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Review Article

Metformin for the Treatment of Type 2 Diabetes Mellitus

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Abstract

Metformin, an old and widely accepted first line agent, is a hypoglycemic drug effective in the treatment of non-insulin-dependent diabetes mellitus. It stimulates the insulin induced component of glucose uptake into skeletal muscle and adipocytes in both diabetic individuals and animal models. It is mainly responsible to acutely decrease hepatic glucose production, achieved by transiently inhibiting mitochondrial respiratory-chain complex 1. Metformin has been established as the drug of choice for the first-line treatment of type 2 diabetes mellitus (T2DM). It stands out not only for its antihyperglycemic properties but also for its effects beyond glycemic control such as improvements in hemostasis and oxidative stress, endothelial dysfunction, insulin resistance, fat redistribution and lipid profiles. Metformin is reported to lower microvascular and macrovascular complications associated with T2DM, reduce fatty liver and restore ovarian function in polycystic ovary syndrome. According to broadly accepted guidelines, it should be administered early at diagnosis of this metabolic disorder, alongside diet and exercise. Metformin may also be efficaciously combined with all other oral hypoglycemic agents, enabling a useful additive effect. Furthermore, it may be prescribed in conjunction with insulin. This combination aims to offset insulin resistance, reduce insulin requirements and minimize weight gain. Potential sites of action of metformin are the glucose transporters and the insulin receptors. Recently, it was suggested that it can be used for the prevention in pre-diabetic populations and as an adjuvant treatment for cancer or gestational diabetes. These emerging new therapeutic areas for metformin will be reviewed together with additional benefits beyond its glycemic effect, a promising new step towards personalized medicine in the treatment of T2DM.

Keywords: *Metformin; Diabetes; Insulin; Hemostasis; T2DM*

Introduction

Diabetes is a chronic condition and an increasing global health problem affecting the proportion of people worldwide. Type 2 Diabetes mellitus (T2DM) is an epidemic disease and a long-term metabolic disorder with increasing incidence mainly caused by insufficient insulin production. It is a progressive disorder characterized by increasing hyperglycemia (high blood sugar level), lack of insulin and insulin resistance. It is one of the most common health problems and a challenging disease in the 21st century [1]. By the year 2025, the number of diabetic patients is set to increase to 69.9 million due to end-stage renal disease (ESRD), increase of the age, with significant increases in cardiovascular disease, obesity and the number of ethnic groups of high risk in the population, retinopathy and neuropathy. Therefore, there is a need to gradually intensify therapy to achieve and maintain glycemic control tight glycemic control is of great importance in T2DM patients [2-4]. Several guidelines have been developed recommending the early addition of basal insulin therapy in patients who do not meet target glycosylated hemoglobin (HbA1c) levels. Additionally, to achieve good metabolic control in diabetes and keep long term, a combination of changes in lifestyle and pharmacological treatment is necessary. Despite the increased burden of the disease and diabetes related complications, only about half of the individuals with T2DM achieve the glycemic goal of HbA1c < 7.0%, suggesting a need for early

and aggressive glycemic control to prevent macro- and micro-vascular complications. Physicians should be familiar with the different types of existing antidiabetic drugs and select the most effective, safe and better tolerated by patients. The pharmacological treatment of T2DM include the following eight classes of approved oral anti-diabetic drugs:

- Biguanides
- Thiazolidinediones
- Glinides
- Sulfonylureas
- Amylin mimetics
- Glucagon-like peptide 1 mimetics and dipeptidyl, alpha-glucosidase inhibitors
- Peptidase 4 inhibitors

Early combination therapy was useful in terms of robust glycemic control due to the complementary mechanism of action of the drugs that target multiple pathophysiological defects of diabetes, and further reduce the clinical inertia associated with stepwise treatment intensification [5,6].

