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Metformin: A magic bullet for diabetic world

Patel Shivam, Nensi Raytthatha and Umesh Upadhyay

Abstract
The first-line oral blood glucose-lowering medication for type 2 diabetes management is now metformin. Gazlega officinalis, a European herbal remedy discovered to be high in guanidine and demonstrated to decrease blood glucose in 1918, is tied to the history of this plant. After extensive testing, metformin was approved for use in the USA in 1995. Its capacity to combat insulin resistance and treat adult-onset hyperglycemia without weight gain or an increased risk of hypoglycemia gradually gained acceptance in Europe. The UK Prospective Diabetes Study discovered long-term cardiovascular advantages of metformin in 1998, offering a new justification to use metformin as the first line of treatment to control hyperglycemia in type 2 diabetes. After being used to treat diabetes for 60 years, metformin has developed into the most often prescribed medication in the world for decreasing blood sugar, with potential for additional therapeutic uses.

Keywords: Metformin, vitamin B12 deficiency, Efficacy of metformin, cardiovascular effect of metformin, insulin

1. Introduction
The oral anti-diabetic medication metformin is credited as being a novel treatment for T2DM. It has received a lot of prescriptions, either alone or in conjunction with insulin and other oral hypoglycemic medications [1]. The body does not metabolize metformin. Metformin that is not absorbed is eliminated with faces. Because of its positive charge and interaction with mitochondrial membrane potential, metformin has beneficial pleiotropic effects that help maintain normoglycemia and energy homeostasis. Despite playing a crucial role, metformin rarely causes negative side effects, especially in people with renal and hepatic impairment. The most severe side effects are lactic acidosis, which have an incidence rate of 20% to 30%. It also includes gastrointestinal issues. Above all, continued usage of metformin results in the development of drug resistance. Hence combinatorial therapy has been focused mainly on adding metformin drugs [2].
An oral anti hyperglycemic medication called metformin is used to treat people with type 2 diabetes mellitus. Metformin has taken over as the first option for treating type 2 diabetes because, unlike insulin and sulfonylureas, it does not cause weight gain. It is even used in obese people with type 1 diabetes to lessen insulin resistance [3]. Metformin is a chemical compound that belongs to the biguanides family. This highly hydrophilic medication has an oral bioavailability of 50 to 60 percent, a plasma elimination half-life of 2 to 6 hours, and a peak plasma concentration that is attained about 3 hours after dosing [4]. The biological half-life of metformin hydrochloride is 1.5-1.6 hours, and it is typically given in large doses 2-3 time's day to treat diabetes effectively. The proximal small intestine is the primary site of absorption [5]. Currently, metformin is sold both as a cohesive white powder that is readily soluble in water and as a hydrochloride salt in the United States and other countries. Metformin hydrochloride has a very high water solubility, making the preparation of a controlled-release device quite challenging. Furthermore, functional excipients are required to alter drug release, increasing tablet size [6].
To examine for changes in solubility, the synthesized metformin salts' solubility tests were carried out in pure water. In a volumetric flask, 30 cc of water were added to each fresh metformin salt. Following that, the flasks were put in a thermostatic vibrator and vibrated for 180 minutes at 50 rpm at room temperature. The samples were removed, filtered using a 0.45-mm syringe filter, and then the RP-HPLC method was used to determine the amount of metformin present. Three copies of each sample were evaluated [7]. 11 different forms of metformin, including hydrochloride, were used in the solubility tests in water. These findings suggest that altering the salt formulation can significantly alter the solubility of metformin [8].

