



Therapeutic and Adverse Effects of Metformin in Diabetes: A Review Article

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Abstract: Metformin is the most often prescribed first-line oral antidiabetic. This review summarized the effects of Metformin on the body, its role in diabetes prevention and treatment, and the adverse effects of metformin administration. A PubMed search for metformin-related papers in diabetic patients was performed. We included articles on any metformin oral dosage in people with or without type 2 diabetes that reported favorable and unfavorable outcomes. Relevant studies from the references provided were reviewed. Metformin controls the blood glucose level by multiple mechanisms. These include increasing the cell sensitivity to insulin and reducing endogenous glucose secretion by the liver. Also, Metformin has been shown to assist in weight reduction in obese patients. Some early investigations showed that lifestyle changes and Metformin significantly reduced the incidence of diabetes in high-risk people, and lifestyle interventions were more effective than Metformin. Some trials indicated Metformin was not associated with any significant endangerment or advantage in terms of cardiovascular incidents. However, Metformin tended to be more effective in longer trials involving younger individuals regarding cardiovascular outcomes. The microvascular complication prevalence was insignificant between Metformin and other treatment interventions including placebo and lifestyle interventions. The gastrointestinal symptoms are common with metformin use as compared to placebo. Metformin increased the risk of lactic acidosis, especially in moderate and severe renal impairment settings, thus considered contraindicated. However, due to the low reported incidence of lactic acidosis associated with Metformin and the potential protective properties on the kidney, heart, and liver, it is advised to carefully balance the risk and benefits of Metformin when treating diabetes. In addition, Metformin has been shown to cause consequences other than gastrointestinal symptoms, such as vitamin B12 deficiency which can lead to hematologic issues, such as anaemia and peripheral neuropathy. Thus, periodic measurement of vitamin B12 for individuals treated with Metformin is recommended.

Keywords: Metformin, Diabetes, effects, Obesity, Cardiovascular.

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I. INTRODUCTION

The International Diabetes Federation (IDF) organization reports approximately 537 million adults with age between 20 to 79 years old are living with diabetes. With this high number of diabetic patients comes a tremendous demand for treatments, research, drugs invention, and regular improvement with the prime objective to tackle diabetes and eventually treat it. Diabetic medications were developed to control the blood glucose level among diabetic patients. According to World Health Organization (WHO), diabetes is one of the most common chronic metabolic diseases, leading to significant complications in many body systems such as cardiovascular, renal, and neurological systems. There are many types of diabetes, yet the most common type is diabetic type 2, which commonly has a late onset and occurs due to insulin resistance. The second most common type is diabetic Type 1, juvenile diabetes. This type has a different mechanism which is an insulin-dependent disease.¹ Metformin is the primary drug that has been used to treat patients with diabetic type 2.² Moreover, Metformin strongly affected patients with high body mass index (BMI). Metformin results in minimum weight gain compared to other medications such as insulin or sulfonylureas.³ Furthermore, a study was conducted to analyze the effect of different types of diabetic medications after ten years of using them. They found that individuals gained about 1 kg with metformin use, about 3 kg with glibenclamide, and 6 kg gained with insulin use.² Therefore, Metformin was the best medication for patients with type 2 diabetes high body mass index (BMI). Moreover, comparing the metformin effect with a combination of other antioxidants, it was found to have a protective retinopathy effect.¹ Regarding Metformin's mechanism of action, it activates the adenosine monophosphate kinase (AMPK) enzyme, leading to decreased gluconeogenesis and glycogen synthesis in the liver, thus reducing blood glucose levels.^{4,5} In this article, we reviewed the impact of Metformin on the body, its function in preventing and treating diabetes, as well as the side effects associated with the use of Metformin.

2. THE ADVANTAGE OF METFORMIN IN COMPARISON TO OTHER MEDICATIONS

Compared to insulin, glibenclamide, and chlorpropamide, Metformin decreased mortality by 30%.² Metformin controls the blood glucose level by different mechanisms which reduce the blood glucose level without increasing the insulin secretion by the pancreas.^{4,5} Furthermore, the main effect of Metformin is to increase the cell sensitivity to the insulin "insulin sensitizer" and reduce endogenous glucose secretion by the liver by decreasing gluconeogenesis and glycogenolysis.^{4,5} Other effects of metformin treatment were reported.⁶ Metformin delays the onset of diabetes and vascular impairment by reducing mitochondrial oxidative stress.⁶

3. ROLE OF METFORMIN IN TYPE 2 DIABETES PREVENTION

Metformin, a biguanide antidiabetic agent, may act by increasing insulin sensitivity, mainly by lipid oxidation and reducing insulin resistance.⁷ Also, it decreases the glucose production by the liver and reduces glucose intestinal absorption which helps to control blood glucose.⁷ Some reported that 500 mg daily of Metformin is the minimum dose necessary to achieve a clinically significant reduction in the haemoglobin A1c (HbA1c) with a mean decrease of 0.9%.⁸

