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Metformin: An Oral Anti-Hyperglycaemic Agent for the Treatment of Type 2 Diabetes

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Abstract

Metformin is one of the safest and most effective first-line glucose-lowering oral drug therapies for overweight and obese type 2 diabetes (T2D) patients, and those with normal kidney function. It is one of the drugs of Biguanide class of anti-diabetic compounds. It prevents the production of hepatic glucose, increases fatty acid oxidation, enhances insulin sensitivity, decreases lipid synthesis, and impedes gluconeogenesis. Sometimes it is used in combination with insulin or other oral medications. It should be used very carefully who have surgery, trauma, heart failure, severe kidney disease, and impaired liver functions. Some patients face side effects of Metformin and they should take it considering possible side effects of it. In this study aspect of Metformin is discussed as a guideline for the proper treatment T2D patients.

Keywords: Type 2 diabetes, metformin, side effects, lactic acidosis

1. Introduction

At present diabetes mellitus (DM) is considered as a global public health concern. Type 2 diabetes (T2D) accounts about 90–95% of cases of all diabetes that do not respond to dietary modifications. It is considered as non-insulin dependent diabetes (da Trindade et al., 2018; Mohajan & Mohajan, 2023a). Metformin (1,1-dimethylbiguanide hydrochloride) is one of the oldest treatments for diabetes, dating back to the 1960s. It is a drug that represents the class of Biguanides. It is the first-line medication and the best choice for patients, and usually use for the treatment of T2D (Fimognari et al., 2006). It is available in different formulations, such as tablets, capsules, oral suspensions, oral solutions or modified-release tablets. It is also recommended for people with pre-diabetes. It reduces hepatic glucose output without altering insulin secretion, and increases uptake of glucose by the periphery, including skeletal muscle (Bannister & Berlanga, 2016).

Metformin works in liver and intestine by stopping to release too more glucose. It lowers blood glucose without altering insulin secretion. As a result, hypoglycaemia is not a concern of this medication (Verdonck et al., 1981). It counters insulin resistance and impacts metabolic, vascular and other physiological functions. It can be combined with insulin to reduce insulin requirements. It is available in both standard- and modified- release forms (Khandwala, 2003). It can be used in pregnancy and breastfeeding on specialists' recommendation for short-term safety (Maruthur et al., 2016).

2. Literature Review

The literature review section is an introductory region of research, which shows the works of previous researchers in the same field within the existing knowledge (Polit & Hungler, 2013). It assists all researchers to improve research questions and to move forward energetically within the current research (Creswell, 2007). Clifford J. Bailey has consulted the historical background of Metformin. His straight forward view is that

Metformin was discovered, forgotten, rediscovered, repurposed, rejected, rescued, exonerated and may have further secrets to reveal (Bailey, 2017).

Mariana Teixeira da Trindade and her coauthors have surveyed the characteristics and properties of Metformin, as well as hold a discussion on the existing analytical methods to green chemistry and their impacts for both the operator and the environment. They are confirmed that it is necessary the awareness of everyone involved in the optimization of the methods applied through the implementation of green chemistry to determine the Metformin (da Trindade et al., 2018). Yasemin Atici and her coauthors have wanted to investigate the effects of Metformin and Metformin-insulin combination used in patients with T2D (Atici et al., 2022).

Michael Z. Liao and his coworkers have tried to characterize the pharmacokinetics of Metformin in pregnant women with gestational diabetes mellitus (GDM) versus non-pregnant controls (Liao, 2020). In a series of articles, Devajit Mohajan and Haradhan Kumar Mohajan have discussed the aspects of overweight and obesity and their related diseases (Mohajan & Mohajan, 2023b-j). Joyce Zalaket and her coauthors in a study have obtained that the use of Metformin contributes to vitamin B_{12} deficiency in 10-30% of diabetics. They have wanted to investigate and characterize any specific associations between taking Metformin and vitamin B_{12} deficiency to establish clear recommendations based on the collected data (Zalaket et al., 2018).

