Applications and side effects of Metformin on chronic Diseases - A review

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Abstract

Metformin being the oldest antidiabetic agent actually lowers the blood glucose level and so far with the minimal side effects still used for the treatment and management of Type 2 Diabetes Mellitus (T2DM). Though it has some adverse side effects but that is negligible when its benefits are studied. Metformin prevents diabetes in high risk and increasing diabetic complications. Recently it is shown in numerous studies that metformin may be related with some protective effect on heart and kidney. All the recent reports have showed that it has also some potential to reduce cancer development. This article presents some pleiotropic effects of metformin and potential benefits in different kinds of patients such as T1DM (Type 1 Diabetes Mellitus), GDM (Gestational Diabetes Mellitus), Polycystic ovarian syndrome (PCOS) etc.

Keywords: Metformin, T2DM, T1DM, GDM, PCOS.

Introduction

Metformin is used by doctors to treat T2DM for almost six decades. The results of the United Kingdom Prospective Diabetes Trial (UKPDS), a multicenter, randomized, prospective study with a median follow-up of 10.7 years, best demonstrated its importance in the management of acute and moderate hyperglycaemia and its complications. In 342 overweight/obese people in those T2DM is newly diagnosed and low cardiovascular (CV) risk, this landmark clinical trial found that only metformin, independent of its glucose-lowering effect, significantly reduced diabetes-related death, myocardial infarction, any diabetes-related endpoints, and all-cause mortality [3]. Intensive glucose control, on the other hand, using sulfonylureas and insulin, had no influence on major adverse cardiovascular events (MACE) (3). In a 10-year post trial of the UKPDS [2], an overall beneficial effect is seen in case of diabetic vascular complications after metformin therapy.

Metformin is also effective in giving a further prevention after primary prevention of cardiovascular events [1,4]. Metformin's cardioprotective properties have also been observed in a number of retrospectives, non-randomized clinical trials, the majority of which were relatively short in duration. However, because of differences in aspects and methodology, the findings of these studies are difficult to interpret, and effect of metformin on the cardiovascular system remains unknown.

The UKPDS results have shown that metformin is preferred compared to other oral hypoglycaemic medications in patients who have primarily affected with T2DM. Furthermore,

metformin's leading role as a first-line oral agent for the treatment of T2DM diagnosed patients is supported by above 60 years of very good clinical practise with this drug. The results of meta-analyses and systematic reviews of randomised, high quality, controlled clinical trials, however, should provide the strongest arguments supporting any given drug as the drug of first choice in the treatment of any disease, according to the principles of evident proofed medicine. In the case of metformin, the majority of such studies found that it provided significant clinical benefits.

About metformin

Galega officinalis, a herbal medication (also known as goat's rue and French lilac, among other names) that is used to diagnose the signs of what we now understand as diabetes since the Middle era [6,7], has a long and violent history. Guanidine and the more or less poisonous galegine are among the alkaloids found in the herb (isoamyleneguanidine).

Two Irish scientists, Werner and Bell, pioneered the synthesis of metformin in 1922, although it had not been utilised in a long time. [8]. Barger and White established the structure of the galegine moiety chemically in 1923 [9]. Preclinical studies with galegine, a less hazardous guanidine-like alkaloid, demonstrated that the hypoglycaemia impact was too strong in rabbits and dogs, resulting in death [10]. The results of the earliest human trials, which was published in 1927 by Muller and Reinwein, showed that galegine had a strong hypoglycaemic impact in people with diabetes but was only modest in people with normoglycemia [10]. Following study backed up these findings, however the unpredictability of glucose concentrations, the short duration of the hypoglycaemic impact, and poor tolerance limiGalega officinalis, a herbal medication (also known as goat's rue and French lilac, among other names) that has been used to treat the early stages of what we now know as diabetes since the Middle era [6,7], has a long and violent history. Guanidine and little poisonous galegine are among the alkaloids found in the herb (isoamyleneguanidine). Since the metformin use in case ofT2DM, a large number of patients is successfully treated with this widely available medication that has a favourable risk/benefit profile and is diagnosed as a first-line drug by IDF guidelines [11]. As a result, it's no surprise that metformin is now a days the most generally prescribed oral antidiabetic drug in the world, with 45–50% of all prescriptions written for it and approx. 150 million people taking it each year [11-13]. The positive experience with the metformin, prove that it is clinically effective, it is safe, pocket friendly, availability, and cost-effectiveness were all factors in the World Health Organization's decision to add it to the list of essential medicines, which are "medicines that satisfy the population's priority health care needs" [14].

