



**International Journal of Research
in
Pharmaceutical and Nano Sciences**
Journal homepage: www.ijrpns.com



A REVIEW ARTICLE - DIABETES MELLITUS AND ANTIDIABETIC DRUGS

G. Lakshmi Devi*¹

¹*Department of Pharmaceutics, MLR Institute of Pharmacy, Hyderabad, Telangana, India.

ABSTRACT

Diabetes (otherwise known as diabetes mellitus, DM) is described as a metabolic disorder in which the body cannot properly store and use the energy found in food. Diabetes is a condition that affects the body's ability to use glucose (a type of sugar) as fuel. Glucose is a form of carbohydrate that comes from foods such as breads, cereals, pasta, rice, potatoes, fruits and some vegetables. Glucose is also synthesized in the liver and is carried in the blood to the rest of the body to fuel cellular processes. Generally insulin is required for the generation of glucose in to cells. Insulin is secreted by pancreas and it regulates production of glucose. Human body require 120-180 mg/dl of glucose to regulate body functions. While during the selection of anti-diabetic drugs mainly focus on range of glucose levels at present, age, body weight and mental condition of the person as well as some other factors. Type 1 Diabetes mellitus is a disorder caused by the insufficient generation of insulin. Which must be injected or inhaled. Diabetes mellitus type 2 is a disease of insulin resistance by cells. Treatments include agents which increase the amount of insulin secreted by the pancreas, agents which increase the sensitivity of target organs to insulin, and agents which decrease the rate at which glucose is absorbed from the gastrointestinal tract. Persistently elevated blood glucose may lead to a diagnosis of prediabetes or diabetes. Prediabetes describes the condition of person and his mental status.

KEYWORDS

Diabetes mellitus types, Blood glucose and Ant diabetic drugs.

Author for Correspondence:

Lakshmi Devi G,
Department of Pharmaceutics,
MLR Institute of Pharmacy,
Hyderabad, Telangana, India.

Email: lakshmi13bph@gmail.com

INTRODUCTION

Diabetes (otherwise known as diabetes mellitus, DM) is described as a metabolic disorder in which the body cannot properly store and use the energy found in food.

More specifically, diabetes is a condition that affects the body's ability to use glucose (a type of sugar) as fuel. Glucose is a form of carbohydrate that comes from foods such as breads, cereals,

pasta, rice, potatoes, fruits and some vegetables. Glucose is also synthesized in the liver and is carried in the blood to the rest of the body to fuel cellular processes.

To use glucose as fuel, insulin is required to get the glucose into cells. Insulin is a hormone (a type of chemical messenger) made by specialized cells in the pancreas. Insulin regulates blood glucose by stimulating the removal of glucose from the blood and its uptake into muscle, liver and fat cells where it can be stored for energy.

Sometimes the body does not make enough insulin or the cells do not respond properly to insulin. Blood glucose levels can then become elevated while the cells are deprived of fuel. When blood glucose levels get too high (hyperglycemia) this can cause damage to the tiny blood vessels in the eyes, kidneys, heart and nervous system, which is why diabetes is associated with an increased risk of cardiovascular disease, kidney disease, loss of vision and neurological conditions.

In general, people with diabetes either have a total lack of insulin (type 1 diabetes) or they have too little insulin or cannot use insulin effectively (type 2 diabetes).

Persistently elevated blood glucose may lead to a diagnosis of prediabetes or diabetes. Prediabetes describes the condition where blood glucose levels are higher than normal but not high enough for a diagnosis of diabetes (Table No.1).

Fast facts on diabetes

- 29.1 million children and adults in the United States - 9.3% of the population - have diabetes (21 million diagnosed, and an estimated 8.1 million undiagnosed)¹².
- 1.7 million new cases of diabetes were diagnosed in people aged 20 years and older in 2012.
- 15.5 million, or 13.6% of all men aged 20 years or older have diabetes.
- 13.4 million, or 11.2% of all women aged 20 years or older have diabetes.
- 37% of Americans aged 20 years or older have prediabetes.

