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# Anti-diabetic Therapies, Strategies for Diabetes Management, and Advancement in Drug Delivery Systems: A Review

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***Abstract*—** *Diabetes Mellitus (DM) stands as a prominent metabolic disorder characterized by impaired insulin activity and/or secretion, leading to various pathological complications such as nephropathy, retinopathy, and cardiovascular issues. This review delves into the intricacies of Diabetes Mellitus (DM), exploring its sub-types, conventional treatment modalities, and the emerging role of nanotechnology in revolutionizing drug delivery for improved therapeutic outcomes. Pathophysiology of Diabetes Mellitus manifests through aberrations in insulin dynamics, leading to hyperglycemia and subsequent tissue damage. Understanding the underlying pathophysiological mechanisms is crucial for devising effective therapeutic strategies. Classification of Diabetes Mellitus is broadly categorized into Type 1 and Type 2, each with distinct etiological factors and treatment approaches. Type 1 DM necessitates insulin replacement therapy, whereas Type 2 DM is primarily managed through oral hypoglycemic agents. Insulin replacement therapy is the cornerstone of treatment for Type 1 DM. It involves administering exogenous insulin to mimic the physiological insulin secretion that is deficient in individuals with T1DM. This aims to maintain blood glucose levels within a normal range to prevent acute as well as long-term complications. Drug therapy for Type 2 Diabetes Mellitus : The pharmacological armamentarium for Type 2 DM includes Insulin Secretagogues, Biguanides, Insulin Sensitizers, α-Glucosidase Inhibitors, Incretin Mimetics, Amylin Antagonists, and SGLT2 Inhibitors. The Complex pathophysiology of DM demands innovatives therapeutic approaches to enhance drug efficacy and patient adherence. Nanotechology offers promising solutions by enabling targeted drug delivery, improved bioavailability, and reduced dosing frequency. Clinical Implications and Future Perspectives Nanotechnology holds immense potential in revolutionizing diabetes management by addressing the limitations of conventional therapies and enhancing therapeutic efficacy. Future research endeavors should focus on translational studies to validate the clinical utility of nanotechnology-based drug delivery systems. In Conclusion, the integration of nanotechnology into Diabetes management offers a paradigm shift in therapeutic approaches, promising targeted drug delivery, improved bioavailability, and enhanced patient outcomes. Continued research and development in this field are imperative to realize the full potential of nanotechnology in combating the global burden of Diabetes Mellitus. In this article, we endeavor to delve into the pathophysiolgy of Diabetes Mellitus (DM), traditional treatment methods for both Type 1 (T1DM) and Type 2 (T2DM) diabetes, alongside innovative drug delivery strategies for managing Diabetes Mellitus.*

***Keywords*— *Pathophysiology of DM, Insulins for Type 1 Diabetes Mellitus, Non-insulin Modalities for Type 2 Diabetes Mellitus, Single-drug Therapy (Monotherapy), Multi-drug Therapy (Combination therapy), Innovative Drug Delivery System***

## I. INTRODUCTION

Diabetes Mellitus (DM) represents a significant public health concern, impacting over **400 million individuals** globally[1]. This metabolic disturbance gradually results in chronic microvascular, macrovascular and neuropathic complications, posing life-threatening risks. DM emerges from either insufficient insulin secretion, pancreatic β cell damage, or insulin resistance linked to insulin non-utilisation. The surge in sedentary lifestyles is a primary factor contributing to the escalating diabetic population, projected to reach **366 millions by 2030** among the elder individuals (>65 years)[2]. Complications associated with DM encompass nephropathy, neuropathy, cardiovascular and renal issues, retinopathy and dietary disorders, among others. Type 1 DM, an autoimmune ailment, impacts pancreatic β cells, hampering insulin utilisation[3]. The major conventional classes of drugs for the treatment of hyperglycemia includes:

1. Sulfonylureas: Enhance release of insulin from pancreatic islets.
2. Biguanides: Reduce hepatic glucose production.
3. Peroxisome proliferator-activated receptors-y(PPARY) agonists: Boost the action of insulin.
4. α – glucosidase inhibitors: Interfere with absorption of glucose in the guts[4].