Clinical aspects of T2DM

Metformin's critical role in the treatment of chronic hyperglycaemia in T2DM it has been established beyond doubt above 60 years of clinical use. Untold numbers of clinical research and real-world experience have proved its efficacy, safety, and tolerability in monotherapy and in combination with other glucose-lowering medications. As a result, the ADA and EASD continue to advocate metformin

administration in conjunction with balanced diet and proper exercise as the initial pharmacologic trial in T2DM patients [16, 17]. We chose to focus on additional potential therapeutic applications of metformin because the role of this particular medicine in T2DM is fully discussed in the existing literature.

Prediabetes

Prediabetes is becoming more common over the world, with the organisation that is International Diabetes Federation estimating that 453.8 million people will have low glucose tolerance by 2050 [18]. People with prediabetes are at a greater risk of having T2DM and cardiovascular disease, such as coronary heart disease and heart failure (HF), cardiovascular mortality, and stroke [19]. These people are frequently overweight or obese, and their IR is high. When lifestyle interventions fail, metformin—a medication that greatly improves insulin sensitivity while only mildly reducing body weight—is used to treat the advancement of early glucose metabolic abnormalities [20]. Furthermore, metformin should be administered in those who are already showing signs of micro vessel disease and fatty liver.

In the landmark Diabetes Prevention Program (DPP), the biggest randomised clinical trial assessing the use of metformin for diabetes prevention, the effectiveness of metformin to postpone or prevent the pathway of prediabetes to diabetic patients was shown. The goal of this trial was to see if a combination of extensive lifestyle changes and metformin could help persons at high risk of diabetes avoid or delay the occurrence of T2DM. In this research, the case of diabetes was 58 percent lower in the lifestyle intervention group and 31 percent lower in the metformin treated group after 2.8 years of follow-up compared to the newly diagnosed group [21]. From the Codyce Multicenter Study, the impact of metformin in patients suffering with little coronary cardiopathy caused by dysglycemia and resistance of insulin was investigated.

Moin *et al*. concluded that metformin is efficacious, safe, acceptable, and cost effective after analysing the findings of 40 trials on the drug's usage for diabetes prevention in persons at greater risk published between 1998 and 2017. As a result, they recommend expanding metformin use in real-world practise, especially in obese people with a BMI of 35 kg/m2, increased fasting glucose levels, and HbA1c levels of 5.7–6.4%, as well as women with a history of gestational diabetes [20]. Metformin is the sole anti-diabetic drug approved by the American Diabetes Association (ADA) for the prevention of T2DM in patients who has prediabetes [21] based on the favourable results of many researches. In some nations, the use of the substance is permitted (e.g., Poland, Turkey, Philippines and the United Kingdom).

Clinical aspects of T1DM

Metformin is frequently used as a supplement for insulin in T1DM since it is shown to impact of IR throughout the body and around the edge in obese juvenile diabetics [22]. As a result, until recently, the primary justification for its use was the lowering in insulin some clinical trials have revealed a

dosage requirement. [22]. The first clinical trials examining the effects of metformin on glucose control in T1DM patients were conducted in the mid-1980s, with mixed results [22]. However, investigations done in the following years yielded more positive outcomes. Some of them found that combining metformin with insulin reduced insulin requirements while improving or maintaining HbA1c levels [132–134]. The findings were published by Vella *et al*. They discovered a considerable lowering in insulin dose requirements, but no reduction in HbA1c [23]. A multicenter clinical trial conducted in the United States in 2013/2014 aimed to see how adding 2000 mg of metformin to basal-bolus insulin helped 140 overweight/obese adolescents with poorly managed T1DM. There was no improvement in glucose control at the conclusion of the six-month treatment with insulin plus metformin, but insulin dose requirement and BMI were much lower than with placebo. Metformin, on the other hand, was linked to a much higher prevalence of gastrointestinal side effects. Author of this review concluded that the findings do not support the findings of metformin to enhance glycaemic control in fatty adolescents with T1DM [23].

