

Prescription pattern of metformin for various indications: a prospective study

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ABSTRACT

Background: Metformin, a biguanide is the most preferred choice of drug in the treatment of type 2 diabetes mellitus. It has many advantages - it does not cause hypoglycaemia and weight gain, prevents insulin resistance besides being cheap and relatively safe. It has other pleiotropic benefits beyond its glucose-lowering effect with preclinical evidence for many indications. This prospective observational study was conducted to assess the prescribing pattern of metformin for various indications by physicians.

Methods: Prescriptions containing metformin were collected from the inpatient and Outpatient Departments of different specialities. The data collected were analysed and grouped on the bases of age, gender, disease condition and analysed for significance.

Results: A total of 218 patients were included in this study. All the prescriptions containing metformin were collected and analysed. Metformin was most extensively prescribed for Type 2 diabetes (51.83%) followed by Polycystic ovarian disease (PCOD) (26.14) and least number of prescriptions were collected for prediabetes (1.37%). Most common age group receiving metformin was 31-40 years (35.77%).

Conclusions: Metformin is the oldest and most widely prescribed as a first choice antihyperglycemic drug for treatment of type 2 diabetes mellitus. There are many experimental and clinical studies which have shown an array of potential benefits of metformin other than in the treatment of diabetes. But its clinical application is limited despite convincing basic evidence. The possible reasons could be absence of recommendations in the guidelines and insufficient evidence for use.

Keywords: Metformin, Pleiotropic effects, Prescription pattern

INTRODUCTION

Type 2 Diabetes mellitus is a disease condition characterised by insulin resistance and progressively increasing insulin secretory defect. Among the many oral pharmacological agents used for the treatment of diabetes, metformin is one of the oldest drug in use.

Metformin, belonging to the Biguanide class of oral antidiabetic drugs, is an insulin sensitizer. It is derived from the herb *Galega officinalis*. It was introduced in the

year 1957, and since then, has been an integral part in the management of Type 2 diabetes.

WHO in 1985 has defined rational use of drugs as 'Patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community.'¹ Appropriate prescriptions are based on sound knowledge of prescriber, understanding of the pathophysiology of disease to be treated and the

knowledge of adverse effects and benefits of the drug use to optimise maximum benefit to the patient at the earliest.²

Apart from its use as an antidiabetic medication, Metformin can be prescribed for many other indications. This study is taken to study prescription pattern of metformin for different indications.

Mechanism of action of metformin

Cellular mode of action of the biguanides remains elusive, but their primary effect is reduction of hepatic glucose production by inhibiting gluconeogenesis which is markedly increased in type 2 diabetes. Other effects include

- Increased glucose uptake and utilisation in peripheral tissues which reduces insulin resistance and enhances peripheral insulin sensitivity
- Impairment of renal gluconeogenesis, slowing of glucose absorption from the Gastrointestinal tract, with increased glucose to lactate conversion by enterocytes, enhanced release of glucagon-like peptide 1, direct stimulation of glycolysis in tissues and reduction of plasma glucagon levels. The biguanide blood glucose-lowering action does not depend on functioning pancreatic beta cells
- Increase fatty acid oxidation
- Lowers circulating low-density and very-low-density lipoprotein.

Metformin inhibits mitochondrial respiratory-chain complex 1 which decreases entry of NADPH into respiratory chain and lower proton motive force, decreasing ATP synthesis at complex V, increasing levels of AMP hence depleting cellular energy stores.^{3,4}

Additionally, there is activation of AMP activated protein kinase (AMPK) in hepatocytes, an important enzyme in metabolic control.⁵ AMPK is the energy sensor of the cell by detecting changes in the ratio of AMP or ADP to ATP. AMP binds the regulatory γ subunit to allosterically activate AMPK and promote phosphorylation of key enzymes and transcription regulators. The net effect is the downregulation of energy consuming, anabolic processes, such as gluconeogenesis and lipid synthesis, along with activation of ATP generating catabolic process such as fat oxidation.