These classes of drugs are either administered as monotherapy or given in combination with other hypoglycemics. Severe hypoglycemia, weight gain, lower therapeutic efficacy owing to improper or ineffective dosage regimen, low potency and altered side effects due to drug metabolism and lack of target specificity, solubility and permeability problems are the major drawbacks associated with the use of the Above-mentioned conventional drugs [5]. Despite the advent of promising anti-hyperglycemic agents, the major challenges in efficient diabetes treartment include optimizing the existing therapies to guarentee optimum and balanced glucose concentrations, as well as reducing long-term diabetes-related complications [6].

Nanoformulation have well-established track record in addressing the issues associated with conventional drug usage [7]. They not only enhance drug solubility but also offer various benefits:

- Reduced dosage
- Rapid onset of action
- Controlled drug release profile
- Fewer side effects
- Optimized drug delivery
- Extended drug half-life
- Minimized patient variability
- Enhanced bioavailability [8].

Nanoformulations often operate at the molecular level to:

- Facilitate cellular drug uptake
- Disrupt efflux mechanisms like the P-glycoprotein(P-gp) pump
- Target specific recepters, thereby improving the pharmacoknetics and pharmacodynamics of numerous anti-diabetic molecules [9,10].

This review delves into:

- The current conventional drugs used in treating type 2 DM
- The associated limitations of their usage.
- The innovative nanoformulations under active research to overcome these limitations of conventional drug use.

## II. ANALYZING THE DISTURBED PHYSIOLOGY IN DIABETES

Following table summarizes the roles of insulin and glucagon in regulating glucose homeostasis[11]:

| Hormones | Secreted | Secretion Stimulus | Action |
|---|---|---|---|
| INSULIN | β cells of Pancreas | High blood glucose | Inhibits liver glucose production via glycogenolysis and gluconeogenesis. Increases glucose uptake by liver muscle. |
| GLUCAGON | α cells of pancreas | Low blood glucose | Stimlates liver to release glucose into bloodstream. |

[12].

Glucagon is secreted by α cells of the pancreas when the glucose concentration is low. Glucose acts by:

1. Antagonizing the effect of insulin by enhancing processes like glycogenolysis and gluconeogenesis in the liver.
2. Additionally, cortisol and catecholamines also increase plasma glucose levels [13].

Other hormones involved in maintaining normal glucose level include:

- Amyline (a 37 amino acid peptide), which is secreted along with insulin. It decreases gastric emptying, enhancing glucose absorption after a meal[16].
- Glucagon-like Peptide-1 (GLP-1) (a 30 amino acid peptide) and Glucose-dependent Insulinotropic Polypeptide (GIP) (a 42 amino acid peptide), which are incretins derived from the gut. These incretins facilitate the synthesis and secretion of insulin from β cells of the pancreas [14,15].

Glucose is not freely absorbed from the intestine or by cells requiring energy. The distribution of glucose to cells is facilitated by glucose transporters, classified into two types:

i. Sodium-glucose co-transporter (SGLT)
ii. Facilitative glucose transporter (GLUT) [17]

Diabetes Mellitus is categorized into two major sub-types with differential causes:

- Type-1 DM (T1DM): The immune system mistakenly attacks the β cells of the pancreas, with genetics playing a vital role.
- Type-2 DM (T2DM): Genetics and lifestyle factors, particularly obesity or overweight increase associated risks [18].

The pathophysiology of Type 2 DM may involve a variety of mechanisms known as the "Omnious octlet", which encompass:

i. Decresed insulin secretion from pancreatic islet cels
ii. Ascend glucagon secretion from pancreatic islet α cells
iii. Increased hepatic glucose production
iv. Neurotransmitter dysfunction and insulin resistance in the brain
v. Enhanced lipolysis
vi. Heightened glucose re-absorption by the kidneys
vii. Reduced effect of incretin in the small intestine
viii. Impaired glucose uptake by peripheral tissues such as skeletal muscle, liver and adipose tissue [19].