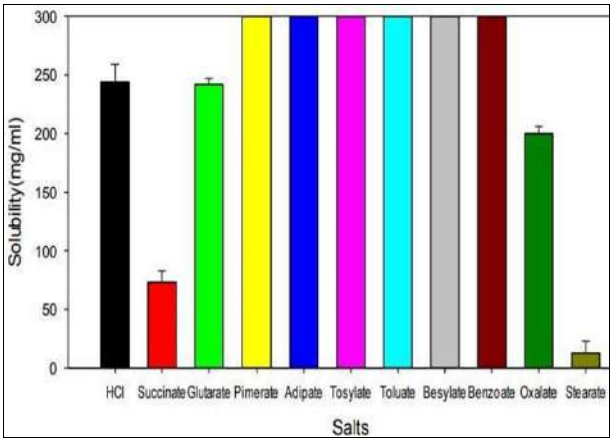


Fig 1: solubility of metformin with various salts in water

This reputation is the result of its potent glucose-lowering properties, affordability, weight neutrality, generally good safety profile, and scant cardio protective evidence. The drug metformin, a derivative of guanidine, was first synthesized in 1922 and approved for use in humans in 1957 as a result of research by Jean Sterne. Guanidine was first derived from the plant Galega officials, also known as the French lilac. Although it was widely used in Europe and other parts of the world before it was eventually approved in the USA in 1994, its popularity soared after that. The effectiveness of the drug has been established in both monotherapy and in combination with other glucose-lowering drugs for type 2 diabetes mellitus. Due to these crucial qualities, this substance has attracted a lot of attention even now, several years after it was included to the diabetes pharmacopoeia. However, recent data suggests that some of the drug's effects may involve stimulation of intestinal release of in cretin hormones. It's interesting that despite this popularity, there is still debate about the drug's exact mechanism of action. Most data point to a reduction in hepatic glucose production being primarily involved. In this article, we'll go over the key points of metformin's clinical use in people with type 2 diabetes [9].

Metformin works by

- Reducing the amount of glucose made by your liver.
- Decreasing the amount of glucose your body absorb.
- Increasing the effect of insulin on your bod [10].

2. History

The mainstay of today's therapy for the treatment of non-insulin-dependent diabetic mellitus is metformin, a key biguanides anti hyperglycemic medication that also significantly lowers the risk of developing the illness. The development of this medication can be credited to early research using Galega officials herb extracts, which helped characterize the blood-lowering properties of an active component known as galegine. In multiple trials conducted in Paris in 1957, metformin was found to lower blood glucose levels in patients with type 2 diabetes but not in healthy people. Unlike sulfonylureas, a different class of oral diabetes medications, metformin largely inhibited the release of glucose from the liver rather than stimulating the release of insulin. Metformin displayed negative gastrointestinal effects in those studies [11].

Similar findings for phenformin were published by an American team in the same year. Ciba-Geigy aggressively promoted that medication, but the prevalence of lactic acidosis and its relationship with phenformin led to a significant decline in its use. Contrarily, metformin was produced by a small French company, and at first, it was just Scotland and France's chosen biguanides. The advantages of metformin were rediscovered in 1995. The UK Prospective Diabetes Study, one of many studies conducted, has had the most significant impact. A randomized, multicenter clinical trial with 3867 participants was conducted and followed up on for ten years. Metformin decreased the risk of myocardial infarction and overall mortality without affecting blood glucose levels. As a result, metformin became the first option for treating obese type 2 diabetic patients. In both prospective and retrospective investigations, the drugs anti-atherosclerotic and cardio protective properties were verified; however, it took another ten years for these conclusions to be formalized as recommendations. Diabetes specialists in the USA and Europe declared metformin to be the medicine of first choice for all type 2 diabetes patients in 2012 [12].

3. Pharmacological effect of Metformin

3.1 Effect of Metformin on glucose lowering

Metformin's primary mode of action is changing how cells use their energy metabolically. Metformin increases the oxidation of free fatty acids and prevents lipolysis in adipose tissue. Notably, metformin inhibits the glucagon pathway by down-regulating mitochondrial complex I, the main access point to NADH, which supports the maintenance of ATP synthesis. This impairs the cyclic adenosine monophosphate and protein kinase a signaling and results in a drop in cellular ATP. Due to lipid oxidation, up-regulation of AMPK boosted insulin sensitivity despite playing a little impact in the glucose-lowering effects of metformin [14]. According to earlier research, elevated plasma levels of plasma plasminogen activator inhibitor 1 are related to insulin resistance. Any effort to lower insulin resistance through diet or medicine, such as metformin, will result in a comparable drop in plasma levels of insulin, PAI-1, and triglycerides, while increasing the activity of the protein globulin fibrinolytic [15].