Gonzalo Jorquera and his collaborators have discussed that not only the clinical and experimental evidence that supports the benefits of using Metformin during pregnancy but also the evidence showing a possible negative impact of this drug on the offspring's development (Jorquera et al., 2020). T. W. Hale and his coworkers have wanted to characterize the milk-to-plasma ratio and infant dose for Metformin in breastfeeding women, and to measure plasma concentrations and assess any effects in their infants. They have hypothesized that Metformin used by mothers is safe for their breastfeed infants (Hale, 2002).

3. Research Methodology

Research is a hard-working search, scholarly inquiry, and investigation that aim at the discovery of new facts and findings (Adams et al., 2007). It is an essential and powerful device to the academicians for the leading in academic disciplines. It drives the global humanity through advancing to make a sustainable peaceful society (Pandey & Pandey, 2015). Methodology in any creative research is the organized and meaningful procedural works that follow scientific methods efficiently (Kothari, 2008). Research methodology provides the principles to the researchers for organizing, planning, designing and conducting a good research. Therefore, it is the science and philosophy behind all researches (Legesse, 2014). It helps to identify research areas and projects within these areas (Blessing et al., 1998).

Reliability and validity are two most important and fundamental features for the evaluation a research (Mohajan, 2017, 2018, 2020). To prepare this article we have taken the help from the secondary data sources. We have consulted published and unpublished articles, published books, conference papers, internet, websites, etc. (Mohajan & Mohajan, 2023k-v). We start main research area with the discussion of historical views of Metformin and then we highlight action policies of Metformin. Then we have tried to discuss doses adjustment strategy of Metformin. We have tried to show the effects of Metformin to a woman during pregnancy and breastfeeding. We have introduced the precautions for Metformin use before the starting of its doses. Then we have tried to show the advantages and disadvantages of Metformin than other medications, and finally we have shown the side effects of Metformin.

4. Objective of the Study

The main objective of this study is to discuss the various activities of Metformin, such as the historical background, doses adjustment, etc. Other subsidiary objectives of the study are as follows:

- to show the advantages of Metformin,
- to highlight on the disadvantages of Metformin, and
- to focus on the side effects of Metformin.

5. Historical Views

Metformin is an old and widely accepted first-line agent that is anti-hyperglycaemic and improves endothelial dysfunction, hemostasis and oxidative stress, insulin resistance, lipid profiles, and fat redistribution (Rojas & Gomes, 2013). Its history is linked to *Galega officinalis* (also known as goat's rue), a traditional herbal medicine in Europe and in 1918 that is found to be rich in guanidine, which lowers blood glucose (Witters, 2001). But the information was disregarded and forgotten. The word "Metformin" was first described in the scientific literature in 1922, by Emil Werner and James Bell, as a product in the synthesis of N, N-dimethylguanidine (Fischer & Ganellin, 2006).

In the 1940s, Metformin was rediscovered in the search for antimalarial agents and repurposed to treat influenza

(Bailey, 2017). French physician Jean Sterne (1909-1997) first used Metformin to treat diabetes in 1957 (Fischer & Ganellin, 2006). It was not popular and in the late 1970s and was discontinued due to high risk of lactic acidosis. In 1994, Metformin is approved and in 1995 it is introduced in the USA (DeFronzo & Goodman, 1995; Pasik, 1997). In 1998, the UK Prospective Diabetes Study (UKPDS) has identified long-term cardiovascular benefits of Metformin, and sets it as the preferred initial agent to manage hyperglycaemia in T2D (UKPDS, 1998). Sixty years after its introduction it has become the most prescribed glucose-lowering medicine worldwide. In 2012, diabetes experts in the USA and Europe have declared that Metformin is the drug of the first choice for all patients with T2D (Qaseem et al., 2012).