- Diabetes contributed to 231,404 deaths in the US in 2007².
- \$245 billion: Total costs of diagnosed diabetes in the United States in 2012².
- Only 5% of people with diabetes have type 1 diabetes, which is an autoimmune disease involving caused by genetic, environmental, and other factors².
- Type 2 diabetes accounts for 95% of diabetes cases and is usually associated with older age, obesity and physical inactivity, family history of type 2 diabetes, or a personal history of gestational diabetes².
- There is no known way to prevent diabetes type 1. Effective treatment requires the use of replacement insulin.
- Type 2 diabetes can be prevented through healthy food choices, physical activity, and weight management. It can also be managed through lifestyle and diet, although insulin or oral medication may be necessary for some people.
- Type 1 and type 2 diabetes were differentiated in terms of causes, symptoms, characteristics, management, incidence. How we can differentiate that two diabetes means by comparing the type -1 and type-2 diabetes (Table No.2). Comparisons will be made across the various sections in this page.
- For the majority of healthy individuals, normal blood glucose level in humans is about 4 mmol/L or 72 mg/dL.

What causes diabetes type 1 and type 2?

Type 1 diabetes occurs when the body's immune system erroneously attacks the pancreatic beta cells, which produce insulin, destroying these cells and reducing the body's ability to produce sufficient insulin to regulate blood glucose levels.

Type 2 diabetes is a condition where the body does not produce sufficient insulin and the body's cells become resistant to the effects of insulin. This results in the build-up of glucose in the blood while cells are starved of energy. This condition is often a

result of persistently high glucose levels as well as obesity and overweight, lifestyle and dietary factors, medications and other issues.

Insulin use not only prevents hyperglycemic emergencies, but is a safeguard that helps to prevent long-term complications of diabetes by correcting fasting and postprandial (after meal) hyperglycemia. Both of the major types of diabetes typically include different stages of disease, beginning with a state where supplemental insulin is not required to a state that does require exogenous insulin for blood glucose control and survival.

Antidiabetic Drugs

Insulin

The hormone insulin is endogenously released from the β cells of pancreas. Patients with type 1 diabetes mellitus have an absolute deficiency of insulin and patients with type-2 diabetes mellitus may also have decreased production of endogenous insulin. Insulin is required for all type-1 diabetic patients as a lifelong treatment. Insulin is commonly used in type-2 diabetic patients as either adjunct therapy to oral antidiabetic agents or as monotherapy as a disease progresses. Various substitutions on insulin molecule and other modifications led to multiple types of insulin. These are characterized and administered based on their pharmacodynamic and pharmacokinetic characteristics such as onset, peak, and duration of action. Most significantly they are classified as rapid-acting, short-acting, intermediate-acting or long-acting types of insulin.

Mechanism of action for drug class

Insulin lowers blood glucose by peripheral glucose uptake, especially in skeletal muscle fat and by inhibiting hepatic glucose production.

Usage for the drug class

Type -1 diabetes mellitus, Type -2 diabetes mellitus, hyperkalemia, DKA/diabetic coma.

Dosing for drug class

Initial dose: 0.5-1 unit/kg per day sub-Q.

Maintenance dose

Maintenance doses to achieve premeal and bedtime glucose level of 90-120 mg/dl.

Renal dosage adjustment

CrCl 10-50 ml/min: administer 75% of normal dose
CrCl < 10 ml/min: administer 25-50% of normal dose.

Adverse reaction

Most common hypoglycemia, weight gain.

Rare/severe/Important

Severe hypoglycemia, edema, lipoatrophy or lipohypertrophy at site of injection.

Drug interactions of Insulin (Increase Hypoglycemic Effect)

Alcohol, Fluoxetine, Sulphonamides, Anabolic steroids, β blocker, Clonidine.

Contraindications for the drug class

Use during severe hypoglycemia. Allergy or sensitivity to any ingredient of the product.

Types of Insulin Insulin Glulisine Brand Name

Apidra. Generic Name

Insulin Glulisine (rapid acting insulin).

Dosage Forms: Injection 100 units/ml.

Dosing: Administer Sub-Q 15 min before or immediately after starting a meal.

Insulin Lispro

Brand Name

Humalog

Generic Name

Insulin lispro (rapid acting insulin).

Dosage Forms

Injection 100 units/ml.

Dosing

Administer Sub-Q 15 min before or immediately after starting a meal.

Insulin NPH

Brand Name

Humuline N, Novolin N

Generic Name

Insulin NPH (intermediate acting insulin).

Dosage Forms

Injection, Suspensions 100 units/ml.

Dosing

PH should mix only with regular insulin. Draw regular insulin into the syringe first; then add NPH insulin into the syringe.

Insulin regular

Brand Name

Humuline R, Novolin R.

Generic Name

Insulin regular (short acting insulin).

Dosage Forms

Injection 100 units/ml.

Dosing

Administer Sub-Q 30 min before a meal.

Insulin Glargine

Brand Name: Lantus

Generic Name: Insulin Glargine

Dosage Forms Injection 100 units/ml.

Dosing

When changing to Insulin Glargine from once-daily NPH, the initial dose of insulin glargine should be the same. When changing to Insulin Glargine from twice-daily NPH, the initial dose of insulin glargine should be reduced by 20% 7 adjusted according to patient response.

Administer once daily

Insulin Detemir

Brand Name

Levemir

Generic Name

Insulin Detemir (long acting insulin)

Dosage Forms: Injection 100 units/ml.

Dosing

- Indicated for once or twice daily dosing
- Once daily is dosed Sub-Q with the evening meal or bed time.
- Twice daily dosed every 12 hours.

Insulin Aspart

Brand Name

Novolog

Generic Name

Insulin aspart (rapid acting insulin).

Dosage Forms

Injection 100 units/ml.

Dosing

Administer Sub-Q 15 min before or immediately after starting a meal.

70% NPH and 30% Regular Insulin Mixture

Brand Name

Humuline 70/30, Novolin 70/30

Generic Name

70% NPH and 30% Regular Insulin Mixture

Dosage Forms

Injection, Suspensions 100 units/ml.

50% NPH and 50% Regular Insulin Mixture

Brand Name

Humuline 50/50

Generic Name

50% NPH and 50% Regular Insulin Mixture

Dosage Forms

Injection, Suspensions 100 units/ml.

75% Intermediate acting Lispro Suspension and 25% Rapid acting Lispro Solution

Brand Name

Humalog Mix 75/25

Generic Name

75% Intermediate acting Lispro Suspension and 25% Rapid acting Lispro Solution.

Dosage Forms

Injection 100 units /ml.

65% Intermediate Acting Insulin Aspart Suspension and 29% Rapid Acting Aspart Solution

Brand Name

Novolog Mix 70/30.

Generic Name

70% Intermediate Acting Insulin Aspart Suspension and 30% Rapid Acting Aspart Solution.

Dosage Forms

Injection 100 units/ml.

Oral hypoglycemic agents

Biguanides

The Biguanides metformin is the drug of choice as initial therapy for a newly diagnosed patient with type 2 diabetes as an adjunct to diet and exercise.

Mechanism of action for drug class

Improves glucose tolerance by lowering both basal and postprandial plasma glucose. Decreases hepatic glucose production, decreases intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.

Metformin

Brand Names

Fortamet, Glucophage, Glucophage XR, Glumetza, Riomet.

Generic Names

Metformin, Metformin extended release.

Dosage Forms

Tablets, Extended release tablets, oral solution.

Dosing

Initial dose

500 mg twice daily with morning and evening meals, 850 mg once daily with meal, 500 mg extended release once daily with meal.

Maintenance dose

2000-2550 mg daily in divided doses or 2000 mg extended release once daily.

Renal dosage adjustment

Not recommended in patients with renal dysfunction (see contraindication below).

Adverse reaction

Most Common

Diarrhea, vomiting, dyspepsia, flatulence, metallic taste, weight loss.

Adverse reaction: Rare/Sever/Important

Lactic acidosis, megaloblastic anemia.

Contraindications

Renal disease, heart failure requiring pharmacologic therapy, acute or chronic metabolic acidosis, active liver disease.

DI-PEPTIDYL PEPTIDASE-4 INHIBITOR

Sitagliptin is the first dipeptidyl peptidase-4 (DPP-4) inhibitor available. It inhibits the breakdown of active GLP-1 through the inhibition of the enzyme DPP-4. Active GLP-1 is released from α cells of pancreas in response to food intake. It regulates blood glucose by increasing secretion of insulin from pancreas.

Mechanism of action for drug class

Inhibition of DPP-4 enhances the activity of active GLP-1, thus increasing glucose-dependent insulin secretion and decreasing level of circulating glucagon and hepatic glucose production⁶.

