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Review Article

Metformin as an antidiabetic agent: A narrative review and update

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Abstract

Metformin (MET)(Standard drug) A biguanide, that lowers insulin resistance by triggering AMP-dependent protein kinase (AMPK). In STZ-induced diabetic rat, metformin lowers blood glucose levels through increasing ß-endorphin production from the adrenal glands, which stimulates opioid u-receptor linkage and increases GLUT-4 gene expression while decreasing PEPCK gene expression. Lactic acidosis, bloating, nausea, metallic taste, mild diarrhea, exhaustion, and vitamin B12 deficiency are a few of the side effects of metformin.

Keywords: Metformin, biguanide, AMP-dependent protein kinase, STZ.

Introduction

Since the 1960s, the biguanide metformin has been used to treat T2DM. The chosen first-line oral blood glucose-lowering medication for the treatment of T2DM is metformin (dimethyl biguanide). Its origins can be traced back to Galega officinalis, commonly known as goat's rue, a traditional herbal remedy used in Europe that was discovered to be abundant in guanidine, which was first demonstrated to decrease blood sugar in 1918.In the 1920s and 1930s, metformin and other guanidine derivatives were created and used to treat diabetes; however, due to toxicity and the availability of insulin, these treatments were eventually abandoned. In the 1940s, metformin was uncovered during the quest for antimalarial drugs. Clinical trials showed that metformin may be used to treat influenza because it occasionally reduced blood glucose levels. The French physician Jean Sterne, who first described the use of metformin to treat diabetes in 1957, pursued this characteristic. Though less effective than other glucose-lowering biguanides (phenformin and buformin), which were often stopped in the late 1970s due to a high risk of lactic acidosis, metformin got less attention. [1-4] Future prospects for metformin were uncertain because of associations with other biguanides, despite clear distinctions. After extensive testing, metformin was approved for use in the USA in 1995. Its capacity to combat insulin resistance and treat adult onset hyperglycemia without weight gain or an increased risk of hypoglycemia gradually gained acceptance in Europe. Metformin's long-term cardiovascular advantages were discovered by the UK Prospective Diabetes Study (UKPDS) in 1998, offering a fresh justification for its use as the first-line treatment for hyperglycemia in T2DM. After being used to treat T2DM for 60 years, metformin has developed into the most

commonly prescribed glucose-lowering drug in the world with promise for additional therapeutic uses. The systemic (IUPAC) name of Metformin is N, N-Dimethyl-imidodicarbonimidic diamide hydrochloride. The molecular formula is: $C_4H_{11}N_5$ .HCl and molecular weight is 165.62g/mole. [1,3]

Figure 1: Galega officinalis. The plant ancestor of metformin, G. officinalis, is also known as professor weed, goat's rue, French lilac, Italian fitch, and Spanish sainfoin. Despite being classified as a noxious weed in many US states, this plant was once utilized as a traditional medicinal in mediaeval Europe. Malcolm Storey, www.bioimages.org.uk, copyright (Image taken on July 1, 2000, in Berkshire, United Kingdom) The journal Diabetes (2017) 60:1566–1576

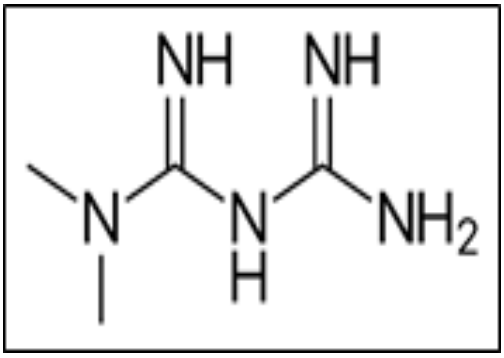

Figure 2: Structure of metformin

Metformin only regulates insulin release indirectly through its effects on fluctuating plasma glucose levels and has no direct effects on pancreatic beta-cells. Treatment for type 2 diabetes is typically associated with a mean weight loss of 2 to 3 kg, mostly because adipose tissue decreases.

