A Brief Overview of Metformin-An anti-diabetic drug to fight cancer and its Importance

Rallabandi Lakshmi Pavani
St. Ann's College of Pharmacy, chirala, Andhra Pradesh.

***Abstract*—Metformin is a biguanide anti – diabetic drug used in conjunction with diet and exercise for glycemic control in type -2 diabetes mellitus. It is also used off - label for insulin resistance in polycystic ovary syndrome (PCOS) .Since epidemiologic data have highlighted the positive effects of metformin to reduce cancer incidence and mortality , many in vitro and in vivo studies as well as a large number of clinical trails have been conducted in order to study its potential .This article aim is to provide an overview of metformin role as an anti-diabetic drug by understanding is mechanism of action , efficiency and importance and also role of metformin in the treatment of cancer.**

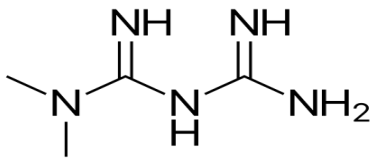
Key words: **metformin, cancer, diabetes mellitus, insulin.**

I. INTRODUCTION

Metformin, or 1,1-dimethylbiguanide, is derived from the alkaloid galegine or iso amylene guanidine, the active substance of Galega officinalis, also known as Goat's Rue, the French lilac or Italian Fitch .

It has been widely used in the treatment of Type 2 Diabetes Mellitus (T2DM) since its approval in 1958 in the United Kingdom and in 1995 in the United States and is currently recommended as first-line therapy for all newly diagnosed T2DM patients (American Diabetes Association, 2014).

The extensive use of this drug with nearly 120 million prescriptions worldwide each year is due to its favourable benefit-risk profile.



(Chemical structure of metformin)

Diabetes mellitus is a group of metabolic disorders in which the blood glucose is higher than normal levels, due to insufficiency of insulin release or improper response of cells to insulin, resulting in high blood pressure. The resultant hyperglycemia produces the classical symptoms of polyuria, polydipsia and polyphagia. It may also cause nerve problems, kidney problems, and blindness, loss of limbs, and sexual dysfunction, increase in heart attack or stroke. Metformin (a biguanide derivative), by controlling blood glucose level decreases these complications. Metformin works by helping to restore the body's response to insulin. It decreases the amount of blood sugar that the liver produces and that the intestines or stomach absorb. Metformin, other than hypoglycemic activity, has been taken with diet and exercise changes to prevent diabetes in people who are at high risk for becoming diabetic. It is also used in women with polycystic ovarian syndrome. Metformin may make menstrual cycles more regular and increase fertility.

As a result of its worldwide spread for over 50 years, some epidemiological, clinical and preclinical data concerning other potential indications of metformin have emerged, and it is also used today as a cardiovascular protective agent an anti-inflammatory, a neuroprotective agent or an anticancer agent.

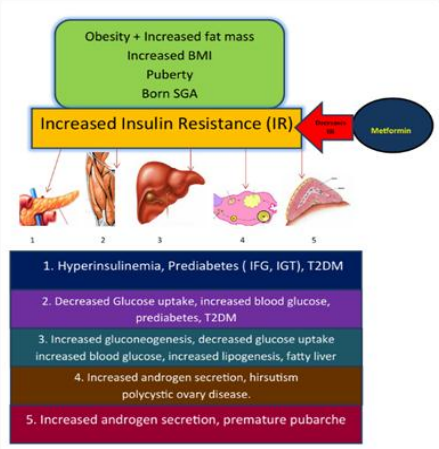
Polycystic ovary syndrome (PCOS) is frequently associated with resistance to insulin and since 1994, metformin 659 has been proposed as a treatment for PCOS. In 2004, National Institute for Health and Clinical Excellence recommended to prescribe metformin for women with PCOS and a body mass index above 25 for anovulation and infertility when other therapies have failed to produce acceptable results .However, several subsequent reviews did not show promising results and did not recommend it further or at least as a first-line medication, except for women with glucose intolerance .The guidelines usually suggest clomiphene to be the first treatment and recommend lifestyle modification independent from drug therapy. A systematic review using comparative trials of clomiphene and metformin found equal results for infertility and A BMJ editorial suggested that metformin should be used as a second choice, if clomiphene treatment fails .Furthermore, a

