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THERAPEUTIC ACTION OF METFORMIN: ITS PHARMACOKINETICS AND PHARMACODYNAMICS

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ABSTRACT

Metformin, a biguanide, is still the standard of oral treatment of type 2 diabetes mellitus (T2DM). Its long-standing position owes to its strong efficacy, good safety profile, and new pleiotropic advantages. This review proposes to make a thorough synthesis of the existing knowledge on metformin's mechanisms, highlighting its pharmacokinetic (PK) and pharmacodynamic (PD) features. Pharmacokinetically, metformin is distinguished by incomplete intestinal absorption through specific transporters (OCT1, PMAT), absence of hepatic metabolism, and sole renal excretion through OCT2 and MATE transporters. Clinically, this profile directly affects its dosing and contraindications. Pharmacodynamically, the key action of metformin is inhibiting hepatic gluconeogenesis. This is done through its intracellular accumulation in hepatocytes and consequent inhibition of mitochondrial respiratory chain complex I. The subsequent rise in the cellular AMP/ATP ratio activates AMP-activated protein kinase (AMPK), a key regulator of cellular energy. AMPK activation and AMPK-independent mechanisms control hepatic glucose and lipid metabolism, enhance peripheral insulin sensitivity, and enhance glucose uptake. Clinically, this is reflected by lowered fasting and postprandial hyperglycemia with negligible risk of hypoglycemia. This review summarizes these molecular and systemic effects, vindicating the justification for metformin's ongoing dominance as a first-line drug in the treatment of T2DM.

KEYWORDS: Metformin, AMPK, OCT1, PMAT, T2DM.

INTRODUCTION

Metformin is an oral biguanide antihyperglycemic drug. Its origin lies in compounds derived from the plant Galega officinalis (French lilac), which was employed in traditional European medicine for its action on glucose levels [1, 2]. Following decades of investigation and clinical research, metformin was licensed for use in the United Kingdom in 1957 and in the United States of America in 1995 [3]. It is now perhaps the most commonly prescribed oral glucose-lowering drug worldwide.

Clinical relevance of metformin is supported by the fact that it is the first-line medication for type 2 diabetes mellitus (T2DM), and this has been widely recommended by leading international societies, such as the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) [4, 5]. Its key position in the treatment of diabetes is further reinforced by its listing on the World Health Organization (WHO) List of Essential Medicines, its effectiveness, safety, and affordability for health systems worldwide [6].

Notwithstanding its extensive clinical use, the exact molecular mechanisms of metformin were contentious over decades. It is currently appreciated that its therapeutic actions are the consequence of a sophisticated interplay between its distinctive pharmacokinetic profile and its deep pharmacodynamic effects. The aim of this review is to integrate the extant body of knowledge into metformin's pharmacokinetics (PK)—what the drug does to the body—and its pharmacodynamics (PD)—what the body does to the drug. By considering its absorption, distribution, metabolism, and excretion and its targets at a molecular level, we can best understand the processes behind its therapeutic effect.

1. Pharmacokinetics (PK): What the Body Does to Metformin

Metformin's therapeutic effect and safety profile are irretrievably coupled with its distinctive PK characteristics. As a hydrophilic cation, its passage through biological membranes is solely reliant on transport proteins and not on passive diffusion [7].

a. A - Absorption

Oral metformin, one of the cornerstones in the treatment of type 2 diabetes, is characterized by a complex absorption profile mainly in the proximal small intestine. The uptake mechanism of the drug is not a simple passive diffusion but an active and saturable one, carrier-mediated. Specific organic cation transporters are involved, among which Organic

Cation Transporter 1 and Plasma Membrane Monoamine Transporter play an especially important role in the efficient uptake of metformin from the intestinal lumen into the bloodstream. These transporters actively facilitate the movement of metformin molecules against a concentration gradient, highlighting the regulated nature of its pharmacokinetics.[8] The saturable nature of this active transport system has profound effects on the bioavailability of the drug metformin. In the fasting state, the bioavailability of this agent is around 50 to 60% on average. This partial bioavailability reflects the saturation of the transport system at that concentration and means that beyond a particular concentration, the transporters cannot ferry additional metformin molecules across the intestinal barrier at an increased rate. At even higher therapeutic doses, the bioavailability will be even more reduced given the now highly saturated transport system, resulting in a plateau in systemic drug exposure despite an escalation in dose administered.[9,10]