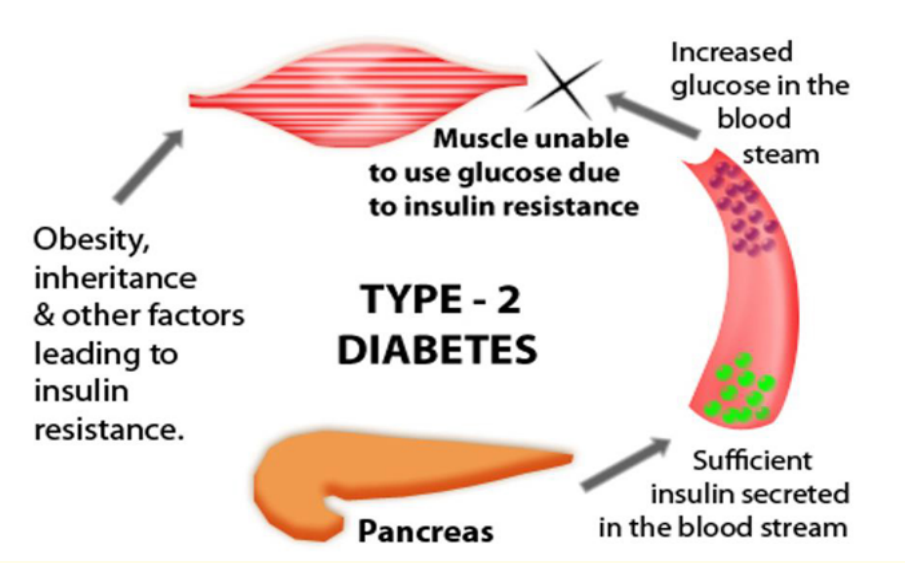

Figure 1: *Type 2 Diabetes. Source: http://danii.org.au/type-2-diabetes/.*

Metformin

Metformin is considered as gold standard anti-diabetic drug and is the first choice of treatment for most of the diabetic patients. It is a safer drug marketed as glucophage which is currently approved as a member of the class of drugs (biguanides) with multiple physiological and molecular effects associated with minimal toxicity.

It is prescribed as first line monotherapy and is globally accepted that its maximum effect is exhibited at 2,000 mg/day, although earlier studies indicate that some individual patients may respond better to higher doses and is widely available in standard and extended-release formulations. Over the past few decades, metformin has become a mainstay of type 2 diabetes management and has a remarkable

therapeutic index for diabetes to treat hyperglycemia worldwide. Depending on the characteristics of each patient, other alternative or second-line treatment options should be individualized. Several different mechanisms mainly via non-pancreatic pathways are included in the reduction of serum glucose level by metformin without increasing insulin secretion. This agent is also known as insulin sensitizer as it increases the effects of insulin.