6. Actions of Metformin

At present the most common oral antihyperglycaemic medication is used for treating T2D is Metformin. The total satisfactory beneficial activities and harmful effects of Metformin are not fully understood (Zheng et al., 2015). Through the researches of many scholars it is realized that Metformin does not cause hypoglycaemia when used as monotherapy. It has no effect on the pancreatic β-cells and it is not metabolized. About one-third of the 463 million T2D patients worldwide use Metformin as their oral medication (Holman, 2007; Galicia-Garcia et al., 2020).

It lowers the levels of blood glucose after food consumption and also lowers the Fasting Plasma Glucose (FPG) in patients who have T2D. It improves carbohydrate and lipid metabolism and decreases glycaemic parameters considerably. It also reduces serum free fatty acid concentrations and corrects dyslipidemia (Chakraborty et al., 2011). It enhances the effect of insulin on the peripheral receptor site. Metformin absorption is relatively slow and may extend over about 6 hours. It is excreted in urine at high renal clearance rate of about 450 ml/min. It is recommended by the most of the physicians because of its low cost and associated safety (Biron, 1980).

7. Doses Adjustment

Metformin should be introduced in low dose and gradually titrate upwards. Starting dose should be 250 to 500 mg once or twice daily. Then the patient should increase the dose gradually up to 1g thrice a day if required within one or two weeks (Pernicova & Korbonits, 2014). For example, 500 mg once daily for first week, 500 mg twice daily in second week, 500 mg thrice daily in third week, and 1 g twice daily in fourth week (Harrower, 2000). Emphasize the importance of taking each dose with food to reduce gastrointestinal side effects. Twice daily dosing is usually more acceptable for compliance. Most people will be adequately controlled with a total daily dose of less than 2g per day, and some may require up to 3 g per day (Drury, 2010).

8. Pregnancy and Breastfeeding

During pregnancy, appropriate level of insulin may be used to maintain blood glucose levels as close to normal as possible (Jorquera et al., 2020). But sometimes oral medians are usually more acceptable; and during pregnancy Metformin is used in clinical practice. Metformin is good short-term safety for both the mother and baby, but unclear long-term safety (Butalia et al., 2017). If Metformin is contraindicated or unacceptable then insulin is essential to treat T2D pregnant women (Balsells et al., 2015).

Compared with insulin, gestational diabetes women treated with Metformin gain less weight and are less likely to develop pre-eclampsia during pregnancy, and also resulted in lower birth weight babies. But growth rate of these babies accelerated after birth (Alqudah et al., 2018). Very small amount of Metformin passes into breast milk, and pre-existing diabetes women can use it safely during breastfeeding (Briggs et al., 2005).

9. Precautions for Metformin Use

Metformin should be discontinued during a severe illness, such as during pneumonia and myocardial infarction, and dehydration. Patients with moderate to severe renal impairment Metformin should be used with caution or avoided when kidney function is declined. It cannot be used who have a history of heart, liver or kidney disease (Fowler, 2008). It cannot be used during dehydrating illnesses, such as diarrhea and vomiting. It must stop about 48 hours before and after X-ray contrast, such as CT scans. For elective surgery, Metformin should be stopped on the day of surgery, and restarted when eating and drinking have restarted. Avoid it in a state of diabetic ketoacidosis (DKA). It should not be used by children younger than 10 years old, and old persons greater than 80 years of age, as the patients are more susceptible to developing lactic acidosis (Cohen, 1979).

Metformin should be avoided in patients with clinical or laboratory evidence of hepatic dysfunction. It is not known whether Metformin passes into breast milk or if it could harm a nursing baby. In these situations, other glucose lowering therapies may be required according to physician’s advice (Umpierrez et al., 2014). After giving birth, hypoglycaemic treatment related to gestational diabetes, such as Metformin should be discontinued (NICE, 2015). If a dose of Metformin is missed must be taken as soon as remember. If it is almost time of next scheduled dose, the missed dose must be skipped. On the other hand, an overdose of Metformin may cause lactic acidosis, and that may be fatal and need to be met with physician immediately (Nasri & Rafieian-Kopaei, 2014).