Moreover, the presence of food in the gastrointestinal tract can affect some of the pharmacokinetic parameters of metformin. Generally speaking, food delays Tmax, indicating a slower rate of absorption, with minimal effects on the total extent of absorption. This means that although the peak concentration might be achieved later, the total amount of metformin absorbed into the systemic circulation is largely consistent.[11]

Given these factors, the common recommendation regarding the administration of metformin with food is to enhance gastrointestinal tolerability rather than to appreciably improve its absorption. Gastrointestinal adverse effects related to metformin include nausea, diarrhea, or abdominal discomfort. Administration of the drug with food can reduce these adverse effects by slowing the release and therefore diluting the concentration of the drug within the gastrointestinal tract, thus generally enhancing patient compliance and overall treatment outcomes. A greater understanding of these complex absorption characteristics is essential for healthcare professionals in order to optimize metformin therapy and ensure maximum efficacy of this medication in achieving and maintaining glycemic control in patients with type 2 diabetes. Such knowledge permits appropriate dosing strategies and patient education, thus contributing to overall diabetes management.[12]

b. D - Distribution

The key features of metformin's pharmacokinetic profile include a minimal amount of plasma protein binding and widespread tissue distribution, both of which contribute to the therapeutic

efficacy of this drug. Poor Plasma Protein Binding: One of the key features of metformin after its absorption into the systemic circulation is its minimal binding to plasma proteins [13]. This limited plasma protein binding is actually a very favorable feature since it ensures that the bulk of the drug remains in its free and pharmacologically active form. This unbound fraction then becomes highly available for interactions with the target tissues to execute the therapeutic effects with full potential and efficient distribution within the body.

Extensive Volume of Distribution and Tissue Uptake: Metformin demonstrates a large apparent volume of distribution (Vd), reflecting its widespread distribution into tissues rather than confinement to the bloodstream [14]. This pharmacokinetic property underlines its widespread distribution and active accumulation in many organs and cellular types. The liver is regarded as the major organ for the main pharmacodynamic action of metformin. Its hepatic accumulation is largely influenced by the organic cation transporter 1 (OCT1) [15, 16], a transport protein critical for metformin's entrance into the hepatocytes.

Beyond the liver, metformin also exhibits considerable accumulation in other important organs, such as the kidneys, salivary glands, and gut. It often reaches concentrations well above those observed in plasma within these tissues [17]. This broad distribution and tissue-specific accumulation form the basis for the varied therapeutic actions of metformin in making it a cornerstone medication in the management of various diseases, including type 2 diabetes. The sustained presence of metformin in these key tissues allows for continuous engagement with its molecular targets, contributing to its sustained glucose-lowering effects and other metabolic benefits.

c. M - Metabolism

Among various therapeutic agents, metformin is outstanding for its unique pharmacokinetic profile, most notably a complete and distinct lack of hepatic metabolism. In contrast to the great number of pharmaceutical compounds being biotransformed in the liver, metformin completely bypasses the complex pathways of the cytochrome P450 (CYP450) enzyme system. Such a feature is not merely an interesting biochemical fact but rather a very important clinical advantage with great implications for patient safety and medication management.[18]

A lack of CYP450 metabolism by metformin means that it neither competes for, induces, nor inhibits these important enzymes responsible for the metabolism of a large percentage of all

prescribed drugs. This property inherently minimizes the possibility of problematic drug-drug interactions. Those patients who are taking other medications that either induce or inhibit the CYP450 enzymes-a very common situation in clinical practice, especially in patients with many comorbidities-are much less likely to see adverse effects or changes in the efficacy of metformin. This is very advantageous in polypharmacy, where many patients are prescribed multiple drugs at once, and the prediction and management of potential drug interactions becomes very complicated and daunting for healthcare providers. The predictability of metformin in this manner simplifies therapeutic regimens and enhances overall patient safety.[19]

Moreover, the lack of metabolism is not limited to the CYP450 system; no other known metabolic pathway seems to be implicated in the disposition of metformin in the body. From the time it is absorbed into the blood to its eventual excretion, the chemical structure of metformin remains totally unchanged. This important fact suggests that the drug is eliminated in its active, unmetabolized form primarily by renal excretion. This "unchanged" elimination further simplifies its pharmacological profile, contributing to its generally favorable safety and tolerability. The direct excretion of the active compound minimizes the formation of potentially toxic metabolites and allows for more straightforward dose adjustments based on renal function, making this agent reliable and one of the most widely used drugs in the management of type 2 diabetes.[17]

d. E - Excretion

Metformin, in the management of type 2 diabetes, is a cornerstone medication with a distinct pharmacokinetic profile of complete and unchanged elimination from the body. The efficient removal mechanism is mediated solely through the kidneys and indicates the critical participation of renal function in its disposition. Such highly efficient renal clearance translates into a relatively short plasma half-life of metformin, usually in the range of about 5 to 6 hours, requiring frequent dosing in order to maintain therapeutic concentrations.[20]

