# PHARMACOLOGICAL AND BIOCHEMICAL MECHANISMS OF ACTION OF METFORMIN IN TYPE 2 DIABETES MELLITUS (LITERATURE REVIEW)

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**Abstract.** According to the World Health Organization, the number of patients with diabetes mellitus worldwide continues to increase steadily year by year, with more than 90% of cases being attributable to type 2 diabetes mellitus. The disease reduces patients' quality of life through cardiovascular, renal, ocular, and nervous system complications and places a substantial economic burden on healthcare systems. Therefore, the treatment of the disease with pathogenetically justified, safe, and effective therapeutic agents remains one of the key challenges in modern medical practice. Metformin has been used as a first-line pharmacological agent for the treatment of type 2 diabetes mellitus for several decades. However, its molecular and biochemical mechanisms of action continue to be actively investigated and supplemented by new findings, including its effects on the gut microbiota and glucagon-like peptide-1 (GLP-1) secretion. Therefore, a comprehensive and systematic analysis of the pharmacodynamic and biochemical basis of metformin's effects is relevant not only from a practical clinical perspective but also as a scientific and theoretical foundation for the development of novel glucose-lowering agents, thereby emphasizing the relevance of this topic.
**Keywords:** metformin, type 2 diabetes mellitus, AMPK, gluconeogenesis, insulin sensitivity, mitochondrial complex I, GLUT4, lactic acidosis, gut microbiota.

## METFORMINNING 2-TOIFA QANDLI DIABETDAGI FARMAKOLOGIK VA BIOKIMYOVIY TA'SIR MEXANIZMLARI (ADABIYOTLAR TAHLILI)

**Annotatsiya.** Jahon sog'liqni saqlash tashkiloti ma'lumotlariga ko'ra, dunyo bo'yicha qandli diabet bilan og'rigan bemorlar soni yildan-yilga barqaror o'sib bormoqda, ularning 90% dan ortig'ini 2-toifa qandli diabet tashkil etadi. Ushbu kasallik yurak-qon tomir, buyrak, ko'z va asab tizimi asoratlari orqali bemor hayot sifatini pasaytiradi hamda sog'liqni saqlash tizimiga katta iqtisodiy yuk soladi. Shu sababli kasallikni patogenetik jihatdan asoslangan, xavfsiz va samarali vositalar bilan davolash tibbiyot amaliyotining dolzarb vazifalaridan biri bo'lib qolmoqda. Metformin o'n yilliklar davomida 2-toifa qandli diabetni davolashda birinchi qatordagi препарат sifatida qo'llanilib kelinmoqda, biroq uning molekulyar-biokimyoviy ta'sir mexanizmlari haqidagi bilimlar hozirgi kunda ham faol o'rganilmoqda va yangi ma'lumotlar bilan boyitilmoqda (masalan, ichak mikroflorasiga va GLP-1 sekretsiyasiga ta'siri kabi yo'nalishlar). Shu bois metforminning farmakodinamik va biokimyoviy asoslarini chuqur va tizimli tahlil qilish nafaqat amaliy klinik ahamiyatga, balki yangi qand pasaytiruvchi vositalarni ishlab chiqish uchun ilmiy-nazariy zaminga ham ega bo'lib, mavzuning dolzarbligini belgilaydi.
**Kalit so'zlar:** metformin, 2-toifa qandli diabet, AMPK, glyukoneogenez, insulin sezuvchanligi, mitoxondrial kompleks I, GLUT4, laktatatsidoz, ichak mikroflorasi.

## ФАРМАКОЛОГИЧЕСКИЕ И БИОХИМИЧЕСКИЕ МЕХАНИЗМЫ ДЕЙСТВИЯ МЕТФОРМИНА ПРИ САХАРНОМ ДИАБЕТЕ 2-ГО ТИПА (ОБЗОР ЛИТЕРАТУРЫ)

**Аннотация.** Согласно данным Всемирной организации здравоохранения, число пациентов с сахарным диабетом во всём мире продолжает стабильно увеличиваться из года в год, при этом более 90% случаев приходится на сахарный диабет 2-го типа. Данное заболевание снижает качество жизни пациентов вследствие развития сердечно-сосудистых, почечных,

офтальмологических и неврологических осложнений, а также создаёт значительную экономическую нагрузку на систему здравоохранения. В связи с этим лечение заболевания с применением патогенетически обоснованных, безопасных и эффективных лекарственных средств остаётся одной из актуальных задач современной медицинской практики. Метформин на протяжении нескольких десятилетий применяется в качестве препарата первой линии для лечения сахарного диабета 2-го типа. Однако молекулярные и биохимические механизмы его действия и в настоящее время активно изучаются и дополняются новыми данными, включая сведения о влиянии препарата на кишечную микробиоту и секрецию глюкагоноподобного пептида-1 (GLP-1). В связи с этим углублённый и систематический анализ фармакодинамических и биохимических основ действия метформина имеет не только практическое клиническое значение, но и формирует научно-теоретическую основу для разработки новых сахароснижающих лекарственных средств, что определяет актуальность данного направления. **Ключевые слова:** метформин, сахарный диабет 2-го типа, AMPK, глюконеогенез, чувствительность к инсулину, митохондриальный комплекс I, GLUT4, лактатацидоз, кишечная микробиота.

