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Metformin: From Diabetes Management to Broader Applications in Weight Reduction and Metabolic Health

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Abstract

Introduction

Metformin is a widely used oral hypoglycemic agent for type 2 diabetes, with origins in medieval European medicine through the use of Galega officinalis. Subsequent centuries of research led to the development of synthetic biguanides, with metformin's approval as an antidiabetic agent in 1957. Since then, its therapeutic applications have broadened to address other metabolic and endocrine disorders, such as obesity, polycystic ovary syndrome (PCOS), and antipsychotic-induced weight gain.

Purpose of the Study

This study aims to review metformin's pharmacological properties, mechanisms of action, and its expanded clinical applications. Specifically, it focuses on metformin’s role in promoting weight loss and improving metabolic health across diverse patient populations, including those without diabetes. The study also addresses evidence gaps and proposes areas for further research on dose optimization and safety in non-diabetic populations.

Materials and Methods

A systematic literature review was conducted using databases such as PubMed and Google Scholar, focusing on studies examining metformin's effects on glycemic control, weight reduction, and metabolic stability.

Conclusions

Metformin's history underscores its evolution from traditional remedies to a versatile pharmacological agent for treating diabetes and other metabolic conditions. Ongoing research

is essential to fully establish its optimal therapeutic parameters and long-term safety for diverse patient groups.

Keywords: metformin, weight reduction, biguanides, mechanisms of action, increased insulin sensitivity, Polycystic ovary syndrome (PCOS)

Introduction

Metformin, a widely used oral hypoglycemic agent for type 2 diabetes treatment, originates from the traditional use of Galega officinalis, a plant known in medieval Europe for its antidiabetic properties. In the 17th century, English herbalist Nicholas Culpeper described its potential benefits, and subsequent research in the late 19th and early 20th centuries identified guanidine, a compound with hypoglycemic effects, though its toxicity precluded clinical application. The development of synthetic guanidine derivatives led to the creation of biguanides with improved safety profiles, culminating in the introduction of metformin as an antidiabetic drug in 1957. Although other biguanides displayed stronger effects, they were withdrawn in the 1970s due to the risk of lactic acidosis. The reapproval of metformin by the FDA in 1995 enabled its broader use, with subsequent studies confirming its efficacy and safety.[1]

In recent years, interest in metformin has extended beyond type 2 diabetes to include other clinical conditions such as obesity, polycystic ovary syndrome (PCOS) [19,20], and antipsychotic-induced weight gain [16, 17, 18]. At the cellular level, metformin's mechanisms—such as inhibition of gluconeogenesis [2, 3], activation of AMPK [4], increased glucose transport into tissues [6, 7, 8, 9], and reduced intestinal glucose absorption [10]—contribute to improved insulin sensitivity and stabilization of metabolic parameters.

Purpose of the study

The purpose of this study is to review and analyze the pharmacological properties, mechanisms of action, and clinical applications of metformin, particularly its role in weight reduction across various patient populations. By examining metformin's multifaceted effects beyond glycemic control—including improvements in insulin sensitivity, lipid metabolism, and overall metabolic stability—the study aims to highlight metformin's potential as an adjunctive treatment in

conditions such as type 2 diabetes, polycystic ovary syndrome (PCOS), and antipsychotic-induced weight gain. Additionally, this review seeks to address current evidence on the drug's efficacy in non-diabetic populations and to identify areas where further research is necessary to optimize its therapeutic use, dosing, and long-term safety.

Materials and methodology

A literature review focused on keywords relatedtothetopic was performed using databases such as PubMed and Google Scholar

The History of Metformin's use

Metformin is an oral hypoglycemic medication and a biguanide derivative widely used in managing type 2 diabetes. The therapeutic history of guanidine derivatives in Europe dates back to the Middle Ages, where Galega officinalis (also known as goat's rue) was employed in traditional medicine for managing symptoms linked to type 2 diabetes. In the 17th century, English herbalist Nicholas Culpeper highlighted the plant's anti-diabetic properties in his work The English Physitian or an astrologo-physical discourse on the vulgar herbs of this nation.