- Gestational diabetes arises due to hormonal shifts during pregnancy, where placental hormones reduce cellular sensitivity to insulin [20, 21].
- Genentic mutations, including monogenic diabetes such as neonatal diabetes and maturity onset diabetes of the young (MODY) [22].
- Conditions like cystic fibrosis and hemochromatosis leading to pancreatic damage from excess iron storage [23, 24].

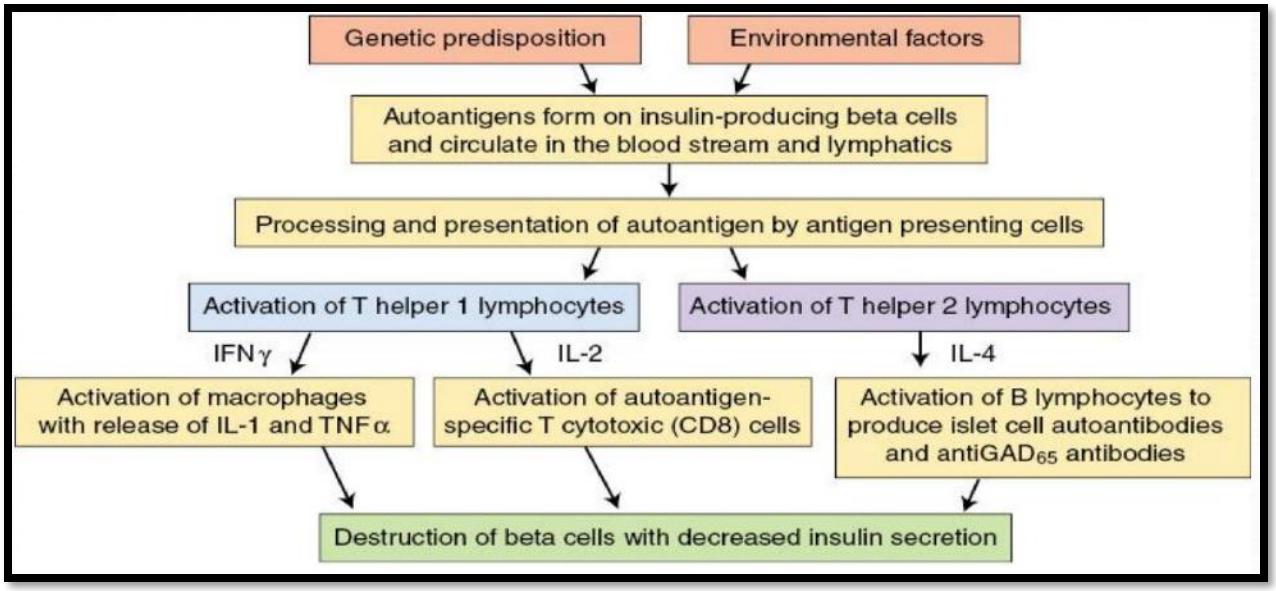


*Fig.1- Pathophysiology of Type 1 Diabetes Mellitus*

- Certain hormonal disorders like Cushing's syndrome, Acromegaly and hyperthyroidism can induce insulin resistance and contribute to diabetes development [25, 26, 27].
- Pancreatic damage or removal, including conditions like pancreatitis, pancreatic cancer or trauma, can impair β-cells function and insulin production, leading to diabetes [15, 28, 29].
- Additionally, several medications, including niacin, certain diuretics, psychiatric drugs, anti-seizure medications, HIV treatments, pentamidine, glucocorticoids, anti-rejection drugs and stains, can impact β-cells function or disrupt insulin regulation [15, 30, 31].

Various factors contribute to an increased risk of diabetes across different types:

- **Type 1 Diabetes (T1DM):** Children or teenagers with a family history of diabetes, particularly if a parent or sibling is diabetic, are at a heightened risk [33].
- **Type 2 Diabetes (T2DM):** Several factors elevate the risk including being overweight, dietary habits, age over 45 years, family history of diabetes, sedentary lifestyle, pre-diabetes or gestational diabetes history, and elevated levels of cholesterol or triglycerides [34-37].
- **Gestational Diabetes:** Risk factors include being overweight, age over 25 years, previous history of gestational diabetes, giving birth to a baby weighing over 9 pounds, family history T2DM, and having polycystic ovary syndrome (PCOS) [38].