**Introduction.** Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by reduced insulin sensitivity and relative insulin deficiency and is one of the most prevalent endocrine disorders worldwide. Metformin (dimethylbiguanide), the first-line pharmacological agent traditionally recommended for the treatment of T2DM, has established a prominent role in clinical practice due to its high efficacy, favorable safety profile, and low cost. Metformin is capable of reducing blood glucose levels without causing a significant risk of hypoglycemia, which distinguishes it from many other glucose-lowering agents. This article reviews the principal pharmacological and biochemical mechanisms of action of metformin in the human body. Metformin is absorbed primarily in the upper portion of the small intestine, with an oral bioavailability of approximately 50–60%. The drug exhibits minimal binding to plasma proteins and undergoes negligible hepatic metabolism. It is eliminated from the body largely unchanged through the kidneys, predominantly via tubular secretion. This pharmacokinetic property makes metformin less susceptible to metabolic drug–drug interactions involving hepatic enzymes; however, it necessitates careful dose selection in patients with impaired renal function, as drug accumulation may increase the risk of metformin-associated lactic acidosis. Major Molecular and Biochemical Target: AMP-Activated Protein Kinase (AMPK)**:** AMP-activated protein kinase (AMPK) occupies a central position in the modern understanding of the pharmacological actions of metformin. Metformin partially inhibits complex I (NADH dehydrogenase) of the mitochondrial respiratory chain. As a result, ATP production is reduced, leading to an increase in the intracellular AMP/ATP and ADP/ATP ratios. These changes promote activation of AMPK through the upstream kinase liver kinase B1 (LKB1). AMPK functions as a cellular energy sensor. Once activated, it promotes catabolic pathways involved in energy production while suppressing energy-consuming anabolic processes. AMPK activation leads to a cascade of metabolic changes, including:

1. Reduced expression of key enzymes involved in hepatic gluconeogenesis, particularly phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase;
2. Suppression of lipogenesis through inhibition of the transcriptional activity of sterol regulatory element-binding protein 1 (SREBP-1);
3. Enhanced translocation of glucose transporter type 4 (GLUT4) to the plasma membrane in skeletal muscle and adipose tissue, thereby increasing glucose uptake by peripheral tissues.

One of the most important and clinically relevant effects of metformin is the reduction of endogenous glucose production by the liver. This effect is mediated not only through AMPK-dependent mechanisms but also through AMPK-independent pathways. Inhibition of mitochondrial glycerol-3-phosphate dehydrogenase alters the cytosolic redox state, increasing the $NADH/NAD^+$ ratio. This change slows metabolic reactions required for gluconeogenesis from lactate and other substrates. In addition, metformin influences glucagon receptor signaling, reducing intracellular cyclic adenosine monophosphate (cAMP) levels and subsequently decreasing protein kinase A (PKA) activity. This attenuates the stimulatory effects of glucagon on hepatic gluconeogenesis and glycogenolysis. Metformin improves insulin sensitivity in skeletal muscle and adipose tissue. This effect involves enhanced insulin

receptor tyrosine kinase activity, increased phosphorylation of insulin receptor substrates (IRS-1 and IRS-2), and activation of the phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) signaling pathway. As a result, translocation of GLUT4 transporters to the plasma membrane is enhanced, leading to increased glucose uptake and glycogen synthesis in skeletal muscle. Research conducted in recent years has revealed additional mechanisms through which metformin exerts its effects at the intestinal level.

**1. Effects on the Gut Microbiota.** Metformin alters the composition and metabolic activity of the gut microbiota and may increase the production of short-chain fatty acids (SCFAs), such as butyrate, which can have beneficial effects on insulin sensitivity.

**2. Enhancement of GLP-1 Secretion.** Metformin may stimulate the secretion of glucagon-like peptide-1 (GLP-1) from intestinal L cells. GLP-1 enhances glucose-dependent insulin secretion and contributes to improved glucose homeostasis.

**3. Delayed Intestinal Glucose Absorption.** Metformin may attenuate postprandial increases in blood glucose by modulating intestinal glucose transport processes and slowing glucose absorption.

**4. Activation of the Gut–Liver Axis.** Activation of AMPK within the intestinal wall may contribute to signaling along the gut–liver axis, thereby influencing hepatic glucose production and providing an additional mechanism for the regulation of glucose homeostasis.

**Metformin, Lactate Metabolism, and the Risk of Lactic Acidosis.** Partial inhibition of mitochondrial complex I may modestly enhance anaerobic glycolysis and increase lactate production. In patients with normal renal function, this effect is generally of limited clinical significance because lactate is efficiently cleared. However, the risk of lactic acidosis may increase in the presence of significant renal or hepatic impairment, tissue hypoxia, or severe alcohol consumption. Therefore, metformin therapy requires particular caution in patients with these conditions. The combined effects of the mechanisms described above result in several clinically important metabolic effects of metformin:

1. Reduction of fasting and postprandial blood glucose levels;
2. Reduction of glycated hemoglobin (HbA1c) by approximately 1–1.5% on average;
3. A weight-neutral effect or modest reduction in body weight;
4. A low risk of hypoglycemia because metformin does not directly stimulate insulin secretion;
5. Potential additional cardioprotective effects, as suggested by a number of clinical studies.

**Conclusion.** The therapeutic efficacy of metformin in type 2 diabetes mellitus is based on a complex and multifaceted network of molecular and metabolic mechanisms. Its principal actions include partial inhibition of the mitochondrial respiratory chain, activation of AMPK, suppression of hepatic gluconeogenesis, improvement of peripheral insulin sensitivity, and additional effects mediated through the gastrointestinal tract and gut–liver axis. A detailed pharmacological and biochemical understanding of these mechanisms is important not only for elucidating the clinical efficacy of metformin but also for facilitating the development of novel and more selective glucose-lowering agents in the future.

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