large review using 27 clinical trials found that metformin was not associated with any increase in the number of live births; however, it improved ovulation rates, especially when it was used in combination with clomiphene Further, a review recommended metformin as a first choice because of positive effects on insulin resistance, hirsutism, anovulation and obesity, which are often associated with polycystic ovary syndrome .The different trial designs might be the reasons for the contradictory results. For example, considering live birth rate instead of pregnancy as the endpoint might have biased a few trials against metformin. Another explanation is that metformin may have different efficacy in different populations. Cancer protection A large case-control study has suggested that metformin might protect patients against pancreatic cancer. In this study, the risk of pancreatic cancer in metformin group was 62% lower than in placebo group who did not use metformin. The participants having sulfonylureas or insulin were found to have a 2.5-fold and 5-fold higher risk of pancreatic cancer, respectively, in comparison to placebo group. Several studies have suggested that diabetic patients using metformin might lower the risk of cancer compared to those using other anti-diabetic drugs. However, the results need confirmation in controlled trials. Metformin has shown a strong antiproliferative effects on colon, pancreatic, breast, ovarian, prostate and lung cancer cells. Preclinical studies have also shown reliable anti-tumoral effects in different animal models. A clinical trial has demonstrated beneficial effect in colon and breast cancer.

II. MECHANISM OF ACTION

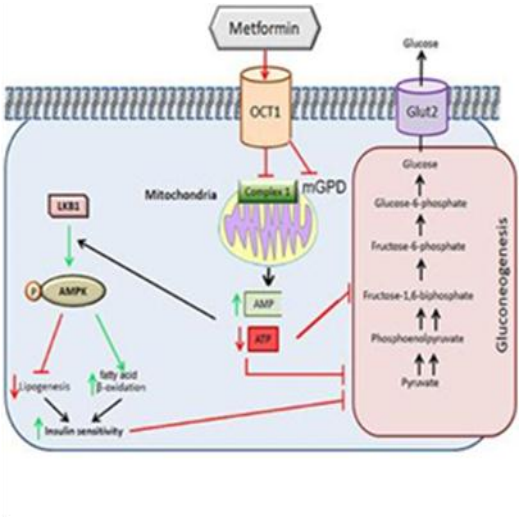
end of the precise molecular (or biochemical) mechanism/s of action remain incompletely understood. It acts by countering insulin resistance, particularly in liver and skeletal muscle. It suppresses hepatic gluconeogenesis, increases peripheral insulin sensitivity in insulin sensitive tissues such as muscle and adipose tissue, and enhances peripheral glucose utilization.

However, the main effect of Metformin appears to be decreasing hepatic glucose production through a mild inhibition of the mitochondrial respiratory-chain complex 1. This transient decrease in cellular energy status promotes activation of adenosine monophosphate-activated protein (AMPK), a well-known cellular energetic sensor.



