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DIFFERENT TYPES OF ANTI-DIABETIC DRUG EFFECT ON PATIENT OF-TYPE 2 DIABETES MELLITUS

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ABSTRACT

Diabetes mellitus (DM) is a metabolic disorder that occurs in the body because of decreased insulin activity and/or insulin secretion. Pathological changes such as nephropathy, retinopathy and cardiovascular complications inevitably occur in the body with the progression of the disease. DM is mainly categorized into 2 sub-types, type 1 DM and type 2 DM. While type 1 DM is generally treated through insulin replacement therapy, type 2 DM is treated with oral hypoglycaemia. The major drug therapy for type 2 DM comprises of insulin secretagogues, biguanides, insulin sensitizers, alpha glucosidase inhibitors, incretin mimetics, amylin antagonists and sodium-glucose co-transporter-2 (SGLT2) inhibitors. Dual drug therapies are often recommended in patients who are unable to achieve therapeutic goals with first line oral hypoglycaemic agents as monotherapy. In spite of the appreciable therapeutic benefits, the conventional dosage forms depict differential bioavailability and short Half-life, mandating frequent dosage and causing greater side effects leading to therapy ineffectiveness and patient non-compliance. Given the pathological complexity of the said disease, nanotechnology-based approaches are more enticing as it comes with added advantage of site-specific drug delivery with higher bioavailability and reduced dosage regimen.

Keywords: Type 2 Diabetes mellitus, Monotherapy, Combination therapy, Novel drug delivery system.

INTRODUCTION

DM is a major public health issue affecting more than 400 million people worldwide. This metabolic disorder is caused either by deficiency of insulin secretion or by damage of pancreatic β cell. Type 1 DM (T1DM) is an autoimmune disorder that affects pancreatic cells which impairs the production of insulin, while type 2 DM (T2DM) is a result of impairment of pancreatic β cells . The major conventional classes of drugs for the treatment of hyperglycemia include sulfonylureas, biguanides, peroxisome proliferator-activated receptor-γ (PPARγ) agonists, and α-glucosidase inhibitors. These classes of drugs are either administered as monotherapy or as combination therapy. In such a scenario, nanoformulations have an established history in drug usage . Nanoformulations not only boost the drug's solubility but also have numerous benefits such as reduced dosage, rapid onset action, controlled drug release profile, less side effects, optimized drug delivery, minimized patient variability, and optimized bioavailability . Most significantly, nanoformulations promote cellular drug uptake or disrupt efflux mechanisms such as the P-

glycoprotein (P-gp) pump or target particular receptors that further strengthen the pharmacokinetics and pharmacodynamics profile of numerous anti-diabetic molecules . [1]

PATHOPHYSIOLOGY OF DIABETES

The homeostasis of glucose in the body is maintained by two hormones namely - Insulin and Glucagon, which play a dominant role in the regulation of glucose homeostasis .

I) Insulin is secreted by β cells.

II) Reduced secretion of insulin from β cells inhibits the production of glucose from liver by glycogenolysis and gluconeogenesis.

III) Dysfunction of neurotransmitters and resistance of insulin occurs in the brain.

IV) Reduction effect of incretin leads to increased glucose uptake from food in Gastro intestinal tract (GIT) .

V) Glucagon is secreted by α cells, and increases the uptake of glucose by liver, muscle, fat tissue.

VI) Increase of lipolysis occurs as well as increase in reabsorption of glucose by kidney occurs .

VII) Declining β-cell function and impaired regulation of hepatic glucose production causes Hyperglycemia (**Fig. 1**) . [2,3]

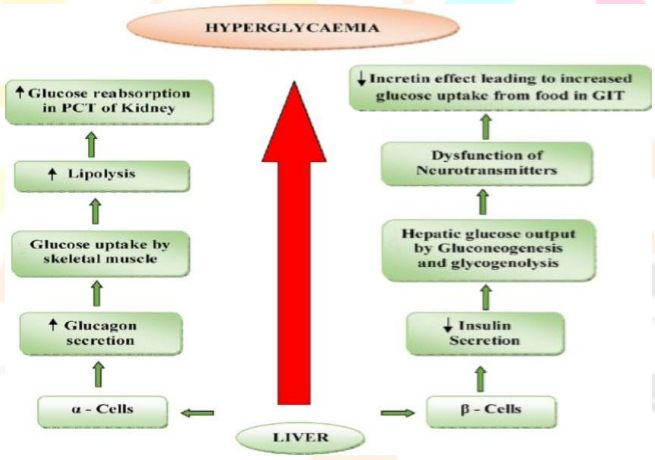

Fig 1: pathophysiology of Diabetes

NON-INSULIN TREATMENT FOR T2DM

These are categorized under the following- Insulin secretagogues, Biguanides and Insulin sensitizers.

Insulin secretagogues

This category of drugs (sulfonylureas and metiglinides) act by increasing the secretion of insulin from pancreas by binding to sulfonylurea receptor (SUR) of ATP. Sulfonylurea includes Tolbutamide, Chlorpropamide, Tolazamide, Glipizide, Glimepiride.

Side effect- dizziness, sweating, confusion and nervousness. It may also include weight gain, stomach upset and dark coloured urine

Biguandies

Biguanides reduce hepatic glucose output by decreasing gluconeogenesis and stimulating glycolysis. They block the breakdown of fatty acid through activation of AMP-dependent protein kinase.

Side effect- Gastrointestinal distress, diarrhoea, nausea, vomiting, & long term is also associated with decreased absorption of vitamin B12 .

Insulin sensitizers

The insulin sensitizers are also known as Peroxisome Proliferator Activated Receptor agonists (PPARs). These receptors are of three sub-types i.e. PPAR α, δ and γ. PPAR α maintains insulin sensitivity, inflammation control, PPAR γ activation improves glucose uptake by skeletal muscles and decreases the glucose production by retarding the gluconeogenesis.

Side effects- oedema, weight gain, macular oedema and heart failure. They may cause hypoglycaemia when combined with other anti-diabetic drugs and also decrease haemoglobin levels and increase bone fracture risk . [4]

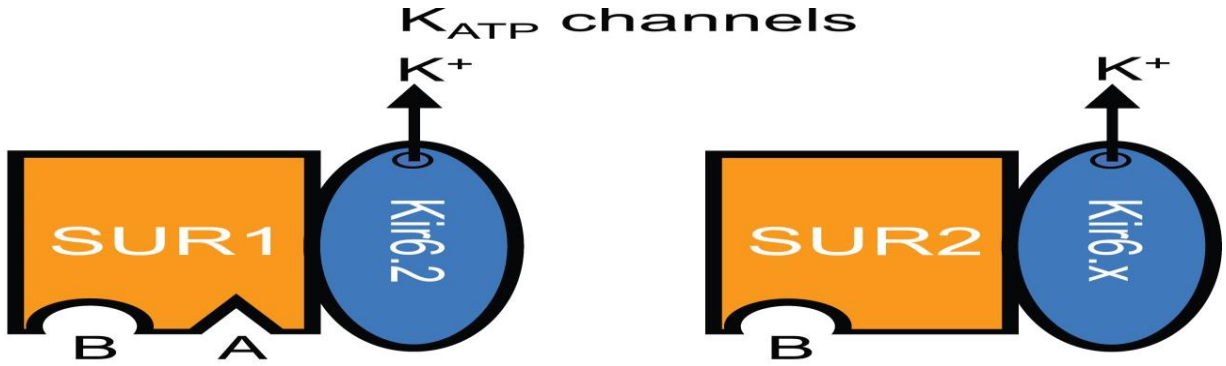

Fig: mechanism of the action of Sulfonyrulea

MONOTHERAPY FOR THE TREATMENT OF T2DM

Monotherapy treatment for T2DM is targeted for the reduction of glycosylated haemoglobin (HBA1c) up to 0.5-1.5%. Metformin is the drug of choice for the first line treatment because of its excellent blood glucose-lowering effect, relatively low adverse effects, long-term safety, low risk of hypoglycaemia and low weight gain (**Table 1**). [5]

Table 1: Monotherapy of anti-diabetic drugs for the treatment of T2DM

Name of the drug	**Outcome /Effect**
Alpha Glucosidase inhibitors (AGIs)	Voglibose is an alpha-glucosidase inhibitor. It delays the absorption of glucose thereby reducing the risk of macro vascular complications. It also reduces cardiovascular risks.
Amylin analogue	Pramlintide is an injectable amylin analogue drug for diabetes. It reduces the rate of glucose absorption from the gastrointestinal tract. It also improves satiety and control weight .[6]

Glucagon-like peptide-1 (GLP-1)	Lixisenatide is a glucagon-like peptide-1. It reduces cardiovascular risks. It also promotes insulin secretion after meals and suppresses the release of glucagon from the pancreas .[7]
Dipeptidyl peptidase-4 inhibitors (DPP-4)	Teneligliptin is a type 2 anti-diabetic drugs. It belongs to the class of inhibitors for dipeptidyl peptidase-4 that is commonly known as gliptins. It also increases to release more insulin and decreases the hormones that cause blood sugar levels to rise .

COMBINATION THERAPY FOR THE TREATMENT OF T2DM

When the monotherapy fails to control the glycaemic parameters in the treated patients, combination therapy is recommended to the patient to achieve the glycaemic control, and thereby delay the deterioration of β cells.

Combination therapy may be dual or triple drug combination therapy. At times oral hypoglycaemics are also combined with insulin. Combination therapy may include other medications like Thiazolidinediones (TZDs): these drugs make the body more sensitive to insulin, which helps lower blood sugar levels (**Table 2**) . [5]

Table 2: Combination therapy of anti-diabetic drugs for treatment of T2DM

NOVEL DRUG DELIVERY SYSTEM FOR ANTIDIABETIC DRUGS FOR T2DM

Name of the drug	**Outcome /Effect**
Metformin and Sulfonylureas / acarbose/thiazolidinedione/glinides	The dual therapy of metformin with Thiazolidinediones helps to reduce cardiovascular disease. Hypoglycaemic effect of metformin & sulfonylureas combination therapy is associated with its high rate of utilisation in secondary health care compared to any other dual therapy. It leads to a significant decrease in patient body fat and body fat mass which improves the level of cholesterol.
Alpha-glucosidase inhibitors (Voglibose) and DPP-IV inhibitors (Linagliptin)	The combination of Linagliptin and Voglibose reduces the weight & improve the glycaemic control. Linagliptin has less effect on postprandial glucose level. Voglibose decreases triglycerides & low density lipoprotein, and increases high density lipoproteins .
SGLT2 inhibitor with sulfonylureas	Both doses reduce systolic blood pressure. They also control LDL cholesterol level.
SGLT2 inhibitor with Biguanides	The dual therapy improves glycaemic control with lowering of glycosylated haemoglobin levels with low risk of hypoglycaemia.
PPARγ agonists_(Pioglitazone and Rosiglitazone) with Biguanides	It reduces cardiac hypertrophy. It improves glucose homeostasis by increasing expression of glucose transporters & enhancing insulin sensitivity. It also decreases tumour necrosis factor-alpha .[8]

NOVEL DRUG DELIVERY SYSTEM FOR ANTIDIABETIC DRUGS FOR T2DM

Novel Drug delivery system (NDDS) is one of the emerging field due to its benefits in reduced dosing frequency and enhanced bioavailability (**Table 3**). These systems can be classified as – **Particulate system –** i) Micro-particulate system, ii) Nanoparticulate system.

Vesicular system - i) Liposome, ii) Niosomes.

Others - i) Self nano emulsifying drug delivery system,
ii) Transdermal drug delivery system. [9]

Table 3 - Different reports on NDDS of anti-diabetic drugs for T2DM

Types of delivery system	**Class of drug**	**Name of drug**	**Effect /outcome**
Liposome	Biguanides	Liraglutide	Liraglutide is an anti-diabetic medication. It can able to lower glucose level for a prolonged period in T2DM. It reduces cardiovascular disease.
Niosome	Insulin secretagogues	Repaglinide	It can regulate the amount of glucose. It helps to prevent kidney damage, blindness, nerve problems.
Nanoemulsion	Insulin sensitizers	Glipizide	It increases the amount of insulin released by the pancreas in order to lower blood glucose. It also prevents different types of body complication.
Self Nano emulsifying drug delivery system	Sulfonylureas	Glimepiride	It is an effective anti-diabetic medication. It maintains blood glucose level. [10]
Nano-formulations in Transdermal patches	Biguanides	Metformin	Metformin is a type medication called Biguanides. It improves insulin sensitivity & lower cholesterol rate .

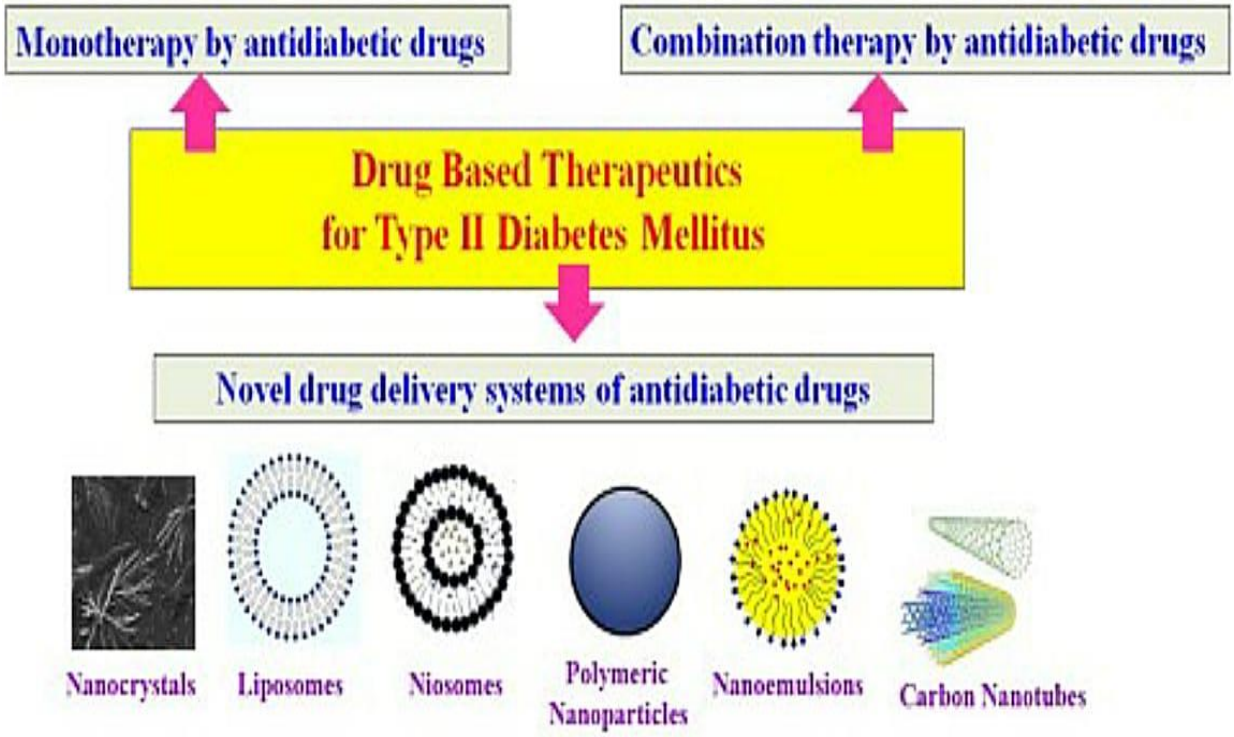

Fig: novel drug delivery system for Anti-Diabetic Drugs for T2DM [9]

CONCLUSION

The rising pattern of sedentary lifestyle and the higher incidences of patients with diabetes, generate a massive demand for anti-diabetic medication. Nanotechnology guarantees to bring in plenty of genuine ground breaking therapeutic advancements in our daily existence. Nanoformulations have contributed immensely to substantial progress in the advancement of nanoparticulate drug delivery systems for anti-diabetic drugs. Long term safety concerns and ethical issues related to nanoformulations along with the latest FDA guidelines for the regulation of the said products need to be implemented in order to facilitate the safety of such products to enhance their efficacy. Active targeting strategies involving the functionalization of suitable ligands or combinatorial drug therapy involving two or more anti-diabetic drugs could suitably regulate glucose levels for longer periods of time. Such perpetual technological advances in nanotechnology offer compelling prospects in the foreseeable future regarding the development of an efficient glucose lowering therapeutic modality .[11]

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