Review Article

METFORMIN: A REVIEW ON THERAPEUTIC ROLE IN DIABETES MELLITUS AND CARDIOVASCULAR DISORDER

K. J. Wadher[1]*, R. P. Kalsait[1], R. B. Kakde[2], M. J. Umekar[1]
[1]Smt. Kishoritai Bhoyar College of Pharmacy, New Kamptee, Nagpur 02, India.
[2] University Department of Pharmaceutical Sciences, Mahatma Jyotiba Fule Shaikshanik Parisar University Campus, Nagpur 33, India.
***Corresponding author's E-mail:** kamleshwadher@gmail.com

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ABSTRACT

Diabetes mellitus is a chronic condition prevalent worldwide. It is estimated that more than 246 million individuals have diabetes, with this number expected to increase to 366 million by the year 2030. The chronic hyperglycemia of diabetes is associated with long term damage to various organs, including the eyes, kidneys, nervous system, heart, and vasculature. India has a long history regarding the epidemiology of diabetes. In an effort to optimize glycemic control and also to reduce the burden of diabetic complications, several classes of oral hypoglycemic agents have been developed. Metformin has now been on the market for more than 50 years and has been established as the first-line agent of choice for the management of type 2 diabetes. In this way, metformin is anticipated to reduce insulin resistance, contribute to weight loss, and play a significant role in the improvement of cardiovascular outcomes.

Keywords: Metformin, Diabetes, Polycystic ovary syndrome, Hyperglycemia.

INTRODUCTION

During the last 20 years type 2 diabetes mellitus has become a major health issue reaching epidemic proportions.[1] It has recently been estimated that nearly 6% of the world's adult populations are affected by this condition.[2] As a result, patients have a considerably increased risk of vascular disease, which may affect macrovascular, i.e. cerebrovascular, coronary and peripheral arterial disease and microvascular disease, i.e. retinopathy, neuropathy and nephropathy.[3,4] Overall, these chronic vascular complications lead to increased morbidity and mortality.[5]

Diabetes mellitus is a chronic condition prevalent worldwide. It is estimated that more than 246 million individuals have diabetes, with this number expected to increase to 366 million by the year 2030.[6] The chronic hyperglycemia of diabetes is associated with long term damage to various organs, including the eyes, kidneys, nervous system, heart, and vasculature. In addition, it is among the leading causes of blindness and renal failure worldwide.[7, 8] It is the fourth leading cause of death by disease and every 10 seconds a person dies from diabetes-related causes in the world. Each year, over three million deaths worldwide are tied directly to diabetes.

Type 2 diabetes is characterized by both disorders of insulin activity as well as inadequate insulin production by the pancreatic beta cells,[9] and is the most common form of diabetes, comprising 90% to 95% of all diabetes cases.[10] It is a disorder that affects the way the body uses digested food for growth and energy. Normally, the food one eats is broken down into glucose, a form of sugar. The glucose then passes into the bloodstream, where it is used by the cells for growth and energy. For glucose to reach the cells, however, insulin must be present. Insulin is a hormone produced by the pancreas, a fist-sized gland behind the stomach. Most people with type 2 diabetes have two problems: insulin resistance — a condition in which muscle, liver, and fat cells do not use insulin properly and reduced insulin production by the pancreas. As a result, glucose builds up in the blood, overflows into the urine, and passes out of the body, never fulfilling its role as the body's main source of fuel.

India the diabetes capital of the world

India has a long history regarding the epidemiology of diabetes. Charaka Samhita, the ancient Indian medical treatise, describes this condition and suggests that being obese was a major risk factor.[11] Diabetes has emerged as a major healthcare problem in India having the highest number of diabetic patients in the world posing an enormous health problem in the country. According to the International Diabetes Federation, there were an estimated 40 million persons with diabetes in India in 2007 and this number is predicted to rise to almost 70 million people by 2025. It is estimated that every fifth person with diabetes will be an Indian. Due to these sheer numbers, the economic burden due to diabetes in India is amongst the highest in the world. The real burden of the disease is however due to its associated complications which lead to increased morbidity and mortality. The International Diabetes Federation estimates that the number of diabetic patients in India more than doubled from 19 million in 1995 to 40.9 million in 2007. It is projected to increase to 69.9 million by 2025. The World Health Organization estimates that mortality from diabetes and heart disease cost India about $210 billion every year and is expected to increase to $335 billion in the next ten years. These estimates are based on lost

productivity, resulting primarily from premature death thus calling India the diabetes capital of the world.