AMPK is a protein kinase ubiquitously expressed in mammalian tissues and involved in regulating energy balance. Activation of AMPK stimulates adenosine triphosphate (ATP)-producing catabolic pathways, while inhibiting ATP-consuming anabolic pathways, thereby, maintaining cellular energy stores. In skeletal muscle, activation of AMPK increases glucose uptake and lipid oxidation. In adipose tissue, activation of AMPK reduces both lipolysis and lipogenesis. Metformin regulates glucose transporter 4 (GLUT4) translocation through AMP activated Protein Kinase (AMPK)-mediated Cbl/CAP Signaling. It enhances insulin signaling in insulin-dependent and -independent pathways [10]. In the liver, activation of AMPK inhibits gluconeogenesis and lipid synthesis but increases lipid oxidation. The activated AMPK decreases flux of free fatty acids and inhibits lipolysis, which may indirectly improve insulin sensitivity through reduced lipotoxicity (reduces hepatic lipogenesis) and exert an indirect effect on hepatic insulin sensitivity to control hepatic glucose output. In the heart, Metformin increases fatty acids uptake and oxidation, and increases glucose uptake and glycolysis. Metformin can also antagonize the action of glucagon, thus reducing fasting glucose levels. In summary, activation of AMPK in skeletal muscle, liver and adipose tissue decreases circulating glucose, lipids, reduces fat accumulation and enhances insulin sensitivity. Additional action of Metformin action is through induction of a profound shift in the faecal microbial community profile in diabetic mice and it has also been proposed that this may contribute to its mode of action possibly through an effect on Glucagon-like peptide-1 (GLP-1) secretion. Moreover, Metformin enhances the expression of the genes encoding the receptors for both GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) in mouse islets and also increases the effects of GIP and GLP-1 on

insulin secretion from beta cells. These incretin-sensitising effects of Metformin appear to be mediated by a peroxisome proliferator-activated receptor α-dependent pathway, as opposed to the more commonly ascribed pathway of Metformin action involving AMP-activated protein kinase. The protective effect on the cardiovascular system cannot be fully explained by its blood glucose-lowering properties. These effects may be partly mediated via beneficial effects on circulating markers of endothelial function (vascular cell adhesion molecule-1 [VCAM-1], E-selectin), fibrinolysis (plasminogen activator inhibitor-1 [PAI-1]) and chronic inflammation (C-reactive protein [CRP]). These mechanisms work together to reduce the levels of circulating glucose, increase insulin sensitivity, and reduce the hyperinsulinemia associated with insulin resistance.



III. PHARMACOLOGICAL EFFECTS OF METFORMIN

Metformin has a half-life of around five hours and undergoes renal excretion with 90% being eliminated within 24 hours. It can be prescribed as 500 mg or 850 mg tablets. In adults , it can be started at the 500 mg dose and increased in weekly increments until the maximum tolerated dose is achieved, normally 2 g/day . The intestinal absorption of Metformin may be primarily mediated by plasma membrane monoamine transporter (PMAT/SLC29A4), which is expressed on the luminal side of the enterocytes. Metformin has an oral bioavailability of 50-60% under fasting conditions, and is absorbed slowly. Peak plasma concentrations (Cmax) are reached within one to three hours of taking immediate-release Metformin and four to eight hours with extended-release formulations. Steady state is usually reached in one or two days. Food decreases the extent of and slightly delays the absorption of Metformin, as shown by approximately a 40% lower mean peak plasma concentration. The plasma protein binding of Metformin is negligible. It should be taken with food to reduce the potential for gastrointestinal side effects. Metformin is undetectable in blood plasma within 24 hours of a single oral dose . After administration of a single oral Metformin HCl 500 mg tablet with food, geometric mean Metformin Cmax and AUC did not differ between adolescents with T2DM (12 to 16 years of age) and gender- and weight matched healthy adults (20 to 45 years of age).

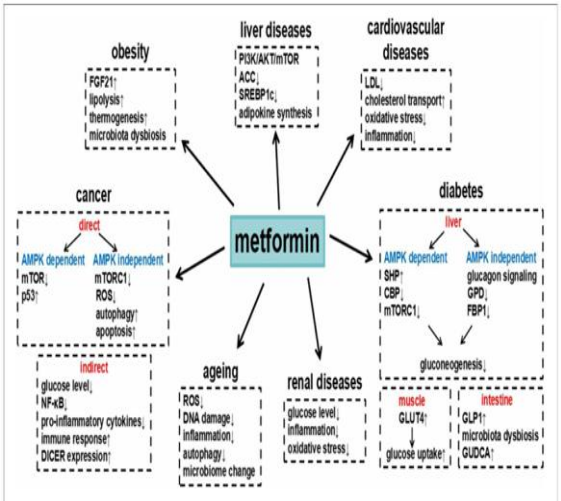
IV.METFORMIN AS AN ANTICANCER AGENT

Accumulating evidence
from *invitro* and *invivo* studies supports the fact that anticancer effects of metformin can be divided into two non-exclusive categories: an indirect effect by reducing the blood glucose and insulin levels, and a direct effect on cancer cells, partially through the activation of AMPK