Madiraju and colleagues have demonstrated that metformin selectively inhibits the mitochondrial isoform of glycerophosphate dehydrogenase, an enzyme that catalyzes the conversion of glycerophosphate to dihydroxyacetone phosphate (DHAP), thereby transferring a pair of electrons to the electron transport chain leading to decrease in cytosolic DHAP and a rise in the cytosolic NADH-NAD ratio, inhibiting conversion of lactate to pyruvate; the use of glycerol and lactate as gluconeogenic precursors therefore drops, and glycerol and lactate levels build up in the plasma. Long-term

metformin dosing reproduced these reciprocal changes in the redox state, which is decreased in the mitochondrion and increased in the cytoplasm.⁵

It has little effect on blood glucose in normoglycemic states and does not affect the release of insulin or other islet hormones and rarely causes hypoglycemia. However, even in persons with only mild hyperglycemia, metformin lowers blood glucose by reducing hepatic glucose production and increasing peripheral glucose uptake. This effect is at least partially mediated by reducing insulin resistance at key target tissues.

Emerging or Non-diabetic indications

Type 1 diabetes

Intensive insulin therapy is the only treatment option in patients with Type 1 diabetes. However, this approach increases the risk of hypoglycemia and also causes weight gain. Clinicians have always been looking for an additional agent which would mitigate these undesirable effects of insulin. Hence there has generally been an off-label use of metformin, especially in overweight patients.

A meta-analysis published in 2010 reviewed 197 trials, of which 9 were found to be relevant. It concluded that addition of metformin reduced the daily insulin requirement by 6.6 U, though it did not have any statistically significant reduction in HbA_{1c}. It also noted that Metformin was associated with reductions in: HbA_{1c} (0.6-0.9% in four of seven studies); (3) weight (1.7-6.0 kg in three of six studies); and (4) total cholesterol (11.6-15.8 mg/dl in three of seven studies).⁶

Obesity

Several clinical trials (Diabetes Prevention Program⁷. Malin et al, have reported that Metformin causes modest weight reduction.⁸ The mean weight loss is in the range of 1-5kgs or 1-3% reduction from mean base line. Metformin attenuates AMPK activity in hypothalamus and reduces appetite by decreasing orexigenic peptides, neuropeptide-Y (NPY), and agouti-related protein (AgRP) and increasing POMC (anorectic) expression and also improves leptin and insulin sensitivity.⁹ Metformin also increases fat oxidation and decreases fatty acid synthesis there by reducing hepatic steatosis.¹⁰

Metformin induced weight loss is not because of energy expenditure as with exercise but due to loss of adipose tissue.¹¹

Polycystic Ovary Syndrome

PCOS is associated with menstrual abnormalities, hyperandrogenism and polycystic ovary on ultrasound.¹² There is insulin resistance (70% of patients) compensated by hyperinsulinemia.¹³

Hyperandrogenism is due to increased testosterone production as a result of Insulin induced increased cytochrome p450c-17 α activity in ovaries and adrenals.¹⁴ This enzyme converts progesterone to 17 α progesterone through androstenedione which is converted to testosterone.

Androgen production also is increased due to inhibition of sex hormone binding globulin (SHBG) and by lowering of insulin like growth factor binding protein - 1 (IGFBP-1) in liver by elevated insulin.¹⁵

Metformin improvement in PCOS is by a dual mechanism viz. decreasing insulin resistance thus reducing circulating insulin levels and by direct ovarian effects. Meta-analysis of several trials showed that metformin treatment increases ovulation, improves menstrual cyclicality, decreases FSH stimulated steroidogenic enzymes and aromatase activity, thereby reducing hyperinsulinaemia and hyperandrogenaemia in PCOS patients.¹⁴

To summarize, the reported effects of Metformin in PCOS include restoring ovulation, reducing weight, reducing circulating androgen levels, reducing the risk of miscarriage and reducing the risk of gestational diabetes mellitus and improving pregnancy outcome.¹⁶

However, the effect of Metformin in PCOS has been inconsistent, with some studies showing a benefit and others not.

At present Metformin in PCOS is indicated in patients with associated Metabolic Syndrome.

Antitumor effect

A new indication of metformin being explored is for management and chemoprevention in cancer. Insulin acts as a mitogen through its activation of mitogen activated protein kinase (MAPK) and phosphoinositol 3 kinase which regulate cell proliferation.¹⁷

Preclinical studies have shown metformin reduces tumor growth by reducing the amount of insulin in the blood, slowing rate of tumor growth. And alternatively, by disrupting complex I of the electron transport chain, cutting the energy supply produced by their mitochondria.¹⁸

Proposed anticancer potential targets of metformin therapy are breast, colon, thyroid, pancreatic, prostate, head and neck tumors, lymphomas and leukemias.¹⁹

Non-alcoholic fatty liver disease (NAFLD)

It is a spectrum of conditions characterized by free fatty acid and triglyceride accumulation in liver (steatosis), to non-alcoholic steatohepatitis (NASH–fatty changes with inflammation and hepatocellular injury or fibrosis), to advanced fibrosis and cirrhosis.²⁰ It is caused by insulin

resistance (through lipolysis and hyperinsulinemia) and obesity (through leptin resistance). It includes both non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH). Insulin resistance is widely considered a pivotal feature of NAFLD.