Renal excretion of metformin is a complex and highly regulated process that goes well beyond the simple process of passive glomerular filtration. Whereas glomerular filtration accounts for the initial movement of the drug from the blood into the renal tubules, active tubular secretion plays a pivotal role in its overall clearance. This active transport takes place mainly in the proximal tubules of the kidney and involves an intricate interplay of specialized

protein transporters.[21]

Organic Cation Transporter 2 (OCT2), on the basolateral membrane of the renal tubular cells (that is, facing the bloodstream), is important for the uptake of metformin from the systemic circulation into the tubular cells. This uptake is an active, saturable process, depending on many physiological and pharmacological factors, including drug concentration, blood flow, and competition by other cations. Inside the tubular cells, metformin is actively transported across the apical membrane-the part of the cell facing the tubular lumen and thus the urine-by Multidrug and Toxin Extrusion proteins, MATE1 and MATE2-K. These efflux transporters efficiently move metformin from the intracellular space into the urine for subsequent excretion from the body. The interplay among OCT2, MATE1, and MATE2-K guarantee a rapid and efficient elimination of the drug.[22,25]

This basic dependence on active renal clearance provides the basis for the major contraindication to metformin: extensive chronic kidney disease (CKD). Individuals with reduced renal function have compromised integrity and function of both glomeruli and tubular transport systems, which results in a substantial decline in metformin clearance. Consequently, the extent to which the drug is efficiently removed from the body becomes severely diminished, leading to accumulation in systemic circulation. This increased concentration of metformin has the potential for significantly enhancing the risk of adverse effects, most notably lactic acidosis, a rare but potentially life-threatening metabolic complication. Renal function, usually measured as glomerular filtration rate (GFR), must therefore be carefully monitored during the prescription of metformin. Dose adjustment in mild to moderate kidney impairment is often required, while the drug is commonly contraindicated in patients with severe CKD in order to avoid potential drug toxicity and ensure patient safety. Monitoring of renal function is essential not only at the beginning but also regularly throughout metformin therapy, especially in patients with pre-existing kidney conditions or those at risk of developing renal dysfunction.[23,24]

2. Pharmacodynamics (PD): What Metformin Does to the Body

The action of metformin to reduce glucose is due to a series of molecular events, mostly originating in the liver, that are triggered after its transport-mediated uptake into hepatocytes.

a. Core Molecular Mechanism

Metformin, one of the most commonly used oral hypoglycemic agents, acts principally in the

liver by targeting major metabolic pathways to enhance glucose homeostasis. It first undergoes uptake into hepatocytes, a process predominantly mediated by OCT1. Following entry into hepatocytes, metformin accumulates within mitochondria, often referred to as the powerhouse of the cell, where energy is produced.[16]

Within the mitochondrial matrix, metformin causes a weak but reversible inhibition of Mitochondrial Respiratory Chain Complex I. This critical step disrupts normal electron flow and, by extension, oxidative phosphorylation, the main process by which ATP is synthesized. The result of such an inhibition is the decrease in mitochondrial production of ATP, thus causing a significant shift in the cellular energy charge. More precisely, there is an increase in the cellular AMP/ATP and ADP/ATP ratios, indicating a condition of energy deprivation inside the cell.[26,27]

This change in cellular energy state is a powerful signal for cellular adaptation. The increased AMP level allosterically activates AMP-activated protein kinase (AMPK), an enzyme considered a cellular energy sensor and a master metabolic regulator. In a cascade of downstream events, the activation of AMPK leads to metformin's glucose-lowering effects, such as increased glucose uptake, reduced gluconeogenesis, and enhanced fatty acid oxidation.[28,29]

Until recently, AMPK activation has generally been regarded as the primary mechanism underlying metformin's therapeutic actions; however, recent evidence suggests the involvement of AMPK-independent pathways. Inhibition of mitochondrial glycerophosphate dehydrogenase has been identified as another significant contributor to the overall therapeutic efficacy of metformin. These multifaceted actions underline the complex interaction of pathways whereby metformin exerts its beneficial effects in metabolic disorders, especially type 2 diabetes.[30,31]

b. Downstream Effects (Mainly through AMPK)