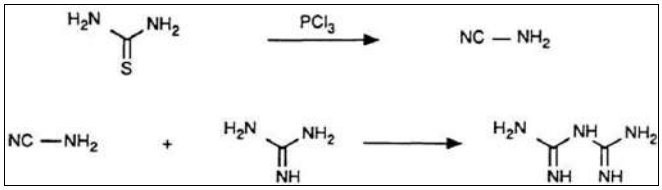
3.2 Effect of Metformin on weight loss

Although lifestyle changes and bariatric surgery are among the most popular weight loss procedures, many patients still have trouble sticking to them. Previous studies have demonstrated a role for metformin side effects in weight loss. Through lowering appetite, diarrhoea contributes to poor nutrition. When compared to the immediate release version, prolonged release metformin demonstrated superior tolerance and drug adherence, according to a randomized controlled trial done by Derosa *et al*. The low frequency of administration and unfavorable consequences were blamed for this. Diabetes Prevention Program, however, shown that metformin's predominant mode of action, reduced food intake, results in a significant weight loss over the course of a long period of time. Metformin will reduce the pancreatic over secretion of insulin by restoring insulin sensitivity in the peripheral tissues. Because of this, there will be considerably less exposure of the insulin receptor in the abdominal fat tissue to insulin, which results in decreased absorption of energy by the abdominal fat tissue and a decrease in the mass of abdominal fat [16].

4. Correlations between chemical and structure of metformin

The first recognized synthesis

Phosphorus trichloride & guanidine were combined in 1878–1879 by RATHKE.



Given that it might be the outcome of a condensation between two guanidine molecules with ammonia elimination, he chose the name "biguanide" for this new substance. The resulting novel product subsequently reacted with a copper sulphates solution to produce pink crystals of the copper-biguanide complex, which was eventually broken down into the sulphate, as RATHKE later observed. By employing a condensation reaction of cyanoguanidine with an ammonia cal solution of cupric sulphate at 110 °C in a sealed tube, the synthesis was significantly enhanced. The sulphate was then produced by treating the resultant complex [17].

4.2 The Golden era of Metformin

Contrarily, the decade that following World War 11 witnessed a tremendous amount of fruitful research, with the development of: biguanides that treat diabetes (1958-1959); paludrine, an excellent antimalarial medicine (1947); and chlorhexidine, a topical antibiotic and disinfectant (1956). In addition, several biguanides were found to have anti carcinogenic properties. Other substances shown antiviral or ant tubercular properties. On the other hand, biguanides are recognized as the precursors of numerous triazines and heterocyclic compounds with potential medical applications. Although there have been many different biguanides researches, considerable work still has to be done, according to KURZER [18].

5. Efficacy of metformin

5.1. Obese diabetic patients

Metformin is generally beneficial in lowering body mass index and high blood insulin levels that show acceptable safety in obese teenagers when combined with lifestyle adjustments. Its long-term impact is not well understood, though. Metformin effectively reduced abdominal fat when compared to placebo in a randomized clinical trial that lasted 26 weeks with type 2 diabetic individuals [19].

5.2. Obese non-diabetic patients

Metformin decreased food consumption, as was previously mentioned. In a double-blind, randomized controlled experiment, Paolisso *et al*. Only a few research examined metformin's effectiveness as a weight-loss aid in practical settings. According to Seifarth *et al*., who treated 154 patients in an outpatient setting over the course of six months with varying metformin doses up to 2500 mg per day, metformin, when administered in high doses, is beneficial for obese and overweight patients regardless of their level of insulin sensitivity at an affordable price [20].

6. Adverse Effects: [21]

- Gastrointestinal side effects
- Diarrhea
- Nausea
- Vomiting
- Some patients experience chest discomfort
- Headache
- Diaphoresis
- Hypoglycemia
- Decreased vitamin B12 levels

6.1 Metformin-induced vitamin B12 deficiency

Long-term use of metformin has been linked to the development of pernicious anemia, which is caused by a vitamin B12 deficiency. In a research by Liu *et al*., a type 2 diabetic patient who had been taking metformin 1000 mg twice day for several years was highlighted. There were 97 pmol/l of vitamin B12 in the blood. Hypothesized a etiology of metformin therapy-induced vitamin B12 deficiency was cognitive impairment and sub-acute combined spinal degeneration. In the same study, another diabetic patient instance had used metformin for 8 years without a prescription and had diarrhoea for 24 months. The average corpuscular volume was 104 fl, the haemoglobin level was 9.4 g/dl, and the level of vitamin B12 was 125 pmol / l. Replacement of vitamin B12 restored normalcy to the diarrhoea and haemoglobin anomalies. Clinicians should be aware of the possibility of vitamin B12 insufficiency caused by metformin in patients with blood disorders, cognitive impairment, subacute combined degeneration of the cord, or diabetic polyneuropathy [22].