Diabetes is the main cause of kidney failure, limb amputation, and new-onset blindness in Indian adults. People with diabetes are more likely than people without diabetes to develop and die from diseases of the heart and blood vessels, called cardiovascular disease. Adults with diabetes have heart disease death rates about two to four times higher than adults without diabetes, and the risk for stroke is two to four times higher among people with diabetes.

Risk Factors for Diabetes in Indians

Type 2 diabetes mellitus epidemic in India is mainly because of sedentary lifestyle, lack of physical activity, obesity, stress and consumption of diets rich in fat, sugar and calories. Societal influences.[12] Various studies have shown that the high incidence of diabetes in India.

Table 1: The Risk Factors for Diabetes in Indians

FACTORS	DESCRIPTION
Age	Indians develop diabetes at a very young age, at least 10 to 15 years earlier than the western population. An early occurrence of diabetes gives ample time for development of the chronic complications of diabetes**.**
Genetics	The prevalence of diabetes increases with a family history of diabetes. The risk of a child developing diabetes with a parental history increases above 50 per cent
Central Obesity	The association of obesity with Type II Diabetes is well known. Even with an acceptable body weight range, weight gain could increase the risk of diabetes
Life style change	The availability of motorised transport combined with the plethora of television and internet programs has reduced the physical activity in all groups of populations is responsible for the development of diabetes
Insulin Resistance	Indians have been found to be more insulin resistant as compared to the other population. They have a higher level of insulin to achieve the same the blood glucose control. A cluster of factors consisting of abnormal fats, high blood pressure, obesity, and abnormal glucose levels known as metabolic syndrome is highly prevalent in Indians.
Urbanisation	Urbanisation is associated with increasing obesity, decreasing physical activity due to changes in lifestyle, diet and a change from manual work to less physical occupations.
Physical and mental Stress	The impact of stress both physical and mental along with lifestyle changes has a strong effect of increasing incidence of type II Diabetes

DIABETES MANAGEMENT

Insulin is a natural hormone produced in the pancreas, which enables cells to absorb glucose obtained from food and convert it into energy. In diabetes, the body either does not make enough insulin or does not respond properly to its own insulin, or both. Type II diabetes is characterized by cellular insulin resistance. The result is excess accumulation of glucose in the bloodstream as cells become resistant to the effects of insulin. As the type II diabetic condition progresses, many people gain weight and develop more fat cells.[13] Treating type II diabetes with insulin-enhancing therapy increases the risk of cardiovascular complications, induces weight gain, and fails to correct the underlying cause of the disease Diet, exercise, proper medication and monitoring are essential in the management of diabetes. Uncontrolled diabetes can lead to various complications and organ damage involving almost all parts of the body.

ANTI DIABETIC AGENTS

In an effort to optimize glycemic control and also to reduce the burden of diabetic complications, several classes of oral hypoglycemic agents have been developed.[14,15] An ideal anti-diabetic drug would enhance cellular insulin sensitivity, inhibit excess intestinal absorption of sugar, reduce excess liver production of glucose, promote weight loss and reduce cardiovascular risk factors.

oral hypoglycemic agents used in the management of type 2 diabetes mellitus.[16] Phenformin was the first biguanide to be marketed in the 1950's, while buformin and metformin soon followed.[17, 18] This review outlines the use of metformin. Not only is this drug the most widely prescribed antidiabetic agent in the management of type 2 diabetes, but it has also been recommended as the first line treatment of choice in patients without contraindications.

METFORMIN: PLACE IN THERAPY

Metformin has now been on the market for more than 50 years and has been established as the first-line agent of choice for the management of type 2 diabetes. This agent should be used alongside lifestyle modification at diagnosis of type 2 diabetes. In this way, metformin is anticipated to reduce insulin resistance, contribute to weight loss, and play a significant role in the improvement of cardiovascular outcomes.