In the Liver: Activation of AMPK in hepatocytes is the primary mechanism behind the therapeutic effect of metformin. AMPK then phosphorylates and inhibits key enzymes and transcription factors involved in hepatic gluconeogenesis [32]. This inhibits the transcription of gluconeogenic enzymes like phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase), thereby decreasing the rate of glucose synthesis and release from the liver [33, 34]. Suppression of hepatic gluconeogenesis is considered the major mechanism

whereby metformin lowers fasting plasma glucose levels. Activated AMPK also positively affects lipid metabolism by inhibiting the synthesis of fatty acids (lipogenesis) and cholesterol, and enhancing fatty acid oxidation [35].

In Skeletal Muscle & Adipose Tissue: Metformin also exerts significant actions in the peripheral tissues. It enhances insulin sensitivity and increases glucose uptake in muscle and adipocytes [36]. This partly comes about by enhancing the translocation of intracellular vesicles' GLUT4 glucose transporters to the cell membrane, so more glucose enters the cells from the bloodstream [37]. This effect is especially beneficial for removing postprandial glucose.

In the Intestine: Only relatively recently has the gut been identified as an important site of action of metformin. Metformin has the ability to enhance the intestinal L-cells to secrete more Glucagon-Like Peptide-1 (GLP-1), which stimulates insulin release and inhibits glucagon [38, 39]. Metformin has also been shown to positively shift the balance of the gut microbiota, and it might reduce intestinal glucose absorption directly as well [40]

c. Insulin-Independent Action

Among the oral antidiabetic drugs, metformin is distinctive for its different mechanism of action, mainly characterized by its inability to directly stimulate insulin secretion from pancreatic beta-cells [41]. This basic difference allows metformin to be classified not as a hypoglycemic drug-one that would actively lower blood glucose levels by increasing insulin release-but rather as a "euglycemic" drug. Its therapeutic efficacy derives from a dual action: it considerably reduces hepatic glucose production and simultaneously increases insulin sensitivity in the peripheral target tissues such as muscle and adipose tissue.

The inability of metformin to exhibit direct insulin secretagogue activity is a critical safety feature. Because it does not force the pancreas to release more insulin, it has an exceptionally low, near-zero, risk of inducing hypoglycemia (dangerously low blood sugar) when administered as monotherapy [42]. This makes it especially appealing as a first-line treatment in Type 2 Diabetes Mellitus, particularly in patients who are susceptible or prone to hypoglycemic episodes with other classes of antidiabetic drugs. This safety profile is also one reason for its wide use and patient compliance, given that fear of hypoglycemia can be a major barrier to effective diabetes management for many.

3. Therapeutic Actions & Clinical Applications

a. Primary Indication: Type 2 Diabetes Mellitus

The primary and established indication of metformin is the management of T2DM. Its complex mechanism results in the reduction of both fasting and postprandial hyperglycemia [43]. Clinically, monotherapy with metformin generally decreases glycosylated hemoglobin (HbA1c) by a notable 1.0-1.5% on average [44]. The key benefit, especially emphasized in the seminal United Kingdom Prospective Diabetes Study (UKPDS), is its correlation with cardiovascular benefits, macrovascular complications reduction, and mortality, which did not occur with other treatments such as insulin or sulfonylureas during that period [45]. Unlike most other diabetes drugs, metformin is weight-neutral or even leads to a moderate weight reduction, which renders it a suitable option for most T2DM patients, who usually are overweight or obese [46].

b. Other & Emerging "Pleiotropic" Effects

In addition to glucose management, metformin has a variety of "pleiotropic" actions. It is commonly used off-label for the treatment of Polycystic Ovary Syndrome (PCOS), in which it is not FDA-approved but useful in the control of underlying insulin resistance, suppression of hyperandrogenism, and enhancement of ovulatory function and menstrual regularity [47, 48]. Metformin has also been promising in Non-alcoholic Fatty Liver Disease (NAFLD), where it can correct liver enzymes and decrease hepatic steatosis by treating insulin resistance and altering hepatic lipid metabolism [49]. Additionally, extensive epidemiological evidence indicates that metformin therapy is linked with decreased risk and better cancer mortality of different cancers [50, 51]. This has instigated vigorous research into its potential anti-neoplastic activity, through both AMPK-dependent and independent mechanisms [52]. Metformin is also now under investigation for its possible anti-aging and longevity-inducing effects, with large-scale clinical trials such as the Targeting Aging with Metformin (TAME) trial now ongoing to test this hypothesis [53].