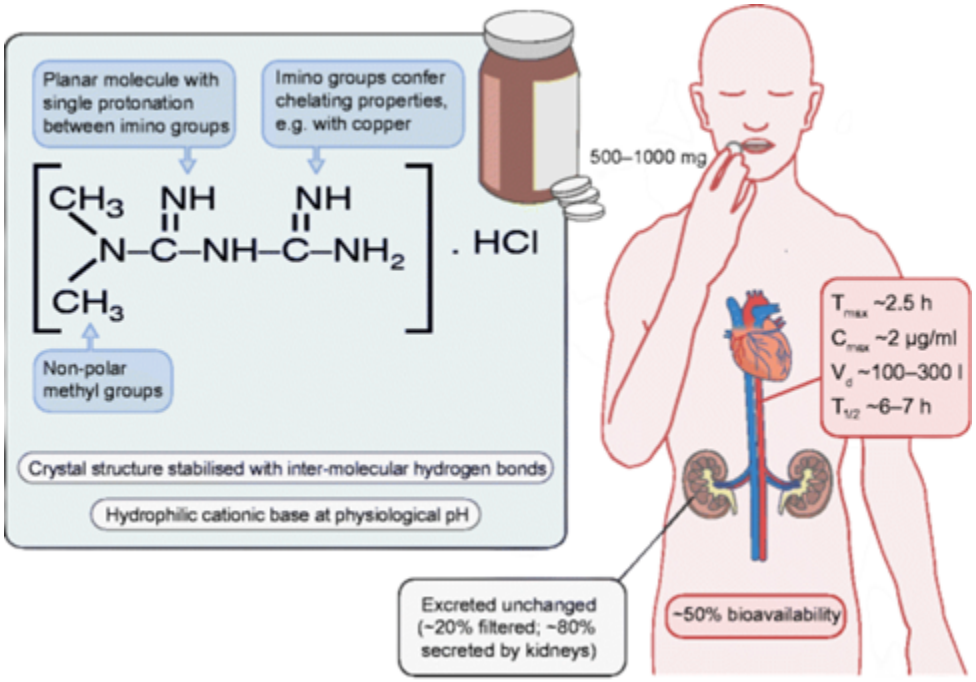

Figure 3: Metformin: Structure and Pharmacokinetics

(Source: Doi: 10.1007/S00125-017-4318-Z)

Mechanism of Action [2-6]

Since the vast majority of patients are obese, metformin's good effect of reducing hunger helps patients lose weight, which is advantageous. Among the currently suggested modes of action are:

1. Enhanced non-oxidative glucose disposal into skeletal muscle and improved recruitment and activity of GLUT-4 glucose transporters, which both improve insulin stimulated glucose transport in the muscle.
2. Increased secretion of glucagon-like peptide-1 (GLP-1).
3. Preserving beta-cell secretory capacity protects beta-cells against glucose toxicity and lipotoxicity.
4. Increased lipolysis inhibition and free fatty acid esterification in adipose tissue.
5. Reduction of appetite.
6. Diminished intestinal carbohydrate absorption leading to reduced post-prandial hyperglycemia.
7. Inhibition of hepatic gluconeogenesis

Anorexigenics, decreased intestinal carbohydrate absorption, suppression of hepatic gluconeogenesis, and enhanced glucose uptake by peripheral tissues are the major causes.

Clinical Use[7-9]

Today, metformin is the medicine of choice for all T2DM patients. Additionally, it is prescribed for polycystic ovarian disease, impaired fasting glucose, impaired glucose tolerance, and prediabetes. Advantages of metformin are:

1. Not hypoglycemic.
2. Supporting weight loss.
3. May help reduce both macrovascular and microvascular problems associated with diabetes.
4. In T2DM, there is no acceleration of cell fatigue or failure.
5. Antihyperglycemic efficacy (0.8–1.2% HbA1c reduction) comparable to other oral medications.
6. The use of metformin has positive effects on various facets of the metabolic illness syndrome (insulin resistance syndrome)

7. It also has a minor favorable effect on lowering serum triglycerides and total cholesterol Reduces obesity, especially central obesity
8. Enhances fibrinolysis by lowering plasminogen activator inhibitor 1 (PAI 1).A rise in macrovascular disease is correlated with the metabolic disease syndrome.