6.2 Metformin-induced hypoglycemia

High doses of metformin eventually caused decreased gluconeogenesis by the liver, decreased glucose uptake, and poor oral absorption, which can result in severe hypoglycemia even if used alone without any anti diabetic drugs. Low levels of GLP-1 secretion may play a role in the development of obesity, whereas high levels may cause hypoglycemia after meals. For both obese type 2 diabetic and obese non-diabetic patients, Mannucci *et al*. studied the effect of metformin 850 mg three times daily on the level of GLP-1. They found that after one month of treatment, levels of GLP-1 postprandial significantly increased in obese type 2 diabetic patients and similarly, in obese with normal oral glucose tolerance test. In spite of there being no other co-ingestions, an overweight PCOS patient who was using metformin for weight loss experienced acute hypoglycemia after taking a toxic amount of the medication for an attempted suicide [19].

7. Application of Metformin in certain disease or disorder

7.1 Effect of Metformin on ageing

One of the biggest issues and financial burdens that both industrialized and developing nations face is human ageing and age-related diseases. A rising body of research revealed that metformin, specifically in nematodes and mice, could prevent ageing and lengthen longevity *in vivo*. According to Cabreiro *et al*., metformin extended the mean longevity of C. elegans by 18%, 36%, and 3% at concentrations of 25, 50, and 100 mM, respectively [23]. According to a recent study, if metformin treatment is initiated early in life, the mean longevity would increase by 14%, and the maximum

lifespan would increase by 1 month. However, as people mature, this benefit would diminish. Numerous research have also examined whether people with T_2 DM can show that metformin has antiaging properties [24].

In addition, a sizable retrospective observational analysis with more than 180,000 participants revealed that T_2 DM patients. The hazardous nature of the study's metformin dose is one potential explanation. Similar to this, a study found that adding 0.1% of metformin to the food of C57BL/6 mice increased mean lifetime by 5.83% but a higher dosage of the drug was hazardous and markedly decreased mean lifespan by 14.4% [25].

7.2 Cardiovascular protective effects of metformin

About 70% of all diabetic patients die from heart and brain macro vascular diseases, which account for the majority of cardiovascular complications in diabetic patients. These complications include macro vascular ones like stroke, coronary artery disease, and myocardial infarction as well as micro vascular ones like kidney disease, retinal injury, and peripheral nerve disease. Metformin has been proven in a number of clinical studies to have cardiovascular preventive effects and to lower the incidence and mortality of cardiovascular events [26].cardiovascular disease prevention properties of metformin may be useful. Obesity, hypertension, insulin resistance, dyslipidemia, and other conditions are risk factors for cardiovascular disease. First, by activating AMPK, metformin may enhance lip metabolism and lower LDL cholesterol levels. Second, weight decrease or less weight increase was linked to metformin [27]. Reduced perception of hunger is assumed to be the mechanism, which leads to less food consumption. Possible mechanisms of metformin blood pressure lowering include reduction of insulin resistance and plasma insulin, Metformin can also reduce oxidative stress, reduce inflammation, and enhance endothelial cell function [28].

7.3 The Neuro-protective impacts of metformin

There are conflicting clinical trials on the potential benefits of metformin for dementia prevention and cognitive enhancement in T2DM patients. In addition, Herath *et al*. demonstrated that, in comparison to other diabetic medications, metformin has a better protective effect on the domains of verbal learning, working memory, and executive function. [29]. In a modest clinical research, Guo *et al*. discovered that treating T2DM patients with depression for 24 weeks with metformin dramatically increased cognitive function and decreased depressed symptoms. Studies on metformin's effects tend to concentrate on tau levels and A formation. Metformin can also lessen oxidative stress, avoid brain mitochondrial dysfunction, boost levels of brain-derived neurotropic factor, lessen neurological impairments, and attenuate cognitive impairment [30].