Clinical aspects of Gestational Diabetes Mellitus

Metformin also has an advantage over newer hypoglycaemic medications in that it is increasingly being used to treat glucose metabolism problems in pregnant women [24]. This is because multiple clinical trials have found that metformin is a good, safe, and affordable treatment option for pregnant patients with gestational diabetes and T2DM, and that it may enhance maternal and perinatal outcomes [24,25]. MiG TOFU studies for gestational diabetes, which showed that metformin had regular pregnancy outcomes to insulin treatment with reduced maternal weight gain and good patient acceptability, have had a significant impact on current medical practise in many countries [25,26]. Metformin and insulin treatment have been proven in a analysis of clinical trials including 1712 pregnant patients with GDM.

Metformin is a pregnancy category B medicine that is deemed safe if there is a therapeutic need for it. All newer hypoglycaemic medicines, unlike metformin, are categorised as pregnancy category C drugs and are not utilised in case of GDM and T2DM during pregnancy because to concerns about serious side effects.

Effects of Metformin in PCOS

Metformin is the only anti-diabetic medicine approved in case of metabolic abnormalities in patients with PCOS. Obesity, insulin resistance, hyperinsulinemia, and other reproductive and metabolic problems are all common symptoms of the syndrome [27]. Metformin can rectify some of these irregularities and minimise the risk of glucose intolerance in women with PCOS by boosting insulin sensitivity in target tissues, as well as lowering androgen levels and managing the menstrual cycle [27]. Metformin, in addition to its antihyperglycemic impact, has been shown to be effective in bleeding issues in patients with PCOS and has a strong ovulation stimulatory effect when compared to placebo [27].

Zeng *et al*. found that metformin medication can enhance pregnancy rate and lower the risk of preterm delivery in an analysis of 13 studies comprising 1606 pregnant patients with PCOS [27]. It may also lower the risk of pregnancy-induced hypertension and early pregnancy loss, as well as increase the rate of vaginal delivery and live births. Metformin also lowers increased blood glucose levels in pregnant women without raising the risk of hypoglycaemia [28]. Metformin use is related with few GDM developments than control diets, according to the most current analysis reported in 2020 [28]. Despite the fact that metformin is not licenced in case of PCOS, it is nonetheless the most widely recommended medicine in women with the condition [28].

Only one modest, short-term trial summarizing the effects of empagliflozin in fatty women with polycystic ovarian syndrome was found in the literature [28]. The findings revealed that therapy with this drug enhanced anthropometric measurements and body composition while leaving hormonal and metabolic markers unchanged. Liraglutide may lower body weight, belly circumference, and eating behaviour, according to the findings of a short-term research involving 36 fatty women with PCOS [29]. GLP-1RAs were found to be more effective than metformin in increasing insulin sensitivity and lowering weight and abdominal fat in a recent comprehensive review and meta-analysis. Author of this paper point out various flaws in the papers that were included in the analysis [29].

Dipeptydyl peptidase-4 is shown to influence adenosine deaminase potentiality, Anti Mullerian Hormone and insulin levels, as well as IR [30]. In a pilot randomised investigation, Ferjan *et al.* found that sitagliptin can reduce weight gain in metformin-intolerant patients with PCOS [30]. Sitagliptin in conjunction with metformin restricted weight gain more efficiently than metformin alone, according to the same authors [31]. As a result, more research is needed to verify that these novel hypoglycaemic medications have a clinical benefit and advantage over metformin in case of PCOS.

Is Metformin safe?

The worldwide potential use of metformin clearly states that it is a high tolerance drug that is used still as a better option for diabetic patients. Very fewer rate of metformin treated patients develop some of gastrointestinal problems and various symptoms like dyspepsia, burning heart, abdominal pain, nausea, vomiting, bloating or diarrhoea [31]. Almost 5% of patients' acute symptoms of gastrointestinal intolerance develop. It is related to high power of metformin in the intestine, that increase secretion of serotonin from chromaffin cells, lowered ileum absorption of the bile acids, increased secretion of GLP-1 from enterocytes and altered microbiome. All these factors have a substantial influence on gastrointestinal regulation, particularly intestinal movement and secretion [31]. Donnelly *et al*. analysed data from A Diabetes Outcome Progression Trial (ADOPT) and UKPDS, and from real-world showed that the use of 1 g of metformin daily increased the risk of anaemia by 2% per year [31]

Conclusion

All the clinical and experimental events suggest that metformin is a potential drug with minimal or negligible side effects that can successfully lower the blood glucose level in patients with T2DM. Moreover, it is also safely used against T1DM, GDM, PCOS etc.

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