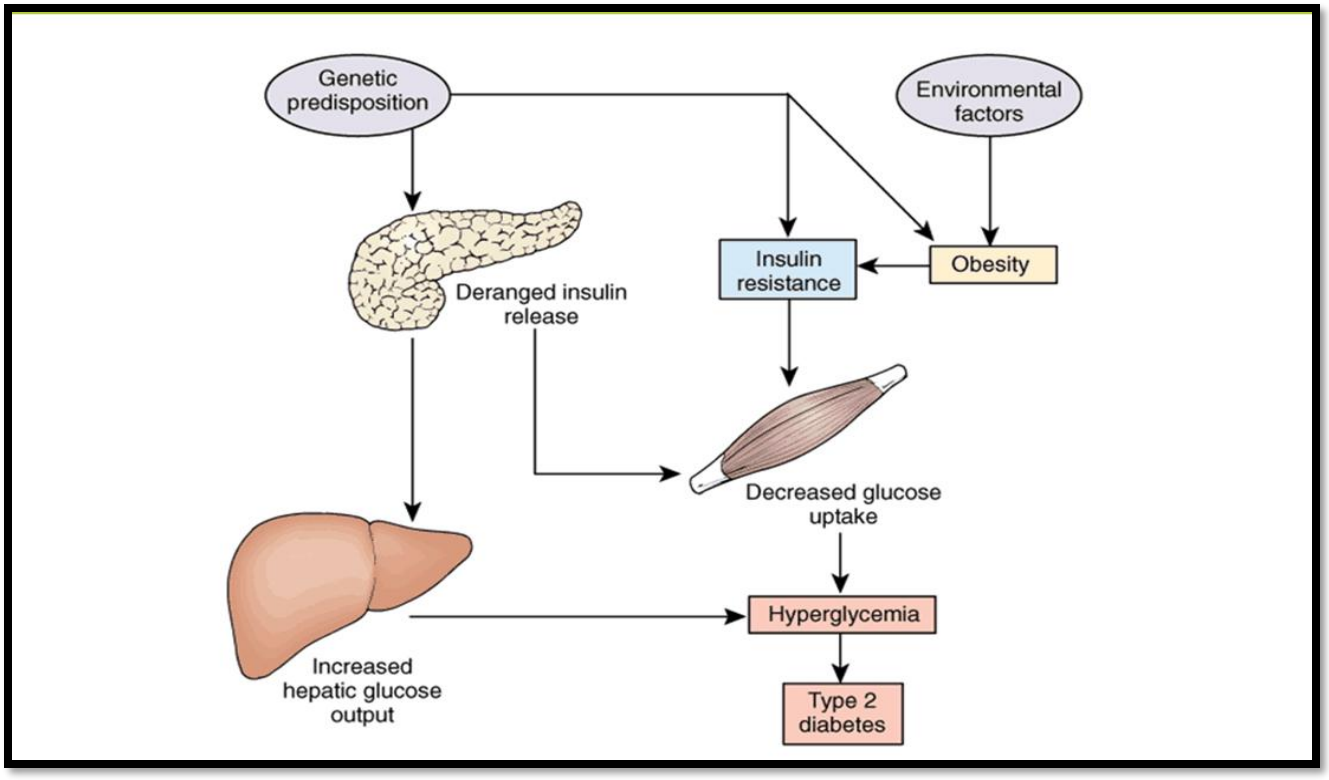


*Fig.2: Pathophysiology of Type 1 Diabetes Mellitus (T2DM)*

Complications of Diabetes:- Diabetes can lead to various complications, both microvascular and macrovascular, including :-

- Microvascular complications: Nephropathy, retinopathy, loss of vision.
- Macrovascular complications: Heart diseases, heart attack, stroke, neuropathy, infections & sores that don't heal, bacterial & fungal infections, depression and dementia [39].