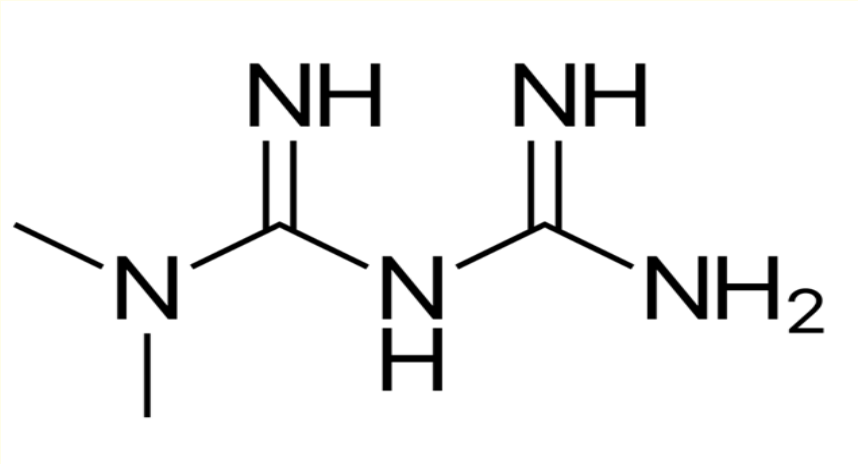

Figure 2: *Metformin.*

Use of metformin is effective in lowering HbA1c by 1% to 2% when used as monotherapy or in combination with other anti-diabetic drugs. It is regarded as the best initial choice, when compared to other oral antidiabetic agents resulting in a decrease in HA1c better or equipotent to sulfonylureas but without a risk of weight gain and hypoglycemia. In 2012, the position statement of the European Association for the Study of Diabetes (EASD), American Association of Clinical Endocrinologists and American Diabetes Association (ADA) recommends metformin as the foundation treatment for T2DM along with diet and exercise. Combinatorial therapy with one or two other anti-diabetic drugs along with metformin is prescribed for effective glycemic control, when metformin monotherapy fails to achieve the recommended standards of care like uncontrolled hyperglycemia.

Mechanism of action

The main mechanisms include anorexiogenesis, reduction of intestinal carbohydrate absorption, inhibition of hepatic gluconeogenesis, as well as increased glucose uptake by peripheral tissues. Metformin activates AMP-activated protein kinase (AMPK) by inhibiting mitochondrial complex 1 thereby, reducing the power supply and further, suppressing ATP production and consequently increasing NADH oxidation. It increases hepatic sensitivity to insulin by lowering the glucose level and decreases hepatic extraction of gluconeogenic substrates (lactate), thereby decreasing gluconeogenesis. Moreover, glucose uptake in the skeletal muscle is increased, whereas glycogenolysis is reduced. AMPK can be represented as a target, capable of mediating the beneficial metabolic effects of metformin. It is a multi-subunit enzyme that is recognized as a major regulator of lipid biosynthetic mechanisms due to its role in the phosphorylation and subsequent inactivation of essential enzymes such as acetyl-CoA carboxylase. Several pharmacological and genetic studies demonstrate that AMPK is required for maintaining glucose homeostasis. Recent research suggests that it has a wider role in metabolic regulation including expression of specific gluconeogenic genes (such as G6Pase) and glucose-stimulated genes linked to hepatic lipogenesis - including fatty acid synthase, muscle glucose uptake, Spot-14, fatty acid oxidation and pyruvate kinase [1]. Chronic activation of AMPK mimics the effects of extensive exercise training as AMPK activation is responsible for inducing the expression of muscle hexokinase and glucose transporters. Therefore, in future it can be considered as an ideal therapeutic target for T2DM. Metformin may hold promise in treating or preventing a whole host of conditions in patients with and without type 2 diabetes. Studies have shown that metformin may be cardioprotective in patients with diabetes, have protective properties against diabetic complications, especially by reducing the diabetes-

related death rate, provide breast and prostate cancer benefits, may help to increase pregnancy rate in polycystic ovary syndrome and can be beneficial in the presence of stable congestive heart failure [2]. The agent also offers neuroprotection that may reduce dementia and stroke risk [7,8].