Metformin reduces hyperinsulinaemia and improves hepatic insulin resistance. Stimulate pyruvate-kinase, fatty acid beta-oxidation, anaerobic respiration (i.e. lactate production) and suppress the expression of lipogenic enzymes.²¹ Studies with metformin have shown discrepant results. Randomized controlled trials have shown improved serum liver enzymes and insulin resistance but inconsistent effects on liver histology.

HIV Lipodystrophy

It is characterized by fat redistribution and insulin resistance and affects a majority of human immunodeficiency virus (HIV) infected individuals who are treated with combination antiretroviral therapy.²² Metformin decreased weight, visceral fat, fasting insulin, and insulin levels during OGTT in HIV patients on HAART.²³

CAD and heart failure

Metformin had been contraindicated in patients with heart failure because of the potential increases in the risk of lactic acidosis resulting from severe tissue hypoperfusion.²⁴ Recent studies suggest that metformin may not be absolutely contraindicated and could be beneficial in such patients.²⁵⁻²⁷ Reduction of Atherothrombosis for Continued Health (REACH) Registry which included Type 2 Diabetic patients with established atherothrombosis showed metformin alone or in combination with sulfonylurea reduced the mortality and the morbidity when compared with sulfonylurea monotherapy.^{10,28-31}

Dysregulated autophagy has been described as a key mechanism for the development of diabetic cardiomyopathy and heart failure. Metformin promotes myocardial preconditioning, reduces cardiomyocytes apoptosis during ischemia, adaptation of cardiomyocytes metabolism during ischemia or the protection against the development of heart failure. Improves oxidative stress, preserve antioxidant function and restrain platelet activation.³²

Advanced age

Label information states that metformin treatment should not be initiated in patients aged more than 80 years unless their creatinine clearance is normal.

The logic behind the suggestion is that such individuals might have some degree of renal insufficiency and are thus more susceptible to developing lactic acidosis.

Metformin has been shown to improve metabolic control without causing lactic acidosis in elderly patients with multiple comorbidities, including explicit contraindications, and its use in patients with type 2 diabetes over the age of 70 with mild renal impairment did not produce a clinically relevant increase in plasma lactate.³³

An estimated GFR as low as 40 ml/min may be acceptable to initiate or to continue metformin.

Metformin and pregnancy

Metformin is categorized as US FDA class B drug with no evidence of fetal or animal teratogenicity but insufficient evidence of safety in human pregnancy. But meta-analyses of two observational studies, did not show an increase in congenital malformations or neonatal deaths.³⁴

The Metformin in Gestational Diabetes (MiG) trial compared metformin and insulin in GDM and found no significant secondary fetal outcomes between metformin and insulin.³⁵

A prospective observational study done for studying the prescription pattern of metformin for various indications. Total of 218 prescriptions (n=218) containing Metformin were randomly collected from different physicians and analysed.

METHODS

This was a prospective observational study conducted in a tertiary care teaching hospital after getting approval from the institutional ethical committee. A total of 218 prescriptions, of both outpatients and inpatients, containing Metformin were scrutinized after taking verbal consent from them. The study was conducted from June 2016 to Nov 2016. The prescriptions containing Metformin were collected from different specialities including Internal Medicine, Cardiology, Paediatrics, Obstetrics and Gynaecology, Endocrinology, Oncology and Psychiatry. Various parameters like patient’s demographic data such as patient’s age, sex, diseases to which it is prescribed were noted and the combination of the diagnosis with Metformin was checked to see if it is approved by current regulations. The gathered data is expressed in the percentile form. Using this data, the frequency and indications of Metformin use was examined.

RESULTS

Out of the 218 patients, 89 (40.82%) were male patients and 129 (59.17%) were females (Table 1).

Age of the patients was ranging between 10 years and above. Metformin was prescribed more to age group 31-40 yrs i.e., 78 (35.77%) and followed by 41 to 50 years of age i.e., 53 (24.31%). We received 47(21.55%)

prescription in the age group 21-30 yrs. 51-60 yrs 25 (11.46%), 61 yrs and above 10 (4.58%), least prescription 5 (2.29%) in age group of 10-20yrs (Table 2).

Table 1: Gender distribution.

Gender	No. of Patients (n=218)	Percentage (%)
Male	89	40.82
Female	129	59.17

Table 2: Distribution of total study population.

Age group (years)	No. of prescriptions (n=218)	% Of prescriptions
10- 20	5	2.29
21 -30	47	21.55
31 -40	78	35.77
41- 50	53	24.31
51 - 60	25	11.46
61 and above	10	4.58

The most frequent diagnosis for which metformin was used is Type 2 diabetes mellitus 113 (51.83%), followed by poly cystic ovarian disease (PCOD) 57 (26.14%). Metformin was also prescribed for adolescence type 1 diabetes mellitus 30 (13.76%), Gestational diabetes mellitus 10 (4.58%), obesity 5 (2.29%) and least prescription received were for prediabetic patients is 3 (1.37%). (Table 3).

Table 3: Common diagnosis.

Disease condition	No. of prescription	% of prescription
Prediabetic	3	1.37
Type 2 DM	113	51.83
Type 1 DM	30	13.76
Polycystic Ovarian disease (PCOD)	57	26.14
Obesity	5	2.29
Gestational Diabetes mellitus (GDM)	10	4.58

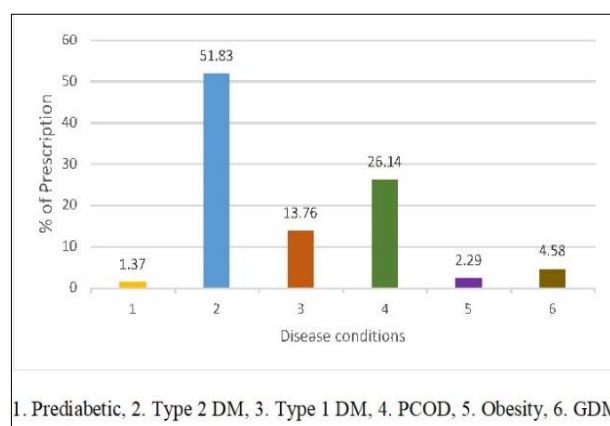


Figure 1: Various indications of metformin.

The various indications of metformin in this study are shown in Figure 1. Table 1 and 2 show the gender and age distribution of the patients having metformin in their prescription. Table 3 shows a summary of metformin prescribed for various conditions and their frequency of prescription.

DISCUSSION

Metformin has been used clinically in the 1950s and now being prescribed to millions of people worldwide. Many clinical trials have demonstrated that metformin, being mainstay in the treatment of Type 2 diabetes, also have numerous therapeutic potential in conditions like cardiovascular diseases, polycystic ovary disease, Type 1 diabetes, obesity and in prevention or treatment of cancer.^{6-8,14,16,19,25-27} The aim of the study was to analyse the proportion of off label prescription of metformin. The present study was carried out in 218 prescription that has metformin written on it and analysed based on age, gender and different indications. The prescriptions received in this study has more number of female patients (59.17%) compared to male patients (40.82%). The more number of prescription belongs to age group 31-40 yrs and most of these prescriptions were for type 2 DM and least in age group between 10-20yrs which comprises of adolescent Type 1 DM. Although Metformin is also prescribed for Cancer, we have not received any prescription during our study.

The results reiterate in the present study is that the bulk of the prescriptions were for use in Type 2 DM (51.8%), though there is convincing pre-clinical evidence of the potential pleiotropic benefits of metformin. However, in the present study we received a small number of prescriptions for off label conditions. These include Type 1 DM (13.76%), PCOD (26.14%), Obesity (2.29%) and GDM (4.58%). The possible reasons could be absence of recommendations in the guidelines and insufficient evidence for use. This study will enlighten the different mechanisms of metformin's action and its limited application. This is, to the best of our knowledge, the first study to examine prescribing patterns of metformin for various (off label) indications done in Telangana.

CONCLUSION

Metformin has come a long way from its humble beginning as a herbal medication. It had a subdued growth after its launch and the use picked up after its introduction in the American market. It is now the first line therapy in the management of Type 2 Diabetes. Now newer indications, beyond glycemic control, are being explored for this venerable and unique molecule. Only time will tell as to its use in other disease conditions. A suitable example would be PCOD in which the initial enthusiasm has waned and the use by majority of guidelines is for metabolic derangement rather than prevention of abortions or menstrual dysfunction. This article underscores the need for conducting larger outcome studies, to gather evidence

regarding the possible use of this drug in other disease conditions.

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