A further advantage is that metformin can safely and efficaciously be combined with all other oral anti-diabetic agents.[19, 20] Such combinations enable an additive effect of metformin and the other agents, whether these act in an insulin-secretary or insulin-sensitizing mode. Similarly, metformin may be administered in conjunction with insulin. All in all, metformin is an excellent choice both in the specialized setting and in primary health care. Metformin works by increasing the number of muscle and adipocyte (fat cell) insulin receptors and the attraction for the receptor.

Table 2: Oral hypoglycemic class of drugs

CLASS	NAME	HALF LIFE	Excretion and safety
THIAZOLIDIONES	Pioglitazone	3-7 h	Avoid in CHF, liver disease.
	Rosiglitazone	5-6.2 h	
BIAGUANIDES	Metformin	4.5 -6 h	Avoid use with renal insufficiency. Caution in liver disease.
	Phenformin		
SULFONYLUREAS	Glimpride	5-9h	Metabolites excreted by the kidney. Avoid in severe renal failure.
	Glipizide	2-4h	
	Glyburide	5-16h	
MEGLINIDES	Repaglinide	1h	Hepatic clearance Safe in advanced renal insufficiency.
	Nateglinide	1.5h	
ALPHA GLUCOSIDASE INHIBITOR	Acarbose	2h	Limited absorption Metabolites safe in mild renal insufficiency Reduce dose with transaminase elevation.
	Miglitol	2h	

PHARMACOKINETIC PROFILE & METABOLISM

Like phenformin, metformin is a derivative of guanidine, the active ingredient in goat's rue that had empirically been used as a treatment for diabetes in the middle ages. In the digestive tract, it is absorbed by the small intestine. [21] Its oral bioavailability ranges between 40% and 60%, and gastrointestinal absorption is virtually complete after 6 hours of oral administration.[22] Following absorption, metformin is rapidly distributed, without binding to plasma proteins. In contrast to phenformin, metformin does not undergo liver metabolism and is excreted unchanged by the kidneys.[22, 23] Mean plasma half-life following oral administration ranges between 4 and 8.7 hours.[24] Plasma half-life is significantly prolonged in patients with renal impairment and shows a close relationship to creatinine clearance. Metformin has no clinically relevant interactions with other drugs, because it is not metabolized and does not inhibit the metabolism of other drugs.

MECHANISM OF ACTION

Metformin, a biquanide, reduces hyperinsulinaemia and improves hepatic insulin resistance.[26] Its major site of action appears to be in the mitochondria, and it has been shown to stimulate pyruvate-kinase, fatty acid beta-oxidation, anaerobic respiration (i.e. lactate production) as well as suppress the expression of lipogenic enzymes.

The main mechanisms include anorexiogenesis, reduction of intestinal carbohydrate absorption, inhibition of hepatic gluconeogenesis, as well as increased glucose uptake by peripheral tissues. Reduced appetite is a useful action of metformin, contributing to weight loss, which is beneficial, given that the vast majority of patients are obese. Diminished intestinal carbohydrate absorption plays a role in reducing post-prandial hyperglycemia, which is now regarded as a cardinal factor in the induction of oxidative stress leading to cardiovascular complications.[19, 25]

Inhibition of hepatic gluconeogenesis and increased peripheral glucose uptake by metformin are major effects that offset insulin resistance, and their molecular basis is being increasingly studied. At the hepatocellular level, metformin acts on the mitochondria by inhibiting Krebs cycle and/or oxidative phosphorylation by activation of AMP kinase.

Table3: Mechanism of action of metformin hydrochloride

Mechanisms of action[20]
Reduction of appetite
Diminished intestinal carbohydrate absorption leading to reduced post-prandial hyperglycemia
Inhibition of hepatic gluconeogenesis: inhibition of Krebs cycle and/or oxidative phosphorylation by activation of AMP kinase
Enhancement of insulin-stimulated glucose transport in skeletal muscle: increased recruitment and activity of GLUT4
glucose transporters and enhanced non-oxidative glucose disposal into skeletal muscle
Increased free fatty acid esterification and inhibition of lipolysis in adipose tissue
Protection of β-cells from glucose toxicity and lipotoxicity: protection of β-cell secretory capacity
Increased secretion of glucagon-like peptide-1 (GLP-1)

SAFETY

Metformin is considered one of the safest oral hypoglycemic agents[20, 27] It reduces insulin resistance, but does not promote insulin secretion from β-cells, and thus it is not associated with increased risk of hypoglycemia. Minor untoward effects include nausea and diarrhea. Such side effects may be minimized by using the sustained-release metformin formulation, which has been shown to be much better tolerated.[27, 28] The major untoward effect is lactic acidosis.[29, 30] It virtually only occurs in patients with obvious contra-indications to metformin use.[31] Contraindications are related to conditions predisposing to tissue hypoxia (congestive heart failure, chronic obstructive pulmonary disease, severe infection or gangrene), to liver disease, as well as to intrinsic or functional reduction of renal function (chronic renal failure, congestive heart failure, advanced age).[32, 33] This is explicable on the basis that metformin is cleared by the kidneys and that elevated serum lactic acid concentration may result either from severe tissue

hypoxia or from reduced hepatic clearance owing to liver. metformin may be safely administered with almost no lactic acidosis.[34, 35]

The cardiovascular system

Patients with type II diabetes often present with a cluster of cardiovascular risk factors like visceral obesity, hypertension, high triglyceride and low high density lipoprotein (HDL) cholesterol levels, and hypofibrinolysis, all of which form insulin resistance and potentially contribute to increased cardiovascular risk. In the United Kingdom Prospective Diabetes Study, metformin was the only medication that reduced diabetes related deaths, heart attacks and strokes.[36, 37] The individuals with visceral obesity treated with metformin showed greater weight loss, a greater decrease in fasting insulin levels and a smaller increase in low density lipoprotein (LDL) cholesterol concentrations than those who received placebo. A decrease in plasminogen activator inhibitor was most associated with the body weight loss in subjects.[38] In the trial, the effects of metformin were most notable on the level of endothelial (artery lining) damage that showed a decrease. The microvascular complications of retinopathy, nephropathy and neuropathy improve due to metformin's ability to decrease damage to arterial lining. The potentially preventive effects of metformin on type II diabetes and evolving cardiovascular complications include a decrease in total cholesterol and low density cholesterol (LDL), free fatty acids, tissue plasminogen activator antigen and insulin levels when patients present with symptoms of hypertension, dyslipidemia, visceral obesity or hyperglycemia

Cancer and cellular immunity

Metformin has been found to suppress the growth of some tumors and enhance the activity of anti-cancer drugs. By giving the immune system a boost, metformin can improve cellular immunity. It has also been found to reduce the incidence of chemically induced cancer in rats.[5, 7]

Contraindications and side effects

Metformin is not recommended for people who have a history of kidney or liver disease, or a history of congestive heart failure. People with a history of alcohol abuse should also avoid taking the drug, as serious lactic acidosis can develop in these individuals. Long term use of metformin may cause malabsorption of vitamin B12.[36, 37] Because of the depletion of B12, supplementation is recommended. When a person begins to take metformin, they may experience some nausea and vomiting, stomach pain, bloating and diarrhea. The latter usually disappear once the person becomes accustomed to the drug.[36]

Polycystic ovary syndrome

Several studies have recorded the use of Metformin in women with PCOS. Metformin is effective in reducing testosterone levels and in making the menstrual cycle more regular. The safety and efficacy of the drug were consistently seen in women with the polycystic ovary syndrome (PCOS).[39]

Obesity

Metformin has been shown to reduce weight gain, hyperinsulinemia, and hyperglycemia in adults with type 2 diabete[40] and to reduce progression from impaired glucose tolerance to diabetes in those without diabetes.[41] These benefits have led to an increase in the use of metformin in obese children with hyperinsulinemia. Metformin appears to be moderately efficacious in reducing BMI and insulin resistance in hyperinsulinemic obese children and adolescents in the short term. Larger, longerterm studies in different populations are needed to establish its role in the treatment of overweight children.[42]

Metformin, the biguanide most widely used for the treatment of type 2 diabetes mellitus[43] may be useful in aiding weight loss. In diabetic patients, it suppresses endogenous glucose production and may also act as an insulin sensitizer. It also helps diabetic patients lose weight or at least keep their weight stable.[44] In addition to its use in treatment of diabetes, metformin has also become commonly prescribed for patients with polycystic ovary syndrome (PCOS), and its use has resulted in weight reduction in those patients as well.[45]

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