contraindication with eGFR <30 ml/min per 1.73 m².

The Australian Diabetes Society practice guidelines recommend against metformin with eGFR <30 ml/min per 1.73 m². Caution with eGFR 30-45 ml/min per 1.73 m².

Metformin and Cardiovascular Outcomes

Management of diabetic patients with heart failure is a complex endeavor. The initial reluctance to use metformin in these patients has given way to a broader acceptance after clinical trials and meta-analyses have revealed that some of the insulin-sensitizing agents lead to adverse cardiovascular events (Table 1).

Metformin has been reported to improve endothelial dysfunction, and to have antiinflammatory properties and reduced oxidative stress, processes that contribute to the disease process in congestive heart failure (CHF).

Treatment with metformin is not associated with an increased risk of lactic acidosis among patients with type 2 diabetes mellitus who have no cardiac, renal or liver failure.

Effects on the Inflammatory Pathway

The benefits of metformin on macrovascular complications of diabetes, separate from its conventional hypoglycemic effects, may be partially explained by actions beyond glycemic control, particularly by action associated with inflammatory and atherothrombotic processes. Metformin can act as an inhibitor of pro-inflammatory responses through direct inhibition of NF- κ B by blocking the PI3K-Akt pathway. This effect may partially explain the apparent clinical reduction of cardiovascular events not fully attributable to metformin's antihyperglycemic action.

There is some evidence that metformin also has a beneficial effect on some components of the antioxidant defense system. It can unregulate uncoupled proteins 2 (UCP2) in adipose tissue and can also cause an increase in reduced glutathione.

Effects on Body Weight

Metformin may have a neutral effect on body weight of patients with T2DM when compared to diet or may limit or decrease the weight gain experienced with sulfonylurea, TDZ, insulin, HAART, and antipsychotics drugs.

Modest weight loss with metformin has been observed in subjects with IGT. However, a meta-analysis of overweight and obese. Non-diabetic subjects, found no significant weight loss as either a primary or as secondary outcome. However, metformin is widely recognized by endocrinologists and dibetologists as a weight reducing agent in clinical practice. Results have found an average weight loss of 5.8 kg (5.6%) under treatment with metformin for 6 months in over weight and obese mostly insulin resistant patients. Metformin is an effective drug to reduce weight in a naturalistic outpatient setting in insulin sensitive and insulin-resistant over weight and obese patients. Metformin may also have a positive effect on metabolic parameters such as waist circumference, fasting insulin and glucose levels and triglycerides.

Effect on Lipid Profile

Metformin is associated with improvements in lipoprotein metabolism, including decreases in LDL-C, fasting and postprandial TGs, and free fatty acids.

Effects on Blood Pressure

The hypertension associated with diabetes has an unclear pathogenesis that may involve insulin resistance. Insulin resistance is related to hypertension in both diabetic and non diabetic individuals and may contribute to hypertension by increasing sympathetic activity,

peripheral vascular resistance, renal sodium retention, and the vascular smooth muscle tone and proliferation.

Data of the effects of metformin on BP are variable, with neutral effects or small decreases in SBP and DBP.

Metformin's Contraindications

The most common contraindications to metformin use in people with type 2 diabetes are renal insufficiency, congestive heart failure, and advanced age (>80 years). Using metformin either in patients of advanced age (>80 years) or in a patient who has reduced renal function, requires one to consider the potential for decreased elimination ability.

Metformin in the Management of Adult Diabetic Patients

Current guidelines from the American Diabetes Association /European Association for the Study of Diabetes (ADA/EASD) and the American Association of Clinical Endocrinologists/ American College of Endocrinology (AAACE/ACE) recommend early initiation of metformin as a first-line drug for monotherapy and combination therapy for patients with T2DM. This recommendation is based primarily on metformin's glucose-lowering effects, relatively, low cost, and generally low level of side effects, including the absence of weight gain.

Metformin's first-line position was strengthened by the United Kingdom Prospective Diabetes Study (UKPDS) observation that the metformin-treated group had risk reduction of 32% ($p=0.002$) for any diabetes-related endpoint, 42% for diabetes-related death and 36% for all-cause mortality compared with the control group. The UKPDS demonstrated that metformin is as effective as sulfonylurea in controlling blood glucose levels of obese patients with type 2 diabetes mellitus. Metformin has also been shown to be effective in normal weight patients.

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