10. Advantages of Metformin

Metformin is an oral medication given to patients with diabetes to improve insulin function. It primarily inhibits hepatic glucose output without altering insulin secretion; and it is not necessarily an insulin sensitizer. Additionally, it increases the sensitivity of muscle cells to insulin, improving peripheral glucose uptake and utilization (Shrestha et al., 2017). As a result, hypoglycaemia is not a concern for Metformin use, and routine blood glucose monitoring is not necessary if Metformin is used as monotherapy (Inzucchi et al., 2015).

Metformin reduces 29% of microvascular complications and 32% of combined diabetes outcomes, whereas insulin and Sulphonylureas accounted for only 25% and 12%, respectively (UKPDS, 1998). It lowers glycated hemoglobin (HbA1c) values up to 1-1.5%. It also reduces plasma triglyceride levels and low-density lipoprotein (LDL) cholesterol levels. It should be taken with or immediately after a meal. Some individuals may not tolerate higher doses, in which case, dose reduction is appropriate (NICE, 2015).

11. Disadvantages of Metformin

Use of Metformin is at an increased risk of lactic acidosis, and should be temporarily discontinued before any radiographic procedure (Verdonck et al., 1981; Fimognari et al., 2006). It is quite unsuited to treat insulin-dependent diabetes mellitus, such as type I diabetes (T1D). Also diabetic ketoacidosis (DKA) cannot be treated with Metformin, and it should be treated with insulin (Charoenpiriya et al., 2022).

Lactic acidosis is characterized by elevated blood lactate levels (>5 mmol/l), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When Metformin is implicated as the cause of lactic acidosis, Metformin plasma levels >5 µg/ml are generally found (Alberti et al., 1977). For long-term use of Metformin can also reduce vitamins B_{12}, B_6, and folic acid absorption, and may cause their deficiency (Tahrani et al., 2007; Bell, 2010; Zalaket et al., 2018). As a result, symptoms of anaemia or peripheral neuropathy may occur and vitamins B_{12}, B_6, and folic acid supplementation is necessary to Metformin users (Houghton, 2008; Porter et al., 2019).

12. Side Effects of Metformin

After use of Metformin the patients may face problem of mild loose stools in 10% initially, which reduces gradually, persistent loose stools in 5%, and marked weight loss (Yerevanian & Soukas, 2019). Sometimes the patients may face acute/chronic liver failure, cardiac failure, and hypotension/sepsis (Tahrani et al., 2007). Sometimes, it may cause a metallic taste in the mouth, gastrointestinal irritation, such as nausea, vomiting, cramps, diarrhea, increased flatulence, and abdominal pain in about 5% patients. These side effects often improve after a few days of continued therapy, or with a small dose reduction (Salpeter et al., 2010).

Some patients have signs of an allergic reaction to Metformin, such as difficult in breathing, hives; and swelling of face, lips, tongue, or throat. Sometimes patients feel one or more mild symptoms, such as muscle pain or weakness, numb or cold feeling in arms and legs, trouble in breathing, feeling dizzy, slow or uneven heart rate, etc. (McCreight et al., 2016). Very rarely, some T2D patients face lactic acidosis, and this seems to be related to impaired liver or kidney function (Khurana & Malik, 2010). In severe kidney disease T2D patients must avoid Metformin and use other oral medications (Heaf, 2014).

13. Conclusions

From this study we have realized that at present Metformin is a widely used pharmacological agent for the treatment of T2D patients. It is the first-line therapy for a safe and effective treatment. The origin of Metformin is herbal treatment. It was discovered, forgotten, rediscovered, repurposed, rejected, rescued, exonerated and finally approved as oral hypoglycaemic agents (OHAs) for T2D patients. It should be used as an adjunct, not an alternative to lifestyle improvements. It can reduce cardiovascular mortality, lower body weight, and has low risk of hypoglycaemia. It should be stopped if the patients feel severe side effects.

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