

REVIEW ARTICLE ON METFORMIN: THE FIRST LINE THERAPY IN DIABETES

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ABSTRACT

Metformin is believed to be the most widely used medication for diabetes which is taken by mouth. Metformin is primarily used for type 2 diabetes, but is increasingly being used in polycystic ovary syndrome.

KEYWORDS : Diabetes, Type of diabetes, Metformin

1. INTRODUCTION OF DIABETES

Diabetes mellitus (DM), commonly referred to as **diabetes**, is a group of metabolic diseases in which there are high blood sugar levels over a prolonged period.^[1] Symptoms of high blood sugar include frequent urination, increased thirst, and increased hunger. If left untreated, diabetes can cause many complications.^[2] Acute complications can include diabetic ketoacidosis, nonketotic hyperosmolar coma, or death.^[3] Serious long-term complications include heart disease, stroke, chronic kidney failure, foot ulcers, and damage to the eyes.^[4]

Diabetes is due to either the pancreas not producing enough insulin or the cells of the body not responding properly to the insulin produced.^[5] There are three main types of diabetes mellitus:

- Type 1 DM results from the pancreas's failure to produce enough insulin. This form was previously referred to as "insulin-dependent diabetes mellitus" (IDDM) or "juvenile diabetes". The cause is unknown.^[4]
- Type 2 DM begins with insulin resistance, a condition in which cells fail to respond to insulin properly.^[4] As the disease progresses a lack of insulin may also develop.^[5] This form was previously referred to as "non insulin-dependent diabetes mellitus" (NIDDM) or "adult-onset diabetes". The primary cause is excessive body weight and not enough exercise.^[4]
- Gestational diabetes is the third main form and occurs when pregnant women without a previous history of diabetes develop high blood-sugar levels.^[3]

Prevention and treatment involve maintaining a healthy diet, regular physical exercise, a normal body weight, and avoiding use of tobacco. Control of blood pressure and maintaining proper foot care are important for people with the disease. Type 1 DM must be managed with insulin injections.^[2] Type 2 DM may be treated with medications with or without insulin.^[6] Insulin and some oral medications can cause low blood sugar.^[7] Weight loss surgery in those with obesity is sometimes an effective measure in those with type 2 DM.^[8] Gestational diabetes usually resolves after the birth of the baby.^[9]

As of 2015, an estimated 415 million people had diabetes worldwide,^[12] with type 2 DM making up about 90% of the cases.^{[11][12]} This represents 8.3% of the adult population,^[12] with equal rates in both women and men.^[13] As of 2014, trends suggested the rate would continue to rise.^[14] Diabetes at least doubles a person's risk of early death.^[2] From 2012 to 2015, approximately 1.5 to 5.0 million deaths each year resulted from diabetes.^{[6][10]} The global economic cost of diabetes in 2014 was estimated to be US\$612 billion.^[15] In the United States, diabetes cost \$245 billion in 2012.^[16]



Figure 1: Overview of the most significant symptoms of diabetes

The classic symptoms of untreated diabetes are weight loss, polyuria (increased urination), polydipsia (increased thirst), and polyphagia (increased hunger).^[17] Symptoms may develop rapidly (weeks or months) in type 1 DM, while they usually develop much more slowly and may be subtle or absent in type 2 DM.

Several other signs and symptoms can mark the onset of diabetes although they are not specific to the disease. In addition to the known ones above, they include blurry vision, headache, fatigue, slow healing of cuts, and itchy skin. Prolonged high blood glucose can cause glucose absorption in the lens of the eye, which leads to changes in its shape, resulting in vision changes. A number of skin rashes that can occur in diabetes are collectively known as diabetic dermadromes.

The following is a comprehensive list of other causes of diabetes.^[18]

- Genetic defects of β -cell function
- Maturity onset diabetes of the young
- Mitochondrial DNA mutations
- Genetic defects in insulin processing or insulin action
- Defects in proinsulin conversion
- Insulin gene mutations
- Insulin receptor mutations
- Exocrine pancreatic defects
- Chronic pancreatitis
- Pancreatectomy
- Pancreatic neoplasia
- Cystic fibrosis

- Hemochromatosis
- Fibrocalculous pancreatopathy
- Endocrinopathies
- Growth hormone excess (acromegaly)
- Cushing syndrome
- Hyperthyroidism
- Pheochromocytoma
- Glucagonoma
- Infections
- Cytomegalovirus infection
- Coxsackievirus B
- Drugs
- Glucocorticoids
- Thyroid hormone
- β -adrenergic agonists
- Statins^[47]

WHO diabetes diagnostic criteria^{[19][20]}

Condition	2 hour glucose	Fasting glucose	HbA1c	
Unit	mmol/l(mg/dl)	mmol/l(mg/dl)	mmol/mol	DCCT %
Normal	<7.8 (<140)	<6.1 (<110)	<42	<6.0
Impaired fasting glycaemia	<7.8 (<140)	$\geq 6.1 (\geq 110)$ & <7.0 (<126)	42-46	6.0-6.4
Impaired glucose tolerance	$\geq 7.8 (\geq 140)$	<7.0 (<126)	42-46	6.0-6.4
Diabetes mellitus	$\geq 11.1 (\geq 200)$	$\geq 7.0 (\geq 126)$	≥ 48	≥ 6.5

Diabetes mellitus is characterized by recurrent or persistent high blood sugar, and is diagnosed by demonstrating any one of the following:^[44]

- Fasting plasma glucose level ≥ 7.0 mmol/l (126 mg/dl)
- Plasma glucose ≥ 11.1 mmol/l (200 mg/dl) two hours after a 75 g oral glucose load as in a glucose tolerance test
- Symptoms of high blood sugar and casual plasma glucose ≥ 11.1 mmol/l (200 mg/dl)
- Glycated hemoglobin (HbA1C) ≥ 48 mmol/mol (≥ 6.5 DCCT %).^[22]

Introduction of metformin

• History

Metformin, marketed under the tradename **Glucophage** among others, is the first-line medication for the treatment of type 2 diabetes.^[50,51] Metformin is generally well tolerated.^[52] It has a low risk of developing low blood sugar.^[50] Metformin is in the biguanide class. It works by decreasing glucose production by the liver and increasing the insulin sensitivity of body tissues.

Metformin was discovered in 1922.^[53] The American Diabetes Association [recommends metformin as a first-line agent to treat type 2 diabetes].^[54,55]

• Mechanism of Action:

The exact mechanism of metformin is incompletely understood. The drug's main effect is to decrease hepatic glucose production.^[56] Metformin also increases insulin sensitivity, which increases peripheral glucose uptake.^[57] Metformin decreases high blood sugar primarily by suppressing glucose production by the liver (hepatic gluconeogenesis).^[56] The "average" person with type 2 diabetes has three times the normal rate of gluconeogenesis; metformin treatment reduces this by over one-third.^[58] The molecular mechanism of metformin is incompletely understood: inhibition of the mitochondrial respiratory chain (complex I), activation of AMP-activated protein kinase (AMPK), inhibition of glucagon-induced elevation of cyclic adenosine monophosphate (cAMP) with reduced activation of protein kinase A (PKA), inhibition of mitochondrial glycerophosphate dehydrogenase, and an effect on gut microbiota have been proposed as potential mechanisms.^[59,60,61]

Activation of AMPK, an enzyme that plays an important role in insulin signaling, whole body energy balance, and the metabolism of glucose and fats was required for metformin's inhibitory effect on the production of glucose by liver cells.^[62]

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