Metformin and chemotherapy
Because of the resistance of cancer stem cells to conventional treatments (*e.g.* chemotherapy or radiotherapy), there is a high rate of cancer relapse. After the end of the treatment, CSCs can reform the tumour bulk *via* their differentiation into non-CSCs and their subsequent proliferation.

Thus, targeting cancer stem cells could have a great potential to allow a total eradication of cancer and prevent a possible recurrence.

V.IMPORTANCE



VI.CONCLUSION

metformin acts as a fundamental anti diabetic drug and it is used for the treatment of various types of cancer and diabetics mellitus.Metformin is a widely used clinical drug with numerous benefits, which through different signaling pathways . The most remarkable feature of metformin is anti-hyperglycemia. Cellular and animal studies have found that metformin inhibited the expression of gluconeogenic genes in AMPK dependent pathway or independent pathway, to suppress hepatic glucose production.According to epidemiological data concerning the lower incidence of cancers within patients taking metformin, numerous *in vitro* and *in vivo* studies have shown a potential of metformin as a chemopreventive agent. Metformin is an oral anti-diabetic drug in the biguanide class for the treatment of type 2 diabetes mellitus, in particular, in overweight and obese people and those with normal kidney function. Metformin has several benefits in patients with type 2 diabetes mellitus, including decreased hyperinsulinemia, weight reduction, augmented fibrinolysis, improved lipid profiles and enhanced endothelial function. Although the use of metformin in diabetes has its safety concerns, its benefits and the recent results indicate that the nephroprotective activity against nephrotoxic agents on metformin and its recent good safety records have led researchers to consider the use of this drug more and more in insulin resistant states even before the development of hyperglycemia.ongoing research provides metformin uses and role in various cancer treatments

VII .REFERENCES

[1] Scheen AJ, Paquot N. Metformin revisited: A critical review of the benefit-risk balance in at-risk patients with type 2 diabetes.

[2] Diabetes Metab . Kirpichnikov D, McFarlane SI, Sowers JR. Metformin: An update. Ann Intern Med.

[3] Hundal RS, Inzucchi SE. Metformin: New understandings, new uses. Drugs

[4] Scarpello JH, Howlett HC. Metformin therapy and clinical uses. Diab Vasc Dis Res .

[5] Gandini S, Puntoni M, Heckman-Stoddard BM, Dunn BK, Ford L, Decensi A, et al. Metformin and cancer risk and mortality: a systematic review and meta-analysis taking into account biases and confounders. Cancer Prev Res. (2014) 7:867–85. doi: 10.1158/1940-6207.CAPR-13-0424

[6] Morales DR, Morris AD. Metformin in cancer treatment and prevention. Annu Rev Med. (2015) 66:17–29. doi: 10.1146/annurev-med-062613-093128 8. Lamanna C, Monami M, Marchionni N, Mannucci E. Effect of metformin on cardiovascular events and mortality: a meta-analysis of randomized clinical trials. Diabetes Obes Metab. (2011) 13:221–8. doi: 10.1111/j.1463-1326.2010.01349.x

[7] Bhat A, Sebastiani G, Bhat M. Systematic review: preventive and therapeutic applications of metformin in liver disease. World J Hepatol. (2015) 7:1652–9. doi: 10.4254/wjh.v7.i12.1652 10. Breining P, Jensen JB, Sundelin EI, Gormsen LC, Jakobsen S, Busk M, et al. Metformin targets brown adipose tissue in vivo and reduces oxygen consumption in vitro. Diabetes Obes Metab

[8] Essentials of medical pharmacology by K.D Tripati