Regular Testing for Diabetes:

Individuals displaying significant symptoms of Diabetes Mellitus or those at risk should undergo regular testing.

Diagnostic Blood Tests for Prediabetes and Diabetes: Tests include:

- Fasting Plasma Glucose (FPG): Measure blood glucose after an 8-hour fast.
- HbA1C Test: Measures blood sugar levels over the previous three months.

Diagnosing Gestational Diabetes: Blood tests are conducted between the 24$^{th}$ and 28$^{th}$ week of pregnancy, including-

- Glucose Challenge Test
- Three-hour Glucose Tolerance Test [20,40]

## III. INSULINS FOR TYPE 1 DIABETES MELLITUS (T2DM)

- Human insulin is synthesized using bacterial recombinant DNA technology.
- Variations in the amino acid sequence of human insulin result in insulins with diverse pharmacokinetics properties.
- The onset, peak effect and duration of action of insulins are influenced by both the type of insulin and its physical and chemical characteristics.
- Insulin is available in various forms, spanning from rapid-acting to long-acting formulations.
- **Types of Insulin Preparations:**

1. Rapid-Onset and Ultrashort-acting Insulin:

- Preparations characterized by rapid onset of action.
- Typically used to manage postprandial glucose spikes.
- Examples include insulin lispro, insulin aspart, and insulin glulisine.

2. Intermediate-Acting Insulin:
   - Formulations designed to provide sustained blood glucose control.
   - Often used to cover longer periods between meals or overnight.
   - Commonly known as NPH (neutral protamine Hagedorn) insulin.
   - Examples include Lente insulin, isophane NPH suspension.
3. Long-Acting Insulin Preparations:
   - Designed for extended blood glucose control.
   - Typically used as basalor background insulin.
   - Examples include insulin glargine and insulin detemir.

- INSULIN COMBINATIONS-

Following are premixed combinations of Human insulins:

- 70% NPH insulin + 30% regular insulin
- 50% NPL insulin + 50% lispro insulin
- 75% NPL insulin + 25% lispro insulin

- **Characteristics of Insulin Preparations:**

1. Physical Form:
   - Rapid-acting and short-acting insulins: clear solutions with small amounts of zinc for stability.
   - Intermediate-acting NPH insulins: Turbid suspension with protamine in phosphate buffer for prolonged action.
   - Inhale rapid-acting insulin: Available as a powder for alveolar absorption.
2. Administration and Absorption:
   - Injected insulins are administered subcutaneously.
   - Inhaled insulin is absorbed through the alveoli.
3. Factors Affecting Duration of Action:
   - Dose
   - Injection site
   - Blood supply to injection site
   - Ambient temperature
   - Physical activity level
4. Clinical Usage:
   - Long-acting insulins are primarily used for basal or background coverage.
   - Rapid-acting insulins are typically employed to manage mealtime glucose spikes.

- **Methods of Insulin Administration:**

1. Subcutaneous Injection:
   - Insulin is administered under the skin.
   - Oral administration is not feasible due to degradation in the gastrointestinal tract.
2. Intravenous Injection:
   - Used in hyperglycemic emergencies with regular insulin.
   - Intravenous infusion is preferred to avoid multiple injections.

3. Insulin Pumps(Open-loop Pumps):
   - Continuous subcutaneous administration.
   - Eliminates the need for multiple daily injections.
   - User-programmable pump delivers personalized basal and bolus doses base on blood glucose levels.
4. Portable Pen Injectors:
   - Cartridges of insulin and replaceable needles.
   - Convenient for self-administration.
5. Aerosol Preparation:
   - Inhaled insulin in finely powdered form.
   - Absorbed through alveolar walls.
   - Challenges lies in creating particles small enough to pass through the bronchial tree without being trapped.

- **Factors Affecting Insulin Activity:**

Insulin-Degrading Enzyme:-

- Also known as Insulin Protease.
- Predominantly found in the liver and kidney.
- Inactivates Insulin.