In research from the late 19th and early 20th centuries, Galega officinalis was shown to contain guanidine, a compound with hypoglycemic properties, although guanidine's high toxicity prevented its direct clinical use. Instead, a milder extract from the plant called galegine (isoamylene guanidine) was briefly used in the 1920s to lower blood sugar levels. In 1926, Frank, Nothmann, and Wagner confirmed the strong anti-diabetic activity of two synthetic diguanides—decamethylenediguanidine (syntalin A) and dodecamethylenediguanidine (syntalin B), which were better tolerated than galegine. As insulin became more accessible, awareness of the toxicity and limited effectiveness of hypoglycemic diguanidine derivatives grew, leading to the cessation of syntalin A and B by the early 1930s, though syntalin B was used in Germany until the mid-1940s.

In 1929, the first synthetic biguanide, biguanide sulfate, was produced. Animal studies suggested that biguanide was non-toxic, yet it was never tested on humans. In 1957, Jean Sterne demonstrated the anti-diabetic properties of dimethylbiguanide, now known as metformin. Although other biguanide derivatives like buformin and phenformin displayed even greater hypoglycemic effects, they were withdrawn in many countries in the late 1970s due to the high risk of lactic acidosis. Following studies by DeFronzo and colleagues and Stumvoll et al., metformin was reapproved for use in the United States in 1995 by the Food and Drug Administration (FDA). [1]

Mechanisms of Action of Metformin

Inhibition of Gluconeogenesis

The precise mechanism by which metformin reduces hepatic glucose production remains unclear. It is suggested that the primary site of metformin's action is in the mitochondria of hepatocytes, where it inhibits the activity of Complex I of the respiratory chain.[2,3] By suppressing cellular respiration, metformin decreases ATP production and the rate of gluconeogenesis. Additionally, this effect may stimulate the expression of glucose transporters, thereby enhancing glucose uptake. It is not yet determined whether metformin's influence on mitochondrial respiration involves directly slowing transport across the inner mitochondrial membrane or if it operates through other, unidentified cellular signaling pathways.[3]

AMPK activation

Based on research findings, it is evident that the inhibition of gluconeogenesis in hepatocytes by metformin is facilitated through the activation of AMP-activated protein kinase (AMPK). AMPK is a heterotrimeric enzyme composed of a catalytic subunit (α) and two regulatory subunits (β and γ). This enzyme functions as an intracellular energy sensor, becoming activated when the ATP/ADP and phosphocreatine/creatine ratios decrease. There are two isoforms of the catalytic subunit: AMPK α1, which is present in all tissue types, and AMPK α2, which is found in skeletal muscle, the heart, and the liver. Studies conducted on patients with type 2 diabetes have also shown an increase in AMPK α2 activity in skeletal muscle and glucose uptake in peripheral tissues under the influence of metformin. [4]

Another mechanism of AMPK activation by metformin is the stimulation of this enzyme by reactive nitrogen species (RNS) derived from mitochondria, whose synthesis is increased under the influence of the drug. [5]

Increased glucose transport

The phenomenon of insulin resistance involves a reduced insulin-dependent glucose uptake, leading to impaired glucose transport in skeletal muscle cells. The disruption in insulin signaling for glucose transport results from a decreased amount of GLUT4 protein on the cell surface. [6] Studies on obese, insulin-resistant rats have shown that metformin use enhances insulin-dependent translocation of GLUT4 and GLUT1 transporters to the adipocyte cell membrane, without affecting de novo synthesis of these transporters. [7] Research has demonstrated that metformin activates the insulin receptor in human hepatocytes by promoting

its phosphorylation. This triggers selective phosphorylation and activation of the insulin receptor substrate (IRS-2), leading to increased glucose uptake through enhanced translocation of GLUT-1. [8] In a study on human fibroblasts obtained from diabetic patients, it was observed that metformin induces the expression of the glucose transporter gene, resulting in increased production of the GLUT-1 protein. [9]