7.4 Antineoplastic impact of metformin

In hamsters, metformin was originally identified in 2001 as an anticancer agent. For the duration of their lives, one group (HF + Met group) received metformin in their water, while the other functioned as the control group (HF group). After 42 weeks of exposure to the pancreatic carcinogen N-nitroso bis-(2-oxopropyl) amine, all hamsters acquired malignant lesions in 50% of the high-fat group, while none were discovered in the HF + Met group [31]. First, a sizable case-control research conducted in Scotland revealed that metformin usage decreased cancer risk in T_2DM patients. Metformin decreased the rates of many gastroenterological malignancies in diabetes patients (total 0.12 (0.08-0.19), colon 0.36 (0.13-0.98), liver 0.06 (0.02-0.16), and pancreatic 0.15 (0.03-0.79), according to a representative population prospective cohort study of 800,000 people. Consumption of metformin was linked not just to a decline in cancer mortality but also in cancer incidence. Metformin was linked to a decreased cancer death rate, and Landman *et al*. demonstrated that the impact was dosage dependent [32]. Particularly in those getting radiotherapy, had the highest advantages as an adjuvant drug in the treatment of colorectal and prostate cancer. But more research needs to be done on metformin dosage. Metformin has been shown to be anticancer in a number of epidemiologic investigations conducted so far, including those on ovarian, breast, prostate, and colorectal malignancies [33].

Additionally, a recent study found that metformin does not improve survival in those with T_2DM who had colorectal cancer [34]. Therefore, the question of whether metformin has an antitumor impact has received a lot of interest. Growing research suggested that metformin can reduce tumour formation. Wu *et al*. first discovered that the nuclear pore complex and an enzyme known as acyl-CoA dehydrogenase family member-10 are the two components of a single genetic route that are responsible for the anticancer effects of metformin. In essence, metformin lowers cellular energy by suppressing mitochondrial respiratory capacity, which limits the passage of the Rag A-Rag CGT Pase heterodimer through the NPC. Through the transcriptional stimulation of ACAD10, this limits the formation of a crucial cellular growth protein known as mTORC1 and increases the lifetime of *Caenorhabditis elegans*. After all, research has shown that metformin loses its ability to inhibit cancer cell development if the nuclear pore is forced to remain open or if ACAD10 is permanently shut down [35].

7.5 Polycystic Ovarian Syndrome / Disease

In between 50% and 70% of PCOS patients, insulin resistance and the ensuing hyperinsulinemia are present. Since 1994, metformin has been used to treat PCOS [36], reversing the majority of the metabolic abnormalities associated with the condition. The dose of metformin used in several research ranged from 850 to 1,700 mg. The mechanism is believed to be mediated by enhanced insulin sensitivity, increased ovarian oestrogen secretion, decreased ovarian androgen synthesis, and increased sex hormone binding globulin production [37].

8. Metformin as a P-gp substrate

The best-studied ABC transporter, P-gp, can be found in the liver, kidneys, gut, brain, and other normal tissues in addition to tumour cells. P-gp is a key component of the blood-brain barrier (BBB) and is found on the luminal surface of brain capillary endothelial cells in the brain [38]. Numerous dipeptidyl peptidase-4 (DPP-4) inhibitors, including sitagliptin, vildagliptin, saxagliptin, and linagliptin [39], as well as a number of anti-diabetic medications, including glibenclamide, rosiglitazone, metformin, and repaglinide, have been discovered to be P-gp substrates. This pattern has led to the hypothesis that, in diabetes situations, this protein is essential for the absorption of medications that it binds to that are given

orally. Only a small number of papers, meanwhile, have concentrated on alterations in intestinal P-gp and / or how these changes affect the PK/PD of anti-diabetic medications in diabetic patients. As a result, we concentrated on intestine P-gp activity in diabetes circumstances. Therefore, it is crucial to keep an eye out for any potential changes in the PK / PD of P-gp substrate medicines while administering oral medications to diabetes patients in the clinic [40].

9. Variable that cause intestinal p-gp expression that change in diabetic state

9.1 Glucose

Under diabetic circumstances, changes in intestinal P-gp may be caused directly or indirectly by hyperglycemia. According to certain *in vitro* investigations. Numerous investigations have demonstrated that intestinal P-gp expression and drug-efflux activity were drastically reduced in a type 1 diabetes animal created by streptozotocin therapy, which kills pancreatic cells. In the early stages of the diabetic condition, declines in intestinal P-gp expression were seen together with an increase in blood glucose levels, as shown in our prior study [41].

9.2 Cytokines

Tumor necrosis factor (TNF), interferon (IFN), and interleukin-6 (IL-6) are examples of inflammatory cytokines these pro-inflammatory cytokines have been shown to change P-gp expression levels by activating certain transcriptional factors, such as nuclear factor -B (NF-B) and activator protein-1, which are mediated by particular cytokine receptors [42].

9.3 Nitric Oxide Synthase

One of the variables that affects P-gp expression in diabetes settings is iNOS, presumably through altering the expression of the pregnane X receptor, one of the major transcriptional regulators of P-gp. Furthermore, inflammatory cytokines and high-glucose stress are known to stimulate the up regulation of iNOS. It plays a role in the progression of disorders connected to hyperglycemia as well as in the development of hyperglycemia itself. In a mouse model of STZ-induced diabetes, intestinal iNOS activity has been found to be enhanced. To our knowledge, however, there haven't been any reports demonstrating that additional forms of NOS are involved in changes to P-gp in diabetes circumstances [43].

9.4 Insulin

We and others have demonstrated that the intestinal P-gp expression levels are considerably reduced in the STZ-induced diabetes mouse model without insulin, despite the fact that there are just a few *in vivo* studies. Additionally, Zhang *et al*. found that insulin treatment can reverse the decreased mRNA and protein expression levels of intestinal P-gp that occur in diabetic circumstances. To describe the potential role of insulin in the modification of intestinal P-gp in greater depth, additional research is required [44].

10. Interaction between p-gp and medications for obesity and diabetes

Different therapeutic medication types with distinct mechanisms of action are utilised in clinical settings to enhance glucose homeostasis. Insulin secretagogues, such as sulfonylureas and glinides, stimulate the secretion of insulin. As part of combination therapy, these medications from various categories are frequently provided simultaneously [45]. Some of these substances, including glibenclamide, rosiglitazone, metformin, and repaglinide, have been discovered to be P-gp substrate medications. Therefore, it is simple to assume that changes in intestinal P-gp activity may occur as a result of the combination of these drugs in diabetic patients, which may impair their PK / PD after oral delivery. There have been reports that intestinal P-gp inhibition or competition may affect the PK / PD of co-administered anti-diabetic pharmaceuticals, even if there are currently no evidence indicating the simultaneous use of anti-diabetic medications alters each other's PK / PD under diabetic conditions via P-gp. In a human study, Lilja *et al*. showed that there can be drug interactions between glibenclamide and clarithromycin, a strong inhibitor of P-gp activity, when both are administered orally. This leads to an increase in the peak plasma concentration of glibenclamide as well as the area under the plasma concentration-time curve [46].

11. Clinical particulars

Treatment of type 2 diabetes mellitus, especially in people who are overweight, when food modification and exercise alone do not produce sufficient glycaemic control.

- In adults, Metformin tablets may be used as monotherapy or in combination with other oral anti-diabetic agents, or with insulin.
- In children from 10 years of age and adolescents, Metformin tablets may be used as monotherapy or in combination with insulin [47].

12. Conclusion

Metformin's incredible journey from herbal origins to renowned medicinal medication has been rocky. It has been found, lost, found again, used again, rejected, saved, cleared, and it still might have more secrets to share. When compared to other pharmacotherapies, metformin is unusual in that it doesn't seem to have a single mechanistic target. Instead, it combats insulin resistance and other physiological functions through a number of small-scale but cumulatively significant effects. The value of such a well-rounded drug necessitates consideration of the contraindications and investigation of additional treatment possibilities.

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