- **Adverse Reactions to Insulin:**

1. Hypoglycemia:
   - More common adverse reaction characterized by symptoms such as tachycardia, confusion, vertigo, and diaphoresis.
   - Treatment for conscious patients experiencing severe hypoglycemia, intravenous infusion of 20-50 mL of 50% glucose solution over 2-3 minutes is recommended. Alternatively, 1 mg of glucagon can be administered via subcutaneous or intramascular injection, typically restoring consciousness within about 15 minutes, followed by food consumption.

2. Lipodystrophy
   - Atrophy of subcutaneous fat can occur due to the availability of highly concentrated insulin preparation with a neutral pH.
   - Hypertrophy of subcutaneous fatty tissue may result from repeated insulin injections at the same site.
3. Allergic reactions and Local Injection Site Reactions
   - Immediate type hypersensitivity reactions may occur, with rare cases of urticaria following histamine release from tissue mast cells sensitized by anti-insulin IgE antibodies.
   - Treatment typically involves anti-histamines and corticosteroids.
4. Weight Gain
   - It can indirectly contribute to weight gain
5. Insulin Immune Resistance:
   - Occurs due to high titer circulating IgE anti-insulin antibodies.

NOTE: Individuals with diabetic renal insufficiency may necessitate modifications to their insulin dosage [91].

## IV. NON-INSULIN TREATMENT MODALITIES FOR TYPE 2 DIABETES

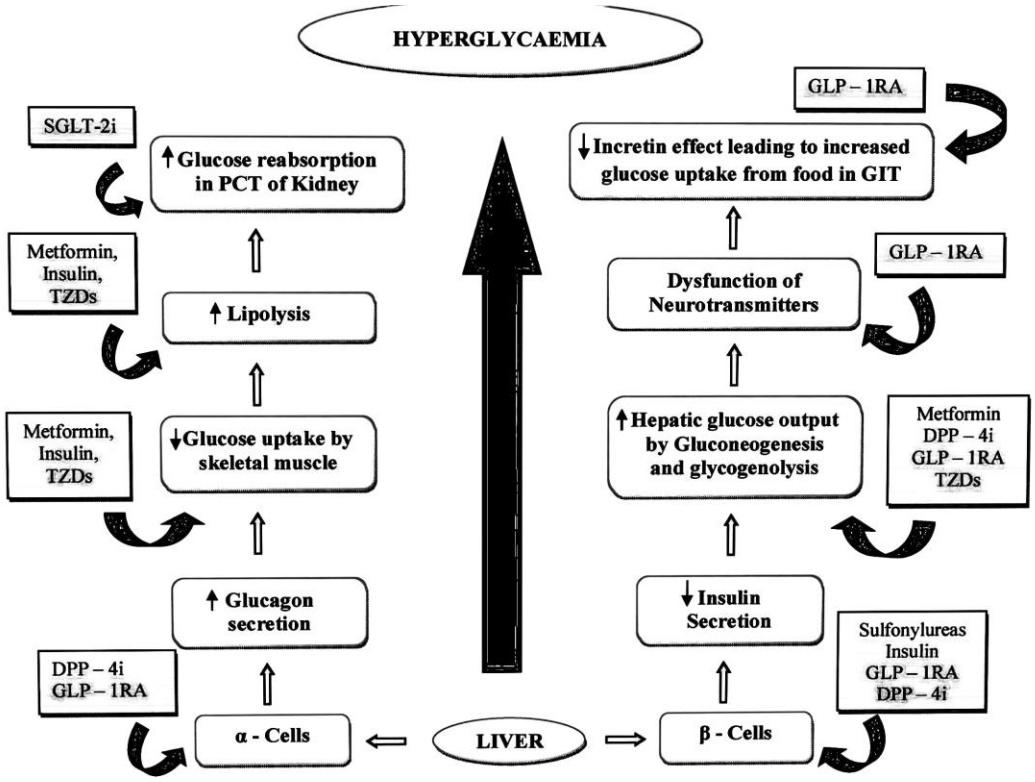


*Fig.3-Targets of therapy for T2DM*

A variety of non- insulin based oral therapies have emerged for treating type 2 DM (Fig.2) which fall under the following categories:

1. Insulin Secretagogues
2. Biguanides
3. Insulin Sensitizers
4. α Glucosidase Inhibitors
5. Incretin Mimetics
6. Amylin Anatagonists
7. SGLT2 Inhibitors

**1. Insulin Secretagogues**

a. Mechanism of Action:-

Insulin Secretagogues, including sulfonylureas and meglitinides, stimulate insulin secretion from the pancreas by binding to the sulfonylurea receptor (SUR) of the ATP-sensitive potassium channel on pancreatic β cells [41].

b. First-Generation Sulfonylureas:-

Tolbutamide, Chlorpropamide,Tolazamide, Acetohexamide belong to the 1st generation of sulfonylures.

c. Second-Generation Sulfonylureas:-

Glibenclamide, Glipizide, and Glimepiride are examples of 2nd generation sulfonylures [42].

d. Advancements of Second Generation:-

The development of Second-Generation sulfonylureas was driven by increased potency, quicker onset of action, shorter plasma half-lives and longer duration of action.

e. Common side-effects:-

Side effects of sulfonylureas commonly include symptoms of low blood sugar levels such as dizziness, sweating, confusion and nervousness [43].

f. Additional Side-effects:-

g. Other side effects may encompass hunger, weight gain, skin reactions, stomach upset, and dark-coloured urine.

h.

i. Drugs:-

Metiglinide serves as the prototype molecules, derived from benzoic acid, within the non-sulfonylurea moiety of Glibenclamide. These agents function by closing the ATP-sensitive potassium channel present on the plasma membrane of pancreatic β cells [43]. Other molecules in the category include Repaglinide and Nateglinide [44].

**2. Biguanides**

a. Mechanism of Action:-

Biguanides function by enhancing the body's response to natural insulin, reducing glucose absorption from the intestine, and decreasing glucose production by the liver. They achieve this by decreasing gluconeogenesis and promoting glycolysis, while also increasing insulin receptor activity [45].

b. Types of Biguanides:-

Biguanides includes Metformin, Phenoformin and Buformin. Phenoformin and Buformin were withdrawn from clinical use due to a high risk of lactic acidosis, whereas Metformin is widely used and associated with a much lower risk of lactic acidosis [46].

c. Effects and Properties:

Biguanides do not cause hypoglycaemia or weight gain. They exhibit anti-hypertriglyceridemic effect and vasoprotective properties. Additionally, they block the breakdown of fatty acids by activating AMP-dependent protein kinase [47].

d. Adverse Effect:-

Common adverse effects of Biguanides include gastrointestinal distress such as diarrhea, cramps, nausea, vomiting and increased flatulence. Long-term use is associated with decreased absorption of vitamin B12 [48].

**3. Insulin Sensitizers**

Insulin sensitizers, also known as Peroxisome Proliferator-Activated Receptor agonists (PPARs), regulate protein and carbohydrate metabolsim to maintain glucose homeostasis. They belonging to the nuclear hormone receptor superfamily of ligand-activated transcription factors [49].

a. PPAR Subtypes:-

There are three subtypes of PPAR receptors: PPARα, PPARδ and PPARγ. Among these, PPARγ is specific for glucose homeostasis. PPARγ agonists, often called "glitazones", such as thiazolidines, increase cell sensitivity to insulin and reduce systemic fatty acid production and uptake [50].

b. Mechanism of Action:-

Activation od PPARγ improves glucose uptake by skeletal muscles and reduces glucose production by inhibiting gluconeogenesis [51].

c. First Generation Moecules:-

*Pioglitazone, Rosiglitazone and Ciglitazone are among the first-generation drugs in this category.

*They associated with common side effects including edema, weight gain, mascular edema and heart failure.