Metformin was also reported to help reduce weight in obese diabetic patients and may help manage lipid disorders in these patients.^{7,9} To assess the efficacy of reduction in the incidence of type 2 diabetes with lifestyle intervention or Metformin, a study randomly assigned 3234 non-diabetic persons with elevated fasting and post-load plasma glucose concentrations to placebo, Metformin, or a lifestyle-modification program.¹⁰ The average follow-up was 2.8 years. Lifestyle changes and Metformin significantly reduced the incidence of diabetes in high-risk people, but lifestyle changes were more effective than Metformin.¹⁰

3.1. Fasting blood glucose and haemoglobin A1c (Hb A1C)

Fasting blood glucose and Hb A1c are used to measure the blood glucose. Fasting blood glucose is counted when fasting for about 8 hours to have correct measures. For Hb A1c, it is not necessary to be fast. Hb A1c is used to diagnose diabetes. It measured blood glucose in the body for the last three months. Hb A1c normal range is between 4 % to 5.7%, from 5.8% to 6.4% in prediabetes, and 6.5% or more in diabetes.¹¹ For fasting blood glucose, it is done in the morning and before breakfast to have the correct measurements. Fasting blood glucose regular reading should be less than 100 mg/dl, from 100 mg/dl to 125 mg/dl in prediabetes, and equal to or more than 126 mg/dl in diabetes.¹¹

3.1.1. Effect of Metformin on cardiovascular events

Several meta-analyses have assessed the impact of Metformin on cardiovascular disease. A meta-analysis of 35 trials indicated Metformin was not associated with any significant endangerment or benefit in terms of cardiovascular incidents ($p = 0.34$). A critical advantage was found in trials versus placebo/no therapy ($p = 0.031$) but not in active-comparator trials ($p = 0.89$). Meta-regression revealed a significant relationship between the impact of Metformin on cardiovascular incidents and trial duration, as well as the lower and higher age for inclusion, implying that the drug tended to be further effective in longer trials involving younger patients. Metformin monotherapy is most certainly related to enhanced survival ($p = 0.076$). However, concurrent usage with sulphonylureas was related to decreased survival ($p = 0.016$).¹² Another meta-analysis involving 13 studies (13,110 patients) investigated metformin efficacy against cardiovascular morbidity or mortality in individuals with type 2 diabetes. Metformin did not significantly impact the primary outcomes of all-cause mortality risk ratio (RR) = 0.99 and cardiovascular death RR = 1.05. Metformin medication did not affect the secondary effects as well: all myocardial infarctions, RR = 0.90; heart failure, RR = 1.03; all strokes, RR = 0.76; peripheral vascular disease, RR=0.90; microvascular complications, RR = 0.83; and leg amputations, RR=1.04. There was a significant association with sulphonylurea as a concurrent medication for myocardial infarction ($p=0.10$ and 0.02 , respectively).¹³ Another meta-analysis of 13 trials (including a sum of 2079 type 2 diabetic patients assigned to Metformin and a comparable number to contrast groups) evaluated the effect of Metformin versus no intervention, placebo, or lifestyle modification, on the cardiovascular outcomes in individuals with type 2 diabetes. Except for stroke, all results preferred Metformin, with limited heterogeneity across studies, yet none reached statistical significance. Effect sizes (Mantel-Haenszel RR) were: all-cause mortality 0.96; stroke 1.04; cardiovascular mortality 0.97; myocardial infarction 0.89; and peripheral

vascular disease 0.81. Despite being the first-line medication for individuals with type 2 diabetes, there is still debate over whether Metformin lowers the risk of cardiovascular disease in these individuals.¹⁴

3.1.2. Effect of Metformin on microvascular complication

To assess the efficacy over 15 years of the addition of Metformin to the Diabetes Prevention Program (DPP) in type 2 diabetes, a multicenter randomized open-controlled trial was conducted in 27 centres across the United States comparing an intensive lifestyle intervention or masked Metformin with a placebo in a cohort selected to be at very high risk of developing diabetes. During a mean follow-up of 15 years, diabetes incidence was decreased by 27% in the lifestyle intervention group (CI 0.65-0.83; $p<0.0001$) and by 18% in the metformin group (CI 0.72-0.93; $p=0.001$), with dwindling differences between groups over time. By year 15, the cumulative incidences of diabetes were 55% in the lifestyle group, 56% in the metformin group, and 62% in the placebo group. The aggregate microvascular outcome prevalence at the end of the study did not change significantly across treatment groups (hazard ratio of placebo 12.4%; metformin 13.0%; lifestyle intervention 11.3%). However, those who did not develop diabetes had a lower rate of microvascular complications than those who did.¹⁵