Members of drug class

Sitagliptin Brand Name

Januvia

Generic Name

Sitagliptin

Dosage Forms Tablets

Usage

Type 2 diabetes mellitus.

Dosing

100 mg daily once with or without food.

Renal dosage adjustment

50 mg once daily: $\text{CrCl} \geq 30$ to < 50 ml/minute. 25 mg once daily: $\text{CrCl} < 30$ ml/minute.

Adverse reaction

Most Common Nasopharyngitis, Nausea, diarrhea, vomiting, hypoglycemia, weight loss.

Adverse reaction

Rare/sever/Important

Acute pancreatitis, rash (Steven-Johnson Syndrome).

Major Drug Interactions

Sitagliptin effects on other drugs. Digoxin: Increased levels.

Sulfonylureas

The sulfonylureas are used as adjuncts to diet and exercise in patient with type-2 diabetes mellitus. Although periodically used as monotherapy, sulfonylureas are more commonly used in combination with other oral antidiabetic agents in patient who do not reach glycemic goals, sometimes in the same formulation. General dosing guidelines are to start with low dose and titrate according to patient response while monitoring signs and symptoms of hypoglycemia, which is common adverse effect. Use caution in patient with renal and hepatic impairment. HbA1c reductions between 1% and 2%.

Mechanism of action for drug class

Lowers blood glucose level by stimulating insulin release from β cells of pancreatic islets.

Glimepiride

Dosage Form

Tablets

Dosing Initial dose

1-2 mg once daily at breakfast.

Maintenance dose

1 -8 mg once daily.

Glipizide

Brand Name

Glucotrol, Glucotrol XL.

Generic Name

Glipizide, Glipizide extended –release.

Dosage Form

Tablets, extended – release tablets.

Dosing

Initial dose

Glucotrol: 2.5-5 mg once daily 30 minutes before breakfast. Glucotrol XL: 5 mg extended- release once daily with breakfast.

Maintenance dose

Glucotrol: 10-40 mg (>15 mg/day should be divided). Glucotrol XL: 5-20 mg extended- release once daily.

Thiazodinediones

The thiazodinediones, pioglitazone and rosiglitazone decrease insulin resistance by enhancing insulin -receptor sensitivity. They are used as adjuncts to diet or exercise in patients with type-2 diabetes mellitus. Although periodically used as monotherapy, thiazodinediones are more frequently used in combination with other oral antidiabetic agents and/or insulin in patients who do not reach glycemic goals. Recent clinical data suggest that patients taking thiazodinediones may be at increased risk of myocardial infarction and death, and so they should be used with caution in patients with history of previous cardiac disease. They are not recommended in patients with NYHA class III and IV heart failure A structurally similar thiazodinedione, troglitazone, was removed from the market due to liver failure and death.

It is recommended to avoid used in patients with hepatic dysfunction. HbA1c reduction is between 1% - 1.5%.

Mechanism of action for drug class

Increase insulin sensitivity by affecting the peroxisome proliferator activated receptor γ (PPAR γ) acting as agonist to these receptors, they decreases insulin resistance in adipose tissue, skeletal muscle and the liver⁴⁻⁶.

Usage for the drug class

Type -2 diabetes mellitus.

Adverse reaction

Most Common

Weight gain. Edema, hypoglycemia (when used with insulin or other oral antidiabetic drugs that may cause hypoglycemia).

Adverse reaction: Rare/sever/Important

Hepatic failure, heart failure, anemia, ovulation in an ovulatory, premenopausal woman, bone loss.

Members of the drug class

In this section: Pioglitazone, rosiglitazone.