*Combining them with other anti-diabetic drugs may lead to hypoglycemia and other adverse effects like decreased hematocrit, hemoglobin levels and increased risk of bone fracture [52].

d. Dual PPARα/γ Agonists:-

Recently, dual PPARα/γ agonists have been developed to reduce the side-effects associated with PPARγ agonists. These drugs, such as Muraglitazar, Tesaglitazar, Alegitazar, Ragaglitazar, Naveglitazar and Saroglitazar, provide synergistic action in maintaining lipid metabolism, insulin sensitivity and inflammation control[53]. However,

the use of Muraglitazar was withdrawn from clinical trails due to cardiotoxicity [54].

e. Shift in Treatment Approach:-

Due to the prevalent side effects associated with first-line drugs, second-line drugs have substituted them as the primary tratment for diabetes mellitus [55].

**4. α- Glucosidase Inhibitors**

a. Mechanism of Action:-

- α- Glucosidase Inhibitors (AGIs) target key enzymes like α-amylase and α- glucosidase, crucial for carbohydrate metabolism [18].

- AGIs, such as Acarbose, Voglibose and Miglitol, slow down carbohydrate absorption in the gastrointestinal tract, delaying the entry of glucose into the bloodstream[57].

b. Effect on Postprandial Hyperglycemia:-

- AGIs function as competitive inhibitors in the small intestine, reducing the digestion rate of carbohydrate like starch.

- This action leads to a decrease in postprandial hyperglycemia, beneficial for managing Type 2 Diabetes Mellitus (T2DM) [56].

c. Benefits in Diabetes Management:-

-AGIs, when combined with other diabetic medications, help reduce post-meal blood sugar levels and lower HbA1c levels [59].

- They also elevated post-meal levels of GLP-1, which aids in delaying digestion and reducing appetite [60].

d. Side Effects and Contraindications:-

- Common side effects of AGIs include bloating, flatulence and gastrointestinal irritation, typically subsiding within a few weeks.
- AGIs are not recommended for individuals with inflammatory bowel diseases, intestinal blockages, or diabetic keto-acidosis [61].
- Acarbose is contraindicated in patients with ulcers in the large intestine, liver cirrhosis and during pregnancy [61,62].

**5. Amylin analogues**

Amylin is a hormone comprising a single chain of 37 amino acids, co-secreted with insulin from β-cells of the pancreas[18]. It plays crucial roles in delaying gastric emptying, suppressing glucagon secretion, and regulating food intake by modulating the appetite center in the brain[63].

a. Importance of Amylin Analogues:

Amylin deficiency is observed in both Type 1 and Type 2 Diabetes Mellitus (T1DM and T2DM)[63]. Consequently, research has focused on developing amylin analogues to maintain glucose homeostasis through mechanism such as:

- Delaying gastric emptying
- Preventing the release of glucagon after meals
- Inhibiting food intake and weight gain by controlling the appetite center[64].

b. Development of Amylin Analogues:

Due to amylin's unsuitability as a drug, characterized by aggregation and insolubility in solution form, chemical analogues have been developed to mimic its action. These analogues are available in parental form and are utilized in the treatment of both T1DM and T2DM[64].

c. Example:

Pramlintide acetate, marketed under the brand name Symlin®, is a notable drug in this class. It is administered via subcutaneous route before meals and shares a similar mode of action as amylin[64,65].

d. Side Effects of Amylin Analogues:

Common side effects associated with amylin analogues include nausea, vomiting, headache, and hypoglycemia when used alongside insulin. However, these side effects typically diminished as patients adjust to the medication[64].

**6. Incretin Mimetics**

a. Introduction:

- Incretins, such as Glucagon-like peptide (GLP) and Glucose-dependent Insulinotropic polypeptide (GIP), are gut-derive peptides that lower blood glucose levels post-meal [66].
- GLP-1, a 36 amino acids peptide secreted by L cells in gut, stimulated insulin secretion similar to pancreatic β-cells [67].
- GLP-1 secretion is triggered by carbohydrate metabolism in intestinal L cells, leading to insulin synthesis and secretion [68].
- GLP-1 has a short half-life (1-2 minutes) due to rapid metabolism of dipeptidyl peptidase- Ⅳ (DDP-Ⅳ) enzymes [18].
- GLP-1 analogues with increased half-life have been developed to treat both Type 1 and Type 2 Diabