Effects of Metformin on Human Metabolic System, Gene Expression and Mechanism of Action

Yuyao Qiao *

Cardiff Sixth Form College, Cardiff, United Kingdom

* Corresponding author: Yuyao.qiao@ccoex.com

Abstract. Metformin, a pivotal medication in type 2 diabetes management, has garnered attention due to its multifaceted effect on the human body. This research explores the diverse effects of metformin, encompassing its role in the metabolic system, molecular mechanisms of action, and influence on gene expression. Metformin's primary mode of action involves enhancing insulin sensitivity, regulating hepatic glucose production, and modulating various metabolic pathways. Beyond glucose control, it has shown promise in addressing conditions like polycystic ovary syndrome, cancer treatment, and even COVID-19 outcomes. At the molecular level, metformin's activation of adenosine monophosphate-activated protein kinase (AMPK) orchestrates a cascade of gene expression changes, contributing to its therapeutic outcomes. However, the variability in findings across studies underscores the intricate nature of Metformin's mechanisms. This research highlights the remarkable journey of metformin, from its herbal origins to its status as a globally recognized therapy, underscoring the importance of continuous research to refine its applications and improve patient care. Understanding metformin's multifaceted effects provides a comprehensive perspective on its broader implications for human health and well-being.

Keywords: Metformin, Gene expression, Human metabolic system.

1. Introduction

Metformin, a well-known and widely prescribed medication, has consistently played a significant role in managing type 2 diabetes mellitus (T2DM). Beyond its primary role in glucose regulation, Metformin has garnered significant attention for its potential effects on various aspects of the human body. With a focus on elucidating the mechanisms and outcomes of metformin administration, this examination seeks to shed light on its broader implications for human health and well-being. Metformin, chemically known as dimethyl biguanide, was initially originated from Galega officinalis, commonly referred to as French lilac, an age-old folk remedy for diabetes. Upon its integration into clinical application during the 1950s, metformin has remained a pivotal therapeutic agent for managing T2DM. Its mode of action primarily centers around reducing hepatic glucose production, enhancing the sensitivity of insulin in peripheral tissues, and inhibiting the absorption of glucose in intestinal tract. These mechanisms work in concert to lower blood glucose levels, making it a fundamental choice in diabetes management.

Metformin, also known as dimethyl biguanide, has emerged as a cornerstone in the management of type 2 diabetes, being the preferred first-line oral agent for lowering blood glucose levels. Its history is deeply rooted in herbal medicine, specifically Galega officinalis, commonly recognized as goat's rue. Guanidine, a compound found in Galega officinalis, was discovered in 1918 to lower blood glucose levels. This discovery paved the way for the synthesis of guanidine derivatives, including metformin, during the 1920s. However, these derivatives were overshadowed by the introduction of insulin therapy. Metformin's journey took an unexpected turn when it was rediscovered in the 1940s during the search for treatments for malaria. Clinical tests revealed its efficacy in treating influenza and, subsequently, its potential in reducing blood sugar levels. French physician Jean Sterne is credited as the first to report the use of metformin for diabetes therapy in 1957 [1]. Despite its initial limited attention due to perceived weaker potency compared to other biguanides like phenformin and buformin, which carried a high risk of lactic acidosis and were eventually discontinued, metformin gradually gained recognition in Europe.

In 1995, metformin was introduced to the United States, further boosting its application in different fields. Long-term studies demonstrated metformin's cardiovascular benefits, solidifying its position as the preferred initial therapy for type 2 diabetes [2]. Six decades after its introduction, metformin has evolved into the most prescribed blood sugar-lowering medication globally, with ongoing research exploring its potential applications beyond diabetes, including in conditions like polycystic ovary syndrome (PCOS), gestational diabetes, and even cancer treatment. It has also shown promise in preventing weight gain and hypoglycemia, making it a valuable tool in diabetes management.

This remarkable journey of metformin, from herbal origins to a globally recognized therapy. Not only it highlights the complexities of drug development, the importance of pharmacological understanding, but also the significance of long-term clinical data in shaping medical practice. It serves as a lesson in reevaluating medications and continually expanding our knowledge to improve patient care. Diabetes comprises a collection of enduring metabolic conditions marked by consistently elevated blood sugar levels resulting from inadequate insulin secretion or inadequate cellular responsiveness to insulin. High blood glucose levels can lead to various health problems, including cardiovascular diseases, nerve damage, and eye conditions. According to WHO's report, diabetes caused about 2 million deaths in 2019 and increased by approximately 3% between 2000 and 2019, while other major NCDs dropped. Type 2 diabetes, alternatively termed non-insulin-dependent diabetes, stands as the most prevalent form, typically manifesting in individuals of middle age or older, characterized by insufficient insulin secretion and diminished cellular sensitivity to insulin. Initial treatment methods may include lifestyle changes, dietary control, and medication.

This research aims to explore the various dimensions of metformin's impact on the human body. In the following sections, this research will delve into three key areas: the effects on the human metabolic system, gene expression and mechanism of action of metformin. Each section will provide an in-depth examination of the existing literature and research findings, offering insights into how metformin exerts its influence and the potential ramifications for human health.

2. Metabolic effects

The section will be dedicated to metformin's effects on the human metabolic system. Beyond its glucose-lowering properties, metformin has been implicated in a multitude of metabolic pathways. Its role in attenuating hepatic gluconeogenesis, an essential process in maintaining blood glucose levels, has been investigated. Furthermore, metformin has been associated with improved insulin sensitivity, making it an attractive option for individuals with insulin resistance, often a precursor to T2DM. In addition, the medication has demonstrated favorable outcomes in terms of body weight regulation and lipid profile improvement, which can have significant implications.

2.1. Metformin's role in glucose and insulin regulation

Metformin, a well-established biguanide medication, has been employed globally for over four decades in the management of T2DM. Its primary mechanism of action centers on enhancing insulin sensitivity in both liver and muscle tissues, which ultimately leads to improved glycemic control. Unlike some antidiabetic medications, metformin does not stimulate insulin secretion, thereby avoiding the risk of hypoglycemia. Instead, it works to mitigate hyperglycemia by primarily targeting insulin resistance, which is a characteristic feature of T2DM. Metformin's ability to improve insulin sensitivity has been well-documented in clinical studies, leading to enhanced cellular glucose uptake and reduced reliance on excessive insulin production.

2.2. Metformin's effects on metabolic pathways

The impact of metformin on metabolic pathways extends beyond insulin sensitivity. It is a medication with diverse and multifaceted actions, affecting various aspects of metabolism. One of its key physiological effects is the activation of adenosine monophosphate-activated protein kinase (AMPK), often referred to as a "metabolic master switch" [3].

Research findings have elucidated several metabolic effects of metformin related to glucose and lipid metabolism. Metformin has been shown to reduce hepatic gluconeogenesis and glycogenolysis, effectively lowering fasting and postprandial plasma glucose concentrations. AMPK activation contributes significantly to this process [3], as shown in Fig. 1.

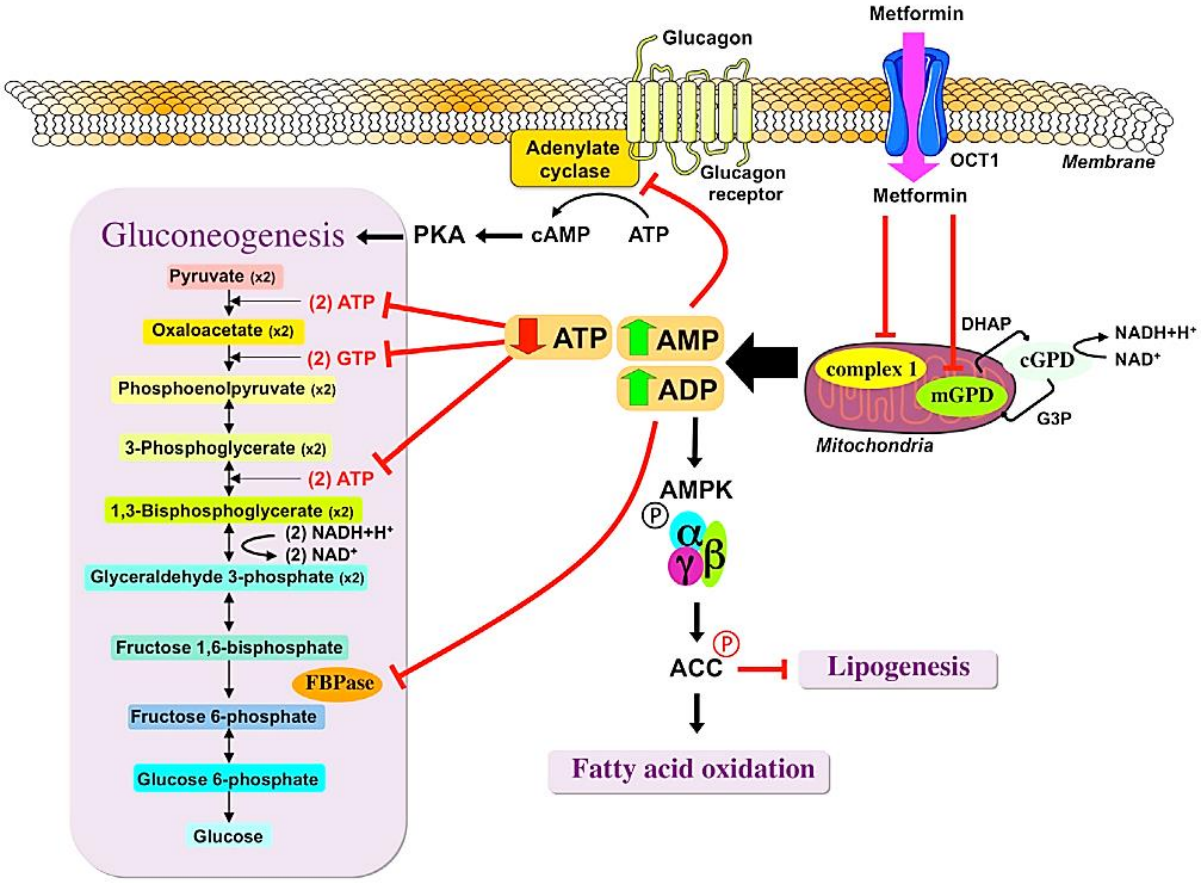


Figure 1. Metformin-induced inhibition for hepatic glucose output [3].

In addition to glucose regulation, metformin has demonstrated its effectiveness in ameliorating lipid metabolism. Individuals with T2DM often present with dyslipidemia, characterized by elevated triglycerides and low-density lipoprotein (LDL) cholesterol levels, which increase cardiovascular risk. Metformin has been associated with improvements in these lipid markers, contributing to better lipid profiles.

2.3. Effects on body weight and other metabolic parameters

Weight management is a crucial aspect of diabetes care, and metformin offers benefits in this regard. Some studies have indicated that Metformin can lead to modest but clinically significant weight loss in individuals with T2DM [4]. This effect is particularly important as excess weight can exacerbate insulin resistance and metabolic dysfunction. Moreover, metformin may influence other metabolic parameters beyond glucose and lipid control. It can contribute to improved blood pressure control, which is vital for reducing cardiovascular complications in individuals with T2DM. Metformin may have a role in reducing chronic inflammation, a factor implicated in various metabolic disorders.

2.4. Exploring combinations and diverse effects

Metformin's metabolic effects are not confined to T2DM. Its potential in combination therapy and in various metabolic and endocrine conditions have been investigated. For instance, metformin has been examined in combination with other medications to assess its impact on metabolic control in patients with PCOS. Moreover, metformin's influence is not limited to diabetes and PCOS. Research

has explored its effects in other conditions, including its potential to reduce proliferative markers in endometrial cancer patients [5], its impact on insulin resistance and metabolic control in patients with type 1 diabetes, and its role in enhancing eicosatetraenoic acid metabolism and inhibiting ovarian cancer [6].

2.5. Potential side effects and limitations

While metformin is generally considered safe and well-tolerated, there are potential side effects to be aware of, particularly in the context of the metabolic system. Gastrointestinal disturbances such as abdominal discomfort and diarrhea are common side effects associated with metformin use. These side effects can often be minimized by titrating the dosage slowly and taking the medication with food [7].

It's worth noting that lactic acidosis, a rare but serious condition, has been reported in association with metformin use, especially in individuals with contraindications such as impaired renal function [2]. However, the incidence of lactic acidosis is very low, with approximately 3 cases per 100,000 patient-years of therapy.

Metformin's influence on the human metabolic system extends well beyond its role in glucose regulation. Through its multifaceted actions on insulin sensitivity, glucose and lipid metabolism, weight management, and more, metformin remains a cornerstone in the treatment of T2DM. Its diverse effects have prompted investigations into its potential application in various metabolic and endocrine conditions, expanding its therapeutic horizon. While it is generally safe, clinicians should be vigilant about potential side effects, particularly gastrointestinal symptoms and lactic acidosis, and ensure appropriate patient selection and monitoring.

3. Gene expression

This section will examine how metformin may influence gene expression. The research has shed light on the medication's ability to modulate gene activity, often through epigenetic modifications. By altering the expression of specific genes and gene pathways, metformin may orchestrate changes in various cellular and physiological processes. This section synthesizes current knowledge on the subject and discusses its implications for understanding metformin's broader therapeutic effects. Metformin's influence on gene expression has garnered significant attention in recent years, as emerging evidence suggests that its therapeutic effects extend beyond the regulation of glucose metabolism. Understanding the mechanisms through which metformin may influence gene expression and summarizing studies that have examined its effects on specific genes and pathways is crucial for unraveling the broader impacts of this widely used medication. This section delves into the complex world of metformin's interaction with gene expression and its relevance to therapeutic outcomes while also addressing variability in findings across research studies.

3.1. Mechanisms of metformin-mediated gene expression regulation

Metformin's primary mode of action involves the activation of the AMPK, which acts as a central regulator of cellular energy homeostasis [3]. AMPK phosphorylation has far-reaching effects on gene expression through its ability to modulate various transcription factors, coactivators, and corepressors.

Metformin's influence on AMPK and PGC-1α can lead to a cascade of gene expression changes. Activation of AMPK inhibits the activity of the mammalian target of rapamycin complex 1 (mTORC1), a key regulator of protein synthesis and cell growth [3]. Inhibition of mTORC1 by Metformin can result in the downregulation of genes involved in anabolic processes, thereby promoting catabolic pathways. Moreover, metformin has been proposed to exert its effects on gene expression through epigenetic modifications. Epigenetic changes, such as DNA methylation and histone modifications, can influence the accessibility of genes to transcriptional machinery. Some studies have suggested that Metformin may alter DNA methylation patterns, particularly in genes

associated with metabolic regulation [8]. These epigenetic modifications could contribute to long-term changes in gene expression profiles, potentially mediating the drug's therapeutic effects.

3.2. Studies on metformin-induced gene expression changes

Metformin's ability to enhance insulin sensitivity is central to its therapeutic action in type 2 diabetes. Metformin can influence the expression of insulin signaling genes. For instance, increased insulin receptor (INSR) expression and improved insulin receptor substrate (IRS) signaling in response to metformin treatment were analyzed. These changes in gene expression contribute to enhanced insulin sensitivity, thereby reducing hyperglycemia. Beyond diabetes, metformin's potential as an anti-cancer agent has generated significant interest. Some studies have explored its effects on cancer-related genes. For instance, metformin may modulate the expression of genes involved in cell cycle regulation and apoptosis, potentially inhibiting cancer cell growth [9]. However, the specific mechanisms in cancer require further investigation.

3.3. Relevance of gene expression changes to therapeutic effects

The gene expression changes induced by Metformin are closely tied to its therapeutic effects. Improved insulin sensitivity, driven by altered expression of insulin signaling genes, is central to glycemic control in type 2 diabetes. The upregulation of mitochondrial biogenesis genes contributes to enhanced energy metabolism and reduced metabolic stress. The suppression of pro-inflammatory genes aligns with the broader goal of reducing inflammation, which is often a driver of insulin resistance and metabolic dysfunction.

Metformin's potential in cancer prevention or treatment is also linked to gene expression changes. By influencing cancer-related genes, metformin may disrupt the abnormal cellular processes that underlie cancer development and progression [9]. However, it's essential to recognize that the exact mechanisms and clinical implications in cancer require further exploration, as the effects may vary depending on cancer type and stage.

3.4. Variability in findings across studies

While the evidence points to metformin's ability to influence gene expression, it's important to acknowledge the variability in findings across different research studies. Factors contributing to this variability include variations in study design, patient populations, dosages, and treatment durations. Additionally, gene expression is highly context-dependent, and the specific genes affected by Metformin may differ in various physiological and pathological conditions. The epigenetic mechanisms through which metformin may induce gene expression changes are complex and not yet fully elucidated. The extent and persistence of these epigenetic modifications and their contribution to therapeutic outcomes remain subjects of ongoing investigation [8].

Metformin's impact on gene expression is a multifaceted aspect of its mechanism of action. Through the activation of AMPK, epigenetic modifications, and interactions with various transcriptional regulators, metformin exerts widespread effects on gene expression profiles. These changes underpin many of its therapeutic benefits, including improved insulin sensitivity, mitochondrial function, and anti-inflammatory effects. However, the variability in findings across studies underscores the complexity of gene expression regulation by metformin and the need for further research to fully unravel its mechanisms and clinical implications, particularly in conditions beyond type 2 diabetes.

4. Mechanism of action

The last section delves into metformin's mechanism of action. A key figure in this scenario involves the stimulation of AMPK, a cellular energy detector that aids in regulating numerous metabolic functions. Metformin has been shown to activate AMPK, thereby influencing cellular processes. Metformin is a cornerstone medication in the management of T2DM due to its multifaceted

mechanisms of action [10]. This section explores the intricate details of how metformin operates at the molecular level to regulate glucose metabolism, improve insulin sensitivity, and counteract the pathophysiological processes associated with diabetes. Metformin can be used to activate AMPK, metformin's inhibition of gluconeogenesis extends to its action on the gluconeogenic transcription factor, sterol regulatory element-binding protein-1c (SREBP-1c), and metformin's ability to enhance insulin sensitivity in skeletal muscle is a direct consequence of AMPK activation. In addition, the reduction in protein kinase A (PKA) activity results in decreased gluconeogenesis, further contributing to metformin's glucose-lowering effect. Metformin appears to play a role in restoring the autophagy process in β-cells, thereby potentially preventing further deterioration in β-cell function and viability.

Metformin's mechanism of action is multifaceted, addressing multiple aspects of glucose metabolism and insulin sensitivity. Its effects on AMPK activation, suppression of gluconeogenesis and lipogenesis, enhanced insulin sensitivity, and modulation of various cellular processes highlight its importance in the management of type 2 diabetes. Additionally, its influence on the gut microbiome, appetite regulation, potential anti-tumorigenic effects, and impact on COVID-19 outcomes underscore the far-reaching implications of this widely used medication.

5. Conclusion

This research explores the intricate mechanisms behind these effects and discusses their potential clinical relevance. The multifaceted influence of metformin extends beyond its immediate role in glucose regulation. This research endeavors to unravel the intricate web of effects that metformin exerts on the human metabolic system, cellular activity, and gene expression. This research will provide a comprehensive understanding of metformin's impact on the human body, shedding light on its broader implications for human health and potential applications beyond diabetes management. This comprehensive research has explored the multifaceted effects of metformin on the human body, with a particular focus on its influence on the metabolic system, cellular activity, and gene expression. Metformin, originally derived from herbal medicine, has evolved into a cornerstone medication for managing T2DM. Its primary mode of action involves enhancing insulin sensitivity, reducing hepatic glucose production, and impacting various metabolic pathways. Beyond its role in diabetes management, metformin has demonstrated its versatility in addressing a range of metabolic and endocrine conditions, including polycystic ovary syndrome and even potential benefits in cancer treatment. At the molecular level, metformin's mechanisms of action involve the activation of the AMPK, which results in a cascade of effects, including the regulation of gene expression. This influence on gene expression plays a crucial role in its therapeutic outcomes, such as improved insulin sensitivity, mitochondrial function, and anti-inflammatory effects. However, it is essential to acknowledge the variability in findings across studies, as gene expression is context-dependent and influenced by various factors. Metformin's journey from its herbal origins to a globally recognized therapy highlights the complexities of drug development, the importance of pharmacological understanding, and the significance of long-term clinical data in shaping medical practice. It is better equipped to enhance patient care and improve health outcomes. In summary, metformin's impact extends far beyond its role as a glucose-lowering medication, reaching into the intricate web of metabolic pathways, cellular processes, and gene expression. This research provides a comprehensive analysis of the current state of knowledge about metformin's multifaceted effects, offering insights into its broader implications for human health and well-being.

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