Side Effects: The most common side effects of metformin therapy are gastrointestinal problems. The gastrointestinal symptoms that are most frequently experienced are metallic taste, anorexia, nausea, stomach pain, and diarrhea[10]. By beginning treatment with low dosages of metformin (500 mg) and gradually increasing the dose, gastrointestinal problems can be reduced. It is beneficial to start medication therapy with the evening meal because taking the medication with meals reduces the symptoms. Another inevitable problem is lactic acidosis. Almost all individuals with compromised renal function have experienced lactic acidosis while using metformin. Thirty percent of diabetic patients receiving long-term metformin treatment have vitamin B12 malabsorption. [1,3,10]

Future propaganda: Biguanides are substrates of OCT1(SLC22A1) which are highly expressed in liver, which forms the major cause for lactic acidosis. Biguanides, such as metformin, are prescribed to treat type 2 diabetes mellitus but have the potentially fatal side effect of lactic acidosis.). (Dykens *et al*., 2008). *OCT1 (SLC22A1), which is strongly expressed in the liver, OCT2 (SLC22A2), which is found in the kidney, and OCT3 (SLC22A3), which is expressed in adipocytes and skeletal muscle, are all substrates of biguanides*. Experimental animals lacking OCT1 have much less hepatic absorption of biguanides and lactic acidosis development. The development of lactic acidosis, which may be caused by biguanide-induced impairment of mitochondrial function and consequently increased glycolytic flux, may be facilitated by OCT1-mediated hepatic uptake of biguanides and uptake into tissues such as kidney and skeletal muscle mediated by other OCTs, according to these findings (Wang *et al*.,2003) Biguanides are exported by the MATE1 transporter, and inhibition of this efflux by a variety of drugs, including tyrosine kinase inhibitors, enhances biguanide toxicity (DeCorter *et al*., 2012).[11]

Metformin and gut microbiome: Type 2 diabetes is frequently treated with metformin. Data from metagenomic studies of gut flora and changes related to type 2 diabetes were mixed. Subsequent research revealed that the outcomes were influenced by metformin's impact on the gut microbiome. 48 microbial pathways and 86 bacterial strains had their relative abundances considerably changed by metformin (Forslund *et al*., 2015; Wu *et al*., 2017). This was connected to modifications in the microbiome's capacity for metabolism, including rises in butanoate production, quinone biosynthesis, sugar derivative degradation, and polymyxin resistance pathways. When metagenomic pathways and gene families were analyzed, it was discovered that E. coli was primarily responsible for these functional alterations brought on by metformin (Vich Vila *et al*., 2020). Microbes may play a role in the therapeutic benefits of metformin on glucose metabolism. [11]

Together with its effects on blood glucose and haemoglobin A1c, the drug metformin can also change the make-up and functionality of the gut microbiota. According to Wu *et al*. (2017), metformin administration boosted short-chain fatty acid metabolism and LPS production, two processes that may be involved in glucose homeostasis. It also encouraged alterations in the abundance of Escherichia and Intestine-bacter. This metformin-treated microbiota increased glucose tolerance and decreased hemoglobin A1c when transferred to germ-free mice (Wu *et al*., 2017). Hence, the therapeutic effects of metformin for type 2 diabetes may be influenced by the gut flora. [11]

Summary

- Metformin is an oral medication used to treat type 2 diabetes.
- It works by decreasing glucose production in the liver and increasing insulin sensitivity in the body.
- Metformin can also be used to treat polycystic ovary syndrome (PCOS) and gestational diabetes.
- Common side effects of metformin include diarrhea, nausea, and abdominal discomfort.
- Metformin can interact with certain medications and should not be used in individuals with kidney or liver disease.
- Regular blood sugar monitoring is necessary while taking metformin.
- Metformin is usually taken with meals and the dosage is adjusted based on individual needs and response to the medication.
- Metformin is not recommended for individuals with severe infections, dehydration, or those undergoing certain medical procedures.
- Metformin is generally considered safe and effective when used as directed by a healthcare provider.

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