4. Adverse Effects, Contraindications, & Drug Interactions

a. Common Adverse Effects

The most common side effects of metformin are gastrointestinal (GI) in character and occur in 30% of patients [54]. They involve diarrhea, nausea, abdominal pain, gas, and a metallic taste. These symptoms are dose-dependent, reversible, and are significantly reduced by initiating therapy with a low dose and gradually titrating the dose, or by taking extended-

release (XR) formulations [55]. Another consideration is the relationship between long-term use of metformin and Vitamin B12 deficiency, which can be caused by decreased absorption in the terminal ileum. Regular monitoring and supplementation are advised for those who use it long-term [56, 57].

b. Rare but Serious Side Effect

The most dreaded, albeit very rare, side effect is Metformin-Associated Lactic Acidosis (MALA) [58]. The mechanism is the over-inhibition of mitochondria and disrupted removal of lactate (which is otherwise removed through gluconeogenesis, which is inhibited by metformin) [59]. It is important to note that MALA is vanishingly rare in individuals with baseline kidney function. The risk only becomes clinically apparent with the presence of certain risk factors that cause drug accumulation or severe tissue hypoxia. These are severe renal impairment (eGFR < 30 mL/min/1.73m²), acute hypoxic conditions (e.g., acute heart failure, sepsis), severe liver disease, and alcohol consumption in excess [60, 61].

c. 0Drug Interactions

Due to its PK profile, metformin's main interactions are pharmacodynamic. Any cationic drugs that are excreted by the renal tubules, e.g., cimetidine or digoxin, can compete with metformin for the same transport systems (OCT2, MATEs) [62]. This has the effect of lowering metformin's renal clearance and raising its plasma concentration, theoretically enhancing the risk of toxicity. Clinically, perhaps the most significant protocol is radiocontrast media. Temporary withdrawal of metformin in patients who are having procedures involving iodinated contrast dye is recommended. The dye itself is known to cause acute kidney injury (AKI); if that happens, metformin would not be able to be excreted, and they would have rapid accumulation and precipitation of lactic acidosis [63].

5. CONCLUSION

Metformin remains the cornerstone of oral pharmacotherapy for type 2 diabetes, a status it has maintained remarkably consistently for more than six decades. This sustained clinical success is due to a unique combination of its pharmacokinetic attributes and an extremely effective pharmacodynamic mechanism of action.

From a pharmacokinetic point of view, metformin's passage through the body is very specifically characterized. Its absorption is highly dependent on certain transporters that ensure its targeted delivery. Crucially, metformin is not metabolized in the body; thus, it is

excreted mostly unmodified and thereby minimizes potential drug interactions that could occur due to metabolic pathways. Its elimination is by active renal excretion.

Equally engaging and multifaceted are the pharmacodynamic actions of metformin. Its primary mechanism involves the powerful reduction in hepatic glucose output, which is a major contributor to elevated blood glucose levels in type 2 diabetes. This occurs by inhibiting mitochondrial complex I within liver cells. This inhibition then triggers the stimulation of Adenosine Monophosphate-activated Protein Kinase (AMPK), an enzyme that is recognized as a master metabolic regulator. The activation of AMPK initiates a cascade of beneficial effects, including increased uptake and utilization of glucose in peripheral tissues, hence increasing insulin sensitivity. This dual action of reducing glucose production and improving insulin response underpins its powerful glycemic control.

Metformin has an impressive list of benefits as a first-line therapeutic agent. It displays strong efficacy in lowering HbA1c levels, the most important measure of long-term blood glucose control. It has an unrivaled safety record as compared to any oral antidiabetic agent, and it can be used on a wide and long-term basis. Besides, metformin is very cheap, thus being an affordable treatment option in all parts of the world. The low risk for hypoglycemia is an important advantage of this agent, considering that hypoglycemia is a common and potentially dangerous side effect in many classes of diabetes medications. Besides its benefits on glycemic control, metformin has beneficial effects on body weight that commonly lead to modest reductions or stabilization of body weight and has shown positive effects on CVD, the most important comorbidity in diabetic patients.

This is a continuously evolving therapeutic narrative for metformin, as ongoing research has unraveled its multifaceted "pleiotropic" actions beyond its indication for diabetes. Its study in other disorders, including PCOS, NAFLD, and even cancers, is a journey of continuous discovery about this wonder drug. These explorations suggest that the full therapeutic potential of metformin is far from exhausted, promising an even broader application in clinical practice in the years to come.

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