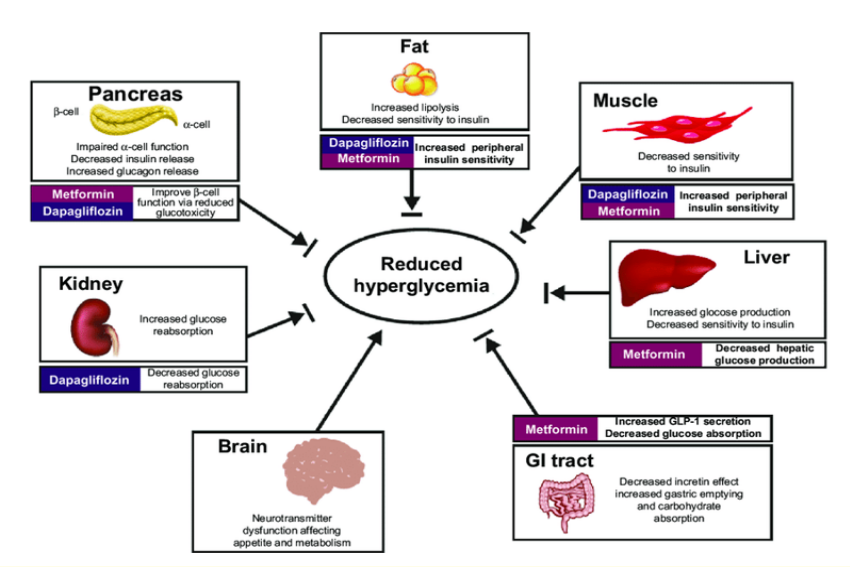

Figure 3: *Mechanism of action of metformin [8].*

Literature Survey

Fonseca., *et al.* 2000 evaluate the efficacy of combination with metformin and rosiglitazone in diabetic patients. They concluded that glycosylated hemoglobin levels, fasting plasma glucose levels, insulin sensitivity, and β-cell function were improved significantly with metformin-rosiglitazone therapy in a dose-dependent manner [9]. Raskin., *et al.* 2003 performed a comparative study to check the efficacy of repaglinide versus nateglinide, when used in a combination with metformin for treatment of T2DM. They concluded that the addition of repaglinide to metformin therapy resulted in reductions of HbA1c and FPG values that were significantly greater than the reductions observed for combination of metformin and nateglinide [10]. Goldstein., *et al.* 2007 assessed the efficacy of initial combination therapy with sitagliptin and metformin in type 2 diabetic patients by conducting a 24-week, randomized, double-blind clinical trial. They suggested that initial combination of sitagliptin and metformin provided substantial and additive glycemic improvement in diabetic patients [11]. Moses (2010) demonstrated combination therapy with repaglinide plus metformin is safe and effective when compared to monotherapy with oral antidiabetic agents in the treatment of T2DM. They indicated that combination of repaglinide and metformin can be used as oral antidiabetic drug (OAD) along with diet and exercise to improve glycemic control in adults with T2DM. This mechanism induces glucose uptake into muscle cells, thus lowers the fasting blood glucose in T2D patients [12]. Park., *et al.* 2014 compared OAD combinations with insulin glargine in patients with uncontrolled T2DM. After 24 weeks of observational study, they demonstrated that the combination therapy of metformin and glimepiride plus glargine insulin in diabetic patients resulted in substantial improvement in glycemic control in comparison to the combination therapy of metformin or sulfonylurea monotherapy plus glargine insulin without any differential increase in the risk of weight gain and hypoglycemia. Further, they suggested that addition of insulin glargine to glimepiride and metformin combination therapy in inadequately controlled T2DM patients was an effective treatment strategy for achieving glycemic control [13]. Quan., *et al.* 2017 explored the effects of various combinations of exenatide, metformin and biphasic insulin as part 30 (BIA30) on T2DM patients [14]. The combination of exenatide and metformin promoted glycemic control, weight loss, β-cell function index, adiponectin

levels and C peptide. They suggested that combination of exenatide and metformin showed better results than the combination of BIA30 and metformin for the T2DM patients. Shete., *et al.* 2018 assess the effectiveness of the combination with metformin and vildagliptin in type 2 diabetic patients. They conducted a 24-week observational study evaluating type 2 diabetic patients with HbA1c levels more than 7.5%. They demonstrated that combination of vildagliptin and metformin was associated with significant and clinically relevant HbA1c reduction from baseline [15].

Conclusion

Diabetes mellitus is a chronic, progressive disease worldwide. Metformin has been established as the drug of choice for the first-line treatment of T2D, and its administration has been strongly suggested at diagnosis of this metabolic disorder, employed as an adjunct with diet and exercise. Thus far, metformin is the only antidiabetic agent which has shown reduced macrovascular outcomes which are likely explained by its effects beyond glycemic control. Individualization of treatment and timely initiation and intensification with combination therapy in these patients could help delay disease progression and long-term complications. In this article, the importance and challenges determining the pharmacogenomic as well as other drivers for inter-individual variation in metformin's responses are summarized. Further, careful study on physiological validation of cell-based metformin and pharmacogenetic studies in humans, mainly focusing on intestinal, hepatic and renal effects should be done to understand the key mechanisms which are active in long-term treatment with metformin in humans.

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