Reduction of intestinal glucose absorption

Metformin also contributes to the reduction of hyperglycemia by inhibiting glucose absorption in the midsection of the small intestine. This action may help lower postprandial blood glucose levels. [10]

Reduction in free fatty acid (FFA) levels

In individuals with type 2 diabetes, elevated levels of free fatty acids (FFAs) are frequently observed. Prospective epidemiological studies have shown that increased FFA levels constitute a risk factor for the progression of type 2 diabetes. Elevated FFAs in peripheral circulation are likely to impair insulin-stimulated glucose uptake in muscle tissue and may also reduce insulin secretion by pancreatic beta cells. Thus, elevated FFA levels not only act as an independent risk factor for the development of type 2 diabetes but also contribute to metabolic dysfunctions in the liver and potentially in pancreatic islets, thereby accelerating disease progression.[11] The impact of metformin on adipose tissue is instrumental in improving glycemic control in type 2 diabetes patients. Research findings have shown that metformin reduces the release of free fatty acids (FFAs) from adipose tissue, leading to lower circulating FFA levels and consequently enhancing glucose uptake in peripheral tissues. [12] Evidence from successive studies suggests that metformin, by reducing elevated levels of free fatty acids (FFAs), may also help restore normal insulin secretion in beta cells whose secretory function has been impaired due to prolonged exposure to high FFA concentrations.[13]

Metformin in Overweight and Obese Individuals without Diabetes

Metformin, a drug commonly used in the treatment of type 2 diabetes, has garnered interest in the context of obese and overweight individuals who do not have diabetes. A systematic review and meta-analysis conducted by Hui et al. (2019) examined the efficacy of metformin in this patient population. The authors indicated that metformin may contribute to weight reduction, improvement of the lipid profile, and decreased risk of cardiovascular diseases. The results suggest that the effects of metformin extend beyond glycemic control, which may be particularly beneficial for individuals with obesity who have additional risk factors. The article emphasized the need for further research to better understand the mechanisms of action of

metformin and to determine the optimal dosing and duration of treatment in non-diabetic populations.[14]

Metformin in the Treatment of Childhood Obesity

Metformin, commonly used in the treatment of type 2 diabetes, is also under investigation for its potential benefits in managing obesity in children and adolescents. The systematic review titled "Systematic Review of the Benefits and Risks of Metformin in Treating Obesity in Children Aged 18 Years and Younger" examines the findings of 14 clinical trials assessing the effects of metformin on body mass index (BMI) and other metabolic parameters in individuals under 18 years of age. Most of these studies suggest that short-term treatment with metformin, when combined with lifestyle interventions, may lead to a modest reduction in BMI compared to lifestyle interventions alone. The average BMI reduction among children receiving metformin was approximately 3.6% from baseline, which is below the recommended 5-10% threshold generally considered clinically significant for weight reduction. Although these effects are statistically significant, their clinical relevance remains uncertain, especially in the context of long-term treatment. Subgroup analyses indicate that younger children with a higher baseline BMI (>35) may derive greater benefit from metformin therapy. The review authors emphasize that to fully determine the efficacy and safety of metformin in pediatric obesity treatment, large, well-designed trials with appropriate control groups and analyses of potential confounders, such as pubertal status and previous failures in lifestyle interventions, are necessary.[15]

Metformin in Weight Reduction Among Psychiatric Patients

Veerman and Cohen (2023) examined the prevention and treatment of weight gain associated with antipsychotic medications, a common adverse effect that poses significant health risks, including metabolic syndrome and cardiovascular disease. Published in Tijdschrift voor Psychiatrie, their review explores pharmacological and non-pharmacological strategies for managing weight gain in patients undergoing antipsychotic therapy, with a particular focus on the use of metformin. The study discusses metformin's efficacy in countering weight gain and improving metabolic profiles in patients who are prescribed antipsychotic medications. Veerman and Cohen highlight metformin's potential to address antipsychotic-induced weight gain by enhancing insulin sensitivity and promoting weight stabilization, which could help mitigate the metabolic side effects that often accompany long-term antipsychotic use. The authors stress the importance of early intervention and individualized treatment approaches to effectively manage weight in this population. Additionally, they call for further research into the optimal dosing of metformin and its long-term safety profile for patients taking

antipsychotics, as well as studies comparing the effectiveness of metformin with other weight management strategies, including lifestyle modifications and alternative pharmacotherapies. This review underscores metformin's promise as a valuable adjunct in psychiatric care, especially for patients at high risk of metabolic complications due to antipsychotic-induced weight gain.[16]

In their systematic review and meta-analysis, Björkhem-Bergman, Asplund, and Lindh (2011) examined the potential application of metformin as a weight-reducing agent in non-diabetic patients taking antipsychotic drugs. This population is particularly susceptible to weight gain, which is one of the most significant metabolic complications associated with antipsychotic treatment and often leads to metabolic syndrome, thereby increasing the risk of cardiovascular diseases. Published in the Journal of Psychopharmacology, the study incorporated data from several randomized clinical trials to evaluate the efficacy of metformin compared to control groups. The findings demonstrated that metformin use led to a statistically significant reduction in body weight, underscoring its potential as an adjunctive intervention for this patient group. The authors suggested that metformin's weight-reducing effect may arise from mechanisms beyond glycemic control, indicating a broader application in psychiatry as a strategy to counteract antipsychotic-induced weight gain. The study results highlight the potential inclusion of metformin as an adjunct therapy that could improve patient quality of life and reduce the risk of metabolic complications. However, the authors emphasize the need for further research to determine optimal dosing, treatment duration, and to assess the long-term safety of metformin use in non-diabetic individuals on antipsychotic medications. [17]

Praharaj, Jana, Goyal, and Sinha (2011), in their systematic review and meta-analysis, examined the efficacy of metformin in counteracting weight gain induced by olanzapine, an antipsychotic drug frequently associated with significant metabolic disturbances in patients. Olanzapine, primarily used in the treatment of psychotic disorders such as schizophrenia and bipolar disorder, is known to cause substantial weight gain and increase the risk of metabolic syndrome. Published in the British Journal of Clinical Pharmacology, the study analyzed data from numerous randomized clinical trials to assess the extent to which metformin may be effective in preventing this adverse effect of olanzapine. The results showed that patients receiving metformin experienced significantly less weight gain or even weight reduction compared to control groups. The authors highlighted that metformin might have a protective effect on patients' metabolism, which could be especially beneficial for individuals at risk of developing metabolic syndrome or cardiovascular diseases. The article noted that metformin's mechanism of action extends beyond glycemic control, suggesting effects on lipid metabolism

and improved insulin sensitivity, which are key aspects of weight management in this patient population. The authors called for further research to better understand the long-term effects of metformin on body weight in patients taking olanzapine and to determine optimal dosing and treatment regimens. These findings suggest that metformin may be an effective and safe adjunctive intervention in psychiatric treatment, particularly for patients susceptible to the metabolic side effects of olanzapine. [18]

Metformin-Induced Weight Reduction in Women with Polycystic Ovary Syndrome

Nieuwenhuis-Ruifrok, Kuchenbecker, Hoek, Middleton, and Norman (2009) conducted a systematic review and meta-analysis to evaluate the efficacy of insulin-sensitizing drugs, such as metformin, in promoting weight reduction among overweight or obese women of reproductive age. Published in Human Reproduction Update, the study aimed to investigate the role of these drugs in weight management and metabolic improvement in women who are particularly susceptible to hormonal disturbances and related health issues, such as polycystic ovary syndrome (PCOS). The analysis included data from multiple randomized clinical trials that allowed for the assessment of metformin's effectiveness as an adjunct for weight management. Results indicated that metformin use was associated with a significant reduction in body weight compared to control groups, suggesting that this drug may be an effective supportive tool for women in this age group who struggle with excess weight. The authors highlighted that metformin’s benefits may extend beyond glycemic control, positively impacting lipid metabolism and enhancing insulin sensitivity. Weight reduction in overweight and obese women may also positively influence hormonal regulation and fertility, which is particularly relevant in conditions such as PCOS. Nieuwenhuis-Ruifrok and colleagues emphasized the need for further research on the long-term effects of metformin in this population to better understand optimal dosing and its impact on reproductive and metabolic health.[19]

Naderpoor, Shorakae, de Courten, Misso, Moran, and Teede (2015) conducted a systematic review and meta-analysis assessing the effectiveness of metformin combined with lifestyle modification in managing polycystic ovary syndrome (PCOS), a condition often characterized by insulin resistance, weight gain, and reproductive and metabolic complications. Published in Human Reproduction Update, this study reviewed data from numerous randomized controlled trials to explore the therapeutic impact of metformin as an adjunct to lifestyle interventions, specifically focusing on weight reduction, insulin sensitivity, and menstrual cycle regulation. The analysis revealed that the combination of metformin with lifestyle changes yielded significantly better outcomes in weight reduction and insulin sensitivity than lifestyle

modifications alone. Furthermore, the combined approach was associated with improved menstrual regularity, an essential factor for reproductive health in women with PCOS. The authors proposed that the weight-reducing and insulin-sensitizing properties of metformin could complement lifestyle interventions, providing a more comprehensive approach to managing the metabolic and reproductive symptoms of PCOS. They highlighted the need for additional research to determine optimal metformin dosing, treatment duration, and long-term effects on reproductive and cardiovascular health. These findings support the use of metformin alongside lifestyle modifications as a viable therapeutic strategy for improving health outcomes in women with PCOS.[20]

Conclusion

The history of metformin use reflects an evolution from traditional medicine to modern pharmacological therapy, highlighting the importance of extensive research into biguanides and their role in treating metabolic disorders. Beginning with the traditional use of Galega officinalis in medieval Europe, through the early 20th-century attempts to use guanidines and their synthetic derivatives, and culminating in the introduction of metformin as an effective antidiabetic agent in the 1950s, the development of biguanide therapy illustrates the lengthy path toward achieving a safe and effective hypoglycemic agent.

Currently metformin, as a pharmacological agent with multifaceted action, plays a significant role not only in the treatment of type 2 diabetes but also in other clinical conditions where improving insulin sensitivity and achieving weight reduction are essential. Through mechanisms such as inhibition of hepatic gluconeogenesis, activation of AMPK, and increased glucose transport to peripheral tissues, metformin contributes to the stabilization of carbohydrate metabolism, which is critical in managing metabolic and endocrine disorders. Its effects on reducing glucose absorption in the intestines and lowering free fatty acid levels further support weight loss and lipid profile regulation, particularly in patients with insulin resistance, polycystic ovary syndrome (PCOS), and those receiving antipsychotic medications. Clinical studies confirm the efficacy of metformin in weight reduction, also suggesting its potential use as an adjunct therapy in select non-diabetic populations. However, further studies are required to fully understand the long-term effects of metformin, especially regarding dose optimization, treatment duration, and the assessment of its safety profile for prolonged use across diverse patient groups.

Disclosure

Author’s contribution

Daniel Zapasek: Conceptualization, writing rough preparation,

Julia Słowik: Writing rough preparation, formal analysis,

Maciej Mamczur: supervision,

Marcin Kuliga: visualization, data curation,

Mateusz Bajak: Methodology, software,

Damian Sowa : check,

Dominik Maciej Feret: writing and editing,

Julia Inglot : project administration

Jadwiga Inglot : resources, investigation,

Michał Szczepański: Project administration

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