Table No.1: Target glucose levels

S.No	Target glucose levels by type	Glucose levels before meals	Glucose levels 2 hours after meals
1	Non-diabetic	4.0 to 5.9 mmol/L	Under 7.8 mmol/L
2	Diabetes type 2	4 to 7 mmol/L	Under 8.5 mmol/L
3	Diabetes type 1	4 to 7 mmol/L	Under 9 mmol/L
4	Children with diabetes type 1	4 to 8 mmol/L	Under 10 mmol/L

Table No.2: Difference between Diabetes type-1 and 2

S.No		Diabetes type 1 ⁶	Diabetes type 2 ⁶
1	Cause	Beta cells in pancreas are attacked by the body's own immune system, therefore reducing insulin production, leading to elevated blood glucose. Insulin is not produced or is produced in insufficient amounts.	Persistently high intakes of dietary sugars leads to excess demands on insulin production, which leads to insulin resistance over time. Receptor cells that have become less sensitive (resistant) to insulin are unable to remove glucose from the blood, leading to higher blood glucose and greater demands on insulin production.
2	Genetic basis	Possibly. In most cases of type 1 diabetes, the patient would need to inherit risk factors from both parents.	Type 2 diabetes has a stronger link to family history and lineage than type 1.
3	Bodily effects	Thought to be triggered by autoimmune destruction of the beta cells. Autoimmune attack may occur following a viral infection such as mumps, rubella cytomegalovirus.	Appears to be related to aging, inactive lifestyle, diet, genetic influence and obesity.
4	Climate	One trigger might be related to cold weather. Type 1 diabetes develops more often in winter than summer and is more common in places with cold climates.	Type 2 diabetes is more common in people with low levels of vitamin D, which is synthesized from sunlight. Vitamin D supports immune function and insulin sensitivity, meaning that those living at a more northerly latitude may face a higher risk of diabetes. ¹³
5	Diet	Early diet may also play a role. Type 1 diabetes is less common in people who were breastfed and in those who first ate solid foods at later ages.	Obesity tends to run in families, and families tend to have similar eating and exercise habits. Diets high in simple sugars and low in fibre and vital nutrients are more likely to lead to diabetes.

CONCLUSION

Diabetes is a condition that affects the body's ability to use glucose (a type of sugar) as fuel. Glucose is a form of carbohydrate that comes from foods such as breads, cereals, pasta, rice, potatoes, fruits and some vegetables. Glucose is also synthesized in the liver and is carried in the blood to the rest of the body to fuel cellular processes.

Type 1 diabetes (formerly called insulin-dependent diabetes), accounts for 25 to 50 out of 100 people who have diabetes. Type 1 diabetes collapse the body's immune system and it will affect on cell functioning to release insulin, simultaneously it will reduce the production of insulin from the body. For

producing energy body require insulin if there is no production of insulin means it will affect on energy production. Type 2 diabetes (non-insulin-dependent diabetes) can develop at any age. In present generation based on their lifestyle, food habits and mental stress leads to Type 2 diabetes. In type 2 diabetes, the body isn't able to use insulin the right way. This is called insulin resistance. As type 2 diabetes gets worse, the pancreas may make less and less insulin. This is called insulin deficiency. In this mainly encountered on the factors which causes diabetes, differences between type 1 and type 2 and their treatment with the help of antidiabetic drugs.

ACKNOWLEDGEMENT

The author wish to express their sincere gratitude to Department of Pharmaceutics, MLR Institute of Pharmacy, Hyderabad, Telangana, India for providing necessary facilities to carry out this review work.

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

REFERENCES

1. WHO Expert Committee on Diabetes Mellitus. *Second Report, Geneva: WHO, Technical Report Series*, 646, 1980, 1-80.
2. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, *Diabetes Care*, 20(7), 1997, 1183-1197.
3. National Diabetes Data Group. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance, *Diabetes*, 28(12), 1979, 1039-1057.
4. Foster D W. Diabetes Mellitus, In Harrison's Principles of Internal Medicine, (Isselbacher K J, Braunwald E, Wilson J D, Martin J B, Fauci A S and Kasper D L, eds) McGraw-Hill, Inc (*Health Professions Division*), 14th Edition, 1998, 2060-2080.
5. Karam J H. Pancreatic Hormones and Antidiabetic Drugs, in Basic and Clinical Pharmacology, (*Katzung, B G, ed*) Appleton-Lange, 1998, 684-703.
6. Cheng A Y and Fantus I G. Oral antihyperglycemic therapy for type 2 diabetes mellitus, *CMAJ*, 172(2), 2005, 213-226.

Please cite this article in press as: Lakshmi Devi G. A review article - diabetes mellitus and antidiabetic drugs, *International Journal of Research in Pharmaceutical and Nano Sciences*, 7(3), 2018, 85-92.