4. METFORMIN TOLERABILITY, SAFETY, AND ADVERSE EFFECTS

4.1. Gastrointestinal

A randomized, double-blind clinical trial compared the effects of Metformin versus placebo medication regarding weight loss and gastrointestinal side effects in patients with diabetes type 2 among the two groups.¹⁶ A total of 3,234 patients from 27 hospitals in the United States were included in the Diabetes Prevention Program (DPP) between 1996 and 1999. The analysis only included the 2,155 randomly allocated to the placebo (1,082) or Metformin (1,073) groups. Participants were ≥ 25 years old, had a BMI of ≥ 24 kg/m², high fasting glucose levels (95 to 125 mg/dL), and impaired glucose tolerance test after 2 hours of oral glucose dosage 75 g (140 to 199 mg/dL). In the absence of gastrointestinal problems, 850 mg of Metformin or placebo was started at once daily and escalated to twice daily after a month. Every year, regular lifestyle advice and recommendations for regular physical activity, a healthy diet, and a healthy weight were provided.¹⁶ The frequency of gastrointestinal symptoms increased with metformin use compared to placebo, although those gradually decreased over time. The average haemoglobin and hematocrit levels during the DPP were marginally lower in the metformin group compared to the placebo group. Haemoglobin and hematocrit levels dropped in the metformin group over the first year after randomization, but no subsequent changes were seen. Metformin users had reduced weight and waist circumference compared to placebo during the DPP. Weight reduction in the metformin group continued to be significantly more significant in the metformin group than in the placebo group during the yearly unblinded follow-ups. Weight reduction was associated with ongoing metformin adherence and was durable for at least ten years of treatment. Overall, Metformin used for diabetes prevention is safe and well tolerated.¹⁶ Metformin medication's most common gastrointestinal (GI) side effects include diarrhoea, nausea, flatulence, indigestion, vomiting, and abdominal pain.¹⁷

Although beginning at a low dosage and titrating slowly may help prevent some GI side effects linked to Metformin. Some individuals are unable to tolerate Metformin at all.¹⁷ The fundamental mechanisms of metformin-induced GI intolerance remain unknown. However, some suggested strategies help to overcome metformin GI intolerance. These include proper titration of immediate-release Metformin, usage of extended-release metformin, gut microbiota modulators, and alternative pharmacological treatments.¹⁷

4.2. Lactic Acidosis

Some individuals may not receive Metformin due to the risk of lactic acidosis. Metformin raises plasma lactate levels dose-dependently by blocking mitochondrial respiration, mainly in the liver.¹⁸ Increased plasma metformin concentrations (as seen in people with renal impairment) and a subsequent event or disease that further disturbs lactate generation or clearance (e.g., cirrhosis, sepsis) are usually required to produce metformin-associated lactic acidosis (MALA). Since these secondary events may be unexpected and the mortality rate for MALA reaches 50%, Metformin has been contraindicated in cases of moderate and severe renal impairment.¹⁸ Nevertheless, the reported incidence of lactic acidosis in clinical practice is extremely low (10 occurrences per 100,000 patient-years). According to several studies, current renal function cutoffs for Metformin are overly cautious, depriving a sizable portion of type 2 diabetic patients of the potential benefits of metformin treatment. However, careful labelling may have been a critical factor in the success of Metformin as the first-line diabetic treatment since its absence would have resulted in excessive patient risk and eventual market removal, as was the case with prior biguanide medications.¹⁸ On the other hand, a substantial new body of research suggests that biguanide, the drug category of Metformin, has protective properties on the kidney, heart, and liver, and maybe even against lactic acidosis itself.¹⁹ Therefore, it is worthwhile to slow down both contraindications and precautions for metformin usage in order to avoid depriving a substantial number of diabetic patients, such as those with kidney, heart, and liver diseases, of its possible advantages.¹⁹

4.3. Vitamin B12 Deficiency

A secondary analysis was conducted from the Diabetes Prevention Program (DPP)/DPP Outcomes Study (DPPOS) that was conducted in 27 centres in the United States.²⁰ The aim was to investigate the potential occurrence of vitamin B12 deficiency in type 2 diabetic patients exposed to Metformin's long-term use to manage diabetes.²⁰ Vitamin B12 is a water-soluble vitamin primarily found in animal products.²¹ Vitamin B12 is a cofactor for DNA synthesis and neuroprotection enzymes. Therefore, vitamin B12 deficiency can result in a variety of clinical outcomes, including hematologic problems (e.g., megaloblastic anaemia) and peripheral neuropathy.²¹ Participants were divided into the metformin group (n= 1073) or the placebo group (n = 1082). B12 level was assessed at 5 years and 13 years in metformin and placebo groups.²⁰ Low B12 (≤ 203 pg/mL) was demonstrated more frequently in Metformin than placebo at 5 years (4.3 vs 2.3%; $P = 0.02$) but not at 13 years (7.4 vs 5.4%; $P = 0.12$). Moreover, combined low and borderline-low B12 (≤ 298 pg/mL) was more prevalent in Metformin at 5 years (19.1 vs 9.5%; $P < 0.01$) and 13 years (20.3 vs 15.6%; $P = 0.02$).²⁰ Metformin usage for several years was associated with an elevated risk of B12 insufficiency. The occurrence of anaemia was more significant

in Metformin but did not vary by B12 status. Neuropathy was more common in Metformin with low B12 levels.²⁰ Patients with type 2 diabetes mellitus treated with Metformin, especially those who take Metformin at large dosages (> 2,000 mg/day) and for an extended period (> 4 years), should be screened for vitamin B12 deficiency frequently.²²⁻²⁴

4.3.1. Use of Metformin in the Elderly

When prescribing Metformin for the elderly, caution is typically advised. In the past, due to ageing, drug use was thought to be contraindicated in some nations. Some authors advise against using Metformin in the elderly because of their patients' deteriorating kidney function.²⁵ Retrospective data show that mortality in metformin-treated patients who develop lactic acidosis is connected to the underlying disease rather than metformin buildup, although the clearance of Metformin may be impaired in the elderly due to deteriorating renal function.²⁶ It's essential to consider the high occurrence of various other illnesses, including heart failure and pulmonary insufficiency, among older people who should not take Metformin. Additionally, the care of elderly patients on metformin treatment should consider depression, cognitive impairment, an absence of recognition of thirst and associated dehydration as potential risk factors for lactic acidosis. Additionally, it has been documented that Metformin may lower folate levels and vitamin B12.^{27,28} A physiologically slight decline in vitamin B12 and folate with advancing age is frequently linked to a risk factor for anaemia.^{29,30} For these reasons, older adults using metformin medication may require routine anaemia tests. Age in and of itself is not a contraindication to metformin treatment.³¹ In fact, there are extremely few incidences of lactic acidosis in old type 2 diabetic patients with no other concurrent condition³², and Metformin is currently routinely utilized in the management of elderly type 2 diabetic patients. Metformin's potential usage in insulin-resistant non-diabetic persons may be particularly relevant to geriatric patients. According to recent data, the metabolic syndrome is present in more than 40% of US adults older than 60.³³ cardiovascular diseases and type 2 diabetes mellitus, two of the most severe health issues affecting persons over 65, are both more likely to occur in patients with this condition. Therefore, identifying and treating metabolic syndrome may be crucial in lowering the overall burden of morbidity and mortality in the aged.³⁴

4.3.2. Use of Metformin in Non-Diabetic Obese Patients

Metformin does not cause weight gain in people with type 2 diabetes, unlike most hypoglycemic medications.³⁴⁻³⁶ Instead, numerous carefully conducted studies have demonstrated that this medication causes diabetic people to lose body weight.^{34,36} Numerous authors have investigated the use of Metformin as an agent to reduce body weight in non-diabetic people. Despite some previous research' encouraging findings³⁸, more current trials have not supported Metformin's effectiveness in treating obesity.^{39,40} A one-year course of metformin medication did not result in any appreciable weight loss in an extensive randomized, double-blind, placebo-controlled investigation on obese non-diabetic patients.⁴¹ Non-diabetic men with abdominal obesity, hypertriglyceridemia, and hypertension showed similar body weight results.⁴² However, compared to placebo, metformin treatment resulted in a considerable and long-lasting weight loss in overweight individuals with impaired glucose tolerance and fasting hyperglycemia.^{43,44} According to two pilot placebo-

controlled studies that showed considerable weight loss in adolescents, younger people may be more responsive to Metformin's weight-reducing effects.^{45,46} There have been a few short studies comparing Metformin to other weight-loss medications. While its effectiveness was not statistically different from orlistat's, Metformin was less effective than either dexfenfluramine or sibutramine.^{47,48} Overall, the evidence does not favour using Metformin as a weight-loss medication for obesity, even if some minor effects on body mass have been noted in numerous studies. Metformin has been demonstrated to reduce food consumption in obese, non-diabetic people.⁴⁹ While a direct impact of Metformin on the central nervous system cannot be completely ruled out, a stimulatory effect of the medication on adipocyte hormones that would reduce appetite seems implausible. Leptin levels have been found to either decrease^{50,51} or remain unchanged while using Metformin.^{45,52} For people who are at high risk of developing diabetes, Metformin has been suggested as a therapeutic option. The Diabetes Prevention Program (DPP) demonstrated a decrease in the prevalence of diabetes mellitus in overweight or obese individuals with fasting hyperglycemia and inadequate glucose tolerance.⁴⁴ Based on the DPP findings, metformin medication for the prevention of type 2 diabetes could be advised for all obese individuals with fasting or post-load hyperglycemia.

4.4. Effect of Metformin On the Polycystic Ovary Syndrome

Polycystic ovary syndrome (PCOS) is a diverse disorder characterized by chronic anovulation, hyperandrogenaemia, and insulin resistance.⁵³ PCOS symptoms include hirsutism, menstrual cyclicity disturbances, and infertility. Current treatments include cyproterone acetate and other anti-androgens (for hirsutism), clomiphene citrate (for anovulation), and FSH/HMG for ovulation induction, which IVF procedures can follow. Many studies indicate that Metformin is an effective treatment for PCOS. Several uncontrolled observations⁵⁴ and placebo-controlled studies⁵⁵ have shown that Metformin reduces circulating androgens and improves menstrual regularity⁵⁶ and hirsutism. The efficacy of Metformin on hirsutism appears to be comparable to that of anti-androgens, with the added benefit of a more favourable effect on insulin sensitivity and cardiovascular risk factors. Metformin and flutamide may provide some benefit over either drug used alone⁵⁷, but this combination needs to be studied further. It is worth noting that adding Metformin to flutamide and estropiprost combination reduces abdominal fat mass and improves adipokine profile in young, lean patients with ovarian hyperandrogenism. The effects of adding Metformin to estropiprost treatment on androgenization are still debatable⁵⁸; currently available data are insufficient to back up the use of metformin-estropiprost combinations for treating hirsutism in PCOS women. The increase in spontaneous and FSH-induced ovulation rate during metformin treatment is still debatable.⁵⁹ Metformin was also found to increase clomiphene-induced ovulation rate in a placebo-controlled trial; several trials have shown that the combination of Metformin and clomiphene is effective in lowering circulating androgens, regularizing menstrual cycles and increasing ovulation and pregnancy rates.⁶⁰ This combination's efficacy in inducing ovulation and pregnancy has been compared to that of hMG treatment George or laparoscopic ovarian drilling.⁶¹ Metformin's mechanism of action in PCOS is complex and only partly understood. Metformin has been shown to inhibit FSH-induced aromatase

activity, resulting in increased ovarian androgen secretion. Furthermore, the drug inhibits cytochrome P450C17alpha activity, as evidenced by a reduction in HCG- or GnRH analogue-induced levels of 17-hydroxyprogesterone⁶², a precursor of androgens. Metformin, on the other hand, decreases ACTH- induced adrenal androgen secretion while increasing sex hormone binding globulin (SHBG).⁶³ Metformin, on the other hand, appears to reduce pulse amplitude in LH episodic release, but not gonadotropin sensitivity to the inhibitory effect of sex steroids.⁶⁴ The effectiveness of Metformin in inducing Pregnancy in PCOS women may be linked to an increase in glycodeolin, a putative marker of endometrial function, as well as circulating Insulin-Like Growth Factor-I Binding Protein I. Recently, a decrease in Mullerian inhibiting substance, possibly due to decreased androgen stimulation of newly recruited follicles, has been reported in obese women with PCOS taking Metformin for a long time.⁶⁵ Additional insulin-sensitizing medications that decrease insulinemia are useful in treating PCOS.⁶⁶ Many of these benefits are likely mediated through reducing circulating insulin levels during metformin administration. Leptin secretion, which inhibits the production of gonadotropins and the production of ovarian and adrenal androgens, has also been linked to the drug's effect on ovarian function. However, reducing circulating leptin levels during metformin treatment is still debatable.⁶⁷ Although the metabolic effects of the medication (such as on blood glucose and lipid profile) are more pronounced when insulin resistance is present, the benefits of metformin treatment for PCOS are remarkable since they are comparable in insulin-sensitive and insulin-resistant patients. Furthermore, metformin medication is effective for both obese and lean women with PCOS; in fact, the effects of metformin therapy on ovulation rate may even be stronger in lean patients than in obese ones.⁶⁸ Relevant is its safety during fetal development's early stages. Metformin medication safety during pregnancy has not yet been thoroughly researched. Metformin use during the first trimester in women with type 2 diabetes has been reported to be safe.⁶⁹ However, compared to women receiving other types of hypoglycaemic therapy, observation of 50 patients treated with Metformin throughout pregnancy revealed a higher incidence of pre-eclampsia and perinatal mortality.⁷⁰ This finding raises the possibility that Metformin may be toxic during the third trimester. In a random experiment with PCOS-positive non-diabetic women, compared to a placebo, using Metformin 850 mg twice a day lessened pregnancy-related postpartum problems.⁷¹ This supports the findings of two uncontrolled studies in which pregnant women with PCOS received Metformin alone or in conjunction with enoxaparin⁷² without any detectable side effects. Together, these findings imply that metformin usage in the first trimester is likely safe, but its use in the latter stages of pregnancy warrants additional research.

4.5. Effect of Metformin on Non-Alcoholic Fatty Liver Disease

Obsessed and insulin-resistant people are usually diagnosed with non-alcoholic fatty liver disease (NAFLD). In most cases, NAFLD presents in a peaceful state, and at other times, it slowly progresses to non-alcoholic Steatohepatitis (NASH). In extreme cases, NAFLD results in a severe liver disease known as cirrhosis or another severe liver disease. Non-alcoholic steatohepatitis (NASH) is a chronic health condition that is characterized by the association of hepatomegaly (a state of the enlarged liver due to an underlying disease such as fatty

and lobular hepatitis), high levels of serum aminotransferase in patients with no symptoms of alcohol abuse or excessive alcohol intake.^{73,74} research has shown that NAFLD and NASH are associated with some metabolic disorders such as type 2 diabetes mellitus, obesity, hypertension, and elevated levels of serum triglycerides, otherwise known as hypertriglyceridemia. Also, NASH is prevalent in patients who are insulin-resistant compared to normal controls.^{73,75} There is a relationship between NASH and a reduced rate at which insulin enhances overall glucose disposal. NASH is also related to the reduced rate at which insulin inhibits hepatic glucose production when the body does not absorb nutrients from food. These are significant features of insulin, which are features of insulin resistance.⁷⁶ Information from the studies reviewed in this section suggests that NAFLD and NASH are most likely to be symptoms or part of the prevalent metabolic syndrome in most patients.^{76,77} Although the development process of NASH is not specific, medical researchers have discovered that Metformin, a drug that helps control blood sugar in diabetes patients, can be used to treat NASH. Initial non-randomized studies on the use of Metformin to treat patients suffering from NASH showed that some patients diagnosed with NASH but do not have type 2 diabetes mellitus recovered from the liver disease within four months of administering Metformin as a treatment for NASH.⁷⁸ Afterwards, a similar trial was conducted on patients suffering from NAFLD but this time, it was done in a controlled environment. The trial result was favourable as patients showed signs of recovery when given Metformin as treatment.⁷⁸ The report of the controlled trial showed that this result was better than when vitamin E was used as the treatment, even though the patients involved in the trial weighed less.⁷⁹ There is also another controlled trial that showed positive outcomes for the treatment of NASH using Metformin, but this trial has not yet been published, and as such, it cannot be cited as a reference in this context. Nevertheless, it is pertinent to note that a published study has shown that Metformin can effectively lower the circulating levels of gamma-glutamyl transpeptidase (GGT) and alanine transaminase (ALT) in obese women.⁸⁰ These studies portray Metformin as a drug that could serve as an effective therapy for health issues related to high levels of gamma-glutamyl transpeptidase. However, this cannot be said for the treatment of NASH using Metformin as its mechanism is still not clear to scientists, primarily as the mechanical process of using Metformin to treat NASH could probably involve the activation of AMP-activated protein kinase (AMPK) in hepatocytes.^{81,82} the reduction of TNF-alpha in hepatic⁸³ or result into serum leptin Hookman reduction. Also, worthy to note is that animal studies using Metformin to treat liver diseases have shown favourable results even though the animals are obsessed.⁸³ This goes to say that Metformin is very effective regardless of its action on food intake. Lastly, it is also pertinent to note that other medications are effective in controlling blood sugar levels and reducing circulating levels of insulin such as thiazolidinediones, which are equally effective in improving fatty liver in humans.^{84,85,86} These discoveries show that the identified effects of Metformin on NASH could be facilitated by the reduction of at least partly, mediated by the decrease of insulin in the blood.

5. CLINICAL TRIALS OF METFORMIN FOR ITS EFFECTS

While the effects of long-term metformin therapy on plasminogen activator inhibitor-1 are debatable^{41,42,87}, it has been demonstrated that obese non-diabetic patients with

insulin resistance who are obese can improve disturbances of hemostasis and fibrinolysis by increasing tissue plasminogen activator⁴⁰⁻⁴² and decreasing fibrinogen⁸⁸ and von Willebrand factor.⁴¹ Metformin was reported to significantly lower the 4-year incidence of metabolic syndrome in the Diabetes Prevention Program.⁸⁹ The long-term impact of Metformin on triglyceride in non-obese patients may be less than that observed in people with type 2 diabetes.^{34,36} The effects of Metformin on the cardiovascular risk factors linked to the metabolic syndrome⁹⁰ indicate that long-term use of this medication may theoretically lower the incidence of cardiovascular disease in obese non-diabetics; however, additional studies with clear endpoints are required before Metformin can be recommended as the preferred method of treating obesity. Significantly, metformin use was linked to a small but consistent weight loss, which may help to explain why there has been a decline in the prevalence of diabetes. Further data are required to evaluate the effectiveness of Metformin in lowering the incidence of cardiovascular disease in patients with fasting or post-load hyperglycemia who are in a high-risk category.⁹¹

5.1. The Mechanism of Action of Metformin

The glucose-lowering effects of Metformin are mainly a consequence of reduced hepatic glucose output (primarily through inhibition of gluconeogenesis and, to a lesser extent, glycogenolysis) and increased insulin-stimulated glucose uptake in skeletal muscle and adipocyte.⁹²⁻⁹⁸ Its main action is to decrease hepatic glucose production, which is increased at least 2-fold in individuals with type 2 diabetes.^{95,99} In a study of the mechanism by which Metformin reduces endogenous glucose production in individuals with type 2 diabetes, the raised plasma glucose level was attributed to a threefold increase in the rate of gluconeogenesis.⁹⁵ Metformin treatment reduced fasting plasma glucose concentrations by 25% - 30% and reduced glucose production,⁹⁵ which are results consistent with those of other investigators.^{93,98} The decrease in glucose production was attributable to a decrease in the rate of gluconeogenesis.⁹⁵ For example, Metformin was shown to decrease gluconeogenesis in the perfused liver, mainly through inhibition of hepatic lactate uptake.¹⁰⁰ Others stated that metformin therapy reduced concentrations of adenosine triphosphate in isolated rat hepatocytes.¹⁰¹ Since adenosine triphosphate is an allosteric inhibitor of pyruvate kinase, the authors suggested that the metformin-mediated reduction in hepatic glucose production comes from increased pyruvate kinase flux. Metformin also reduces gluconeogenic flux by inhibition of pyruvate carboxylase-phosphoenolpyruvate carboxykinase activity and possibly through increased conversion of pyruvate to alanine.⁹⁷ Metformin also helps insulin-induced suppression of gluconeogenesis from multiple substances, such as lactate, pyruvate, glycerol, and amino acids⁹⁴, and combats the gluconeogenic activity of glucagon.¹⁰² The exact mechanism through which Metformin decreases hepatic glucose production remains unclear, but its main location of action appears to be hepatocyte mitochondria, where it disrupts respiratory chain oxidation of complex I substrates.^{102,103} Inhibition of cellular respiration reduces gluconeogenesis¹⁰² and may induce expression of glucose transporters and, hence, glucose utilization.¹⁰⁴ It is not clear whether Metformin works on mitochondrial respiration directly by slow permeation across the inner mitochondrial membrane¹⁰² or by unidentified cell-signalling pathways.¹⁰³ It has been suggested that biguanides bind specifically and competitively to divalent cation sites on proteins, thus

disturbing the intracellular handling of calcium (Ca), especially in the mitochondria.^{105,106} In several tissues, such as skeletal muscle and adipocytes, Metformin helps the trafficking of glucose transporters 4 and 1 to the plasma membrane.^{92,94,107} Metformin may increase glucose transport activity of glucose transporter 4. To some degree, glucose transporters 1.⁹⁴ The effects of Metformin on peripheral insulin-sensitive tissues require the exitance of insulin for its full action. Metformin improves most of the biological actions of insulin, such as glucose transport and glycogen and lipid synthesis, in individuals with preexisting insulin resistance.⁹⁴ It helps glucose transport in cultured skeletal muscle without insulin.^{108,109} Metformin stimulates insulin and tyrosine kinase action in insulin-like growth factor-1 receptors of vascular smooth-muscle cells independently of insulin activity.¹⁰² The drug stimulates tyrosine kinase in *Xenopus* oocytes, with successive activation of inositol 1,4,5-triphosphate production and glycogen synthesis.¹¹⁰ Therefore, Metformin has metabolic effects on insulin-sensitive tissues that may participate in its glucose-lowering effect. Metformin has been found to decrease free fatty acid oxidation by 10%-30%.⁹²⁻⁹⁶ Increased free fatty acid levels are frequently seen in diabetes and obesity¹¹¹, and they participate in raised hepatic glucose production and the emergence of insulin resistance.^{112,113} Increased fatty acid oxidation prevents main glycolytic pathway enzymes by accumulating acetyl coenzyme A and citrate, by-products of free fatty acid oxidation.¹¹⁴ Increased glucose 6-phosphate concentrations, in turn, prevent the hexokinase enzyme, leading to decreased glucose uptake and oxidation.¹¹⁴ Moreover, free fatty acid prevents insulin receptor substrate-1-associated PI3-kinase action¹¹⁵, and consequently attenuates transmembrane glucose transport.¹¹¹ By reducing free fatty acid levels, Metformin enhances insulin sensitivity and may also facilitate the correction of impaired insulin secretion by beta cells.¹¹⁶ Metformin has no direct impact on beta cell function¹¹⁷, but it can enhance insulin secretion that has been changed by long-term exposure to free fatty acid or hyperglycemia.¹¹⁶ Metformin may also enhance hyperglycemia by attaining high concentrations in the small intestine^{94,118} and reducing intestinal absorption of glucose, an activity that may participate in reduced postprandial blood glucose levels.^{113,119} It has been hypothesized that increased glucose consumption in the small intestine of Metformin-treated individuals may inhibit further glucose transport to the hepatic circulation.¹¹⁹

6. PRACTICAL CONSIDERATIONS IN METFORMIN THERAPY

Metformin is considered first-line antidiabetic therapy for the management of type 2 diabetes. Its early inclusion in treatment algorithms is supported by lack of weight gain, minimal risk of hypoglycemia, and its mechanism of action to combat insulin resistance. In addition, recent prospective and retrospective investigations have validated Metformin's cardio protective and anti-atherosclerotic benefits.¹²⁰ It appears to reflect a combination of glucose-independent actions on the vascular endothelium, suppressive effects on glycation, oxidative stress and the generation of adhesion molecules, promotion of fibrinolysis, and beneficial effects on the lipid profile.¹²⁰ Although avoiding bothersome gastrointestinal tolerability concerns necessitates careful dose titration, the risk of significant adverse impact is regarded minimal if contraindications (particularly concerning renal status) are followed.¹²⁰ Clinical practice, however, frequently deviates from guidelines, and multiple studies have sought to catalogue the frequency with which Metformin has been misused in

various clinical contexts.¹²¹⁻¹²³ These studies have shown surprising results: between 21.4% and 73% of patients had at least one contraindication or condition where Metformin should be used with caution.¹²¹⁻¹²³ According to one study, 87% of patients who were previously taking Metformin continued to use it even though they had a new contraindication. In contrast, 24.5% of patients receiving Metformin had preexisting contraindications to its usage.¹²¹ In another study, age, kidney function, and simultaneous cationic medication use were the most common contraindications.¹²³ Lactic acidosis was extremely rare or non-existent in all studies. However, confounding variables influencing the outcome could not be ruled out because these investigations were observational. Furthermore, most instances were recorded during inpatient stays, with limited analysis of metformin use in the outpatient context.^{121,122} An obese person with type 2 diabetes mellitus who has normal kidney function (creatinine concentration 133 m dL [1.5 mg/dL] in men and 124 m dL in women or creatinine clearance 1.17 mL/s without coexisting symptomatic congestive heart failure or a hypoxic respiratory condition) would be an ideal patient for metformin treatment.^{92,117,124} Metformin medication is contraindicated in cases of liver failure, drunkenness, and active mild to severe infection.^{92,117} The use of radiocontrast material in a diabetic patient may aggravate already poor kidney function and produce metformin accumulation, resulting in hazardous doses of medication. Furthermore, general anaesthetic delivery may result in hypotension, resulting in renal hypo perfusion and peripheral tissue hypoxia, with consequent lactate buildup.^{32,93,117} As a result, if radiocontrast material must be administered or urgent surgery is indicated, Metformin should be postponed and hydration should be preserved until intact kidney function is confirmed at 24 and 48 hours following the intervention.^{92,93,117} older adults should take Metformin carefully since their lower lean body mass may provide falsely low creatinine concentrations that don't accurately represent lower glomerular filtration rates. To avoid gastrointestinal effects, metformin therapy should be started with a single dosage of medicine (often 500 mg) administered with the patient's largest meal. Medication dosages can be raised in 500-mg increments every 1 to 2 weeks, based on glycemic control, until a target blood glucose level is attained, or the maximum daily recommended metformin dose of 2550 mg is achieved.^{92,125} These metformin side effects, such as diarrhoea and abdominal pain, are dosage dependent and can typically be prevented by careful titration and, in some circumstances, dose decrease.¹¹⁷ Hypoglycemia is uncommon after metformin monotherapy because Metformin only partially inhibits gluconeogenesis in the liver and does not boost insulin production.^{94,117} Lactic acidosis seems unrelated to plasma metformin concentrations²⁶, and even in those with chronic renal dysfunction, metformin accumulation does not always result in lactic acidosis.¹²⁶ Lactic acidosis is nearly

II. REFERENCES

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frequently associated with coexisting hypoxic conditions, which are likely to be to account for the accompanying high mortality rate. In a study, 91% of patients receiving Metformin who experienced lactic acidosis also had a contributing condition, including congestive heart failure, renal disease, chronic obstructive pulmonary disease, or age more than 80.³² Therefore, Metformin should not be administered to individuals with these previous conditions. Large quantities of alcohol, whether consumed chronically or acutely, may exacerbate the impact of Metformin on lactate metabolism. Therefore, it's crucial to have a thorough history of alcohol usage before beginning metformin medication.^{32,93}

7. CONCLUSION

Metformin is an effective oral medication in managing and preventing type 2 diabetes mellitus. However, there is no definite safety using Metformin in the diabetic population. The advantages of Metformin, such as better insulin sensitivity, blood glucose control, and weight loss, have been well demonstrated. Despite being the first-line treatment for people with type 2 diabetes, there is still disagreement on whether Metformin reduces the risk of cardiovascular disease in these patients. Metformin side effects include an increased risk of lactic acidosis, gastrointestinal symptoms, and vitamin B12 deficiency. This review implies that patients and health providers should be mindful of Metformin's role in preventing and treating type 2 diabetes and its long-term effects to create a balance between the risks and the benefits and to adapt evidence-based strategies to decrease the related side effects.

8. ETHICAL STATEMENT

All the data in this study were collected from public repositories such as PubMed. Since its use is unrestricted, open to use and publish, and publicly available, permissions from those record holders were not needed.

9. AUTHORS CONTRIBUTION STATEMENT

Abdulaziz Mohammed Alatawi and Afaf Fayed Albogami designed the study. Sarah Salem Aldharman was involved in planning and developing the theoretical framework. Hyder Osman Mirghani Mohamed supervised the work. Ruba Saleh Alghamdi and Salwa Mohammed Majrashi aided in interpreting the results and worked on the manuscript. Nawari Essa Boobaid contributed to the design. All authors discussed the results and commented on the manuscript.

10. CONFLICT OF INTEREST

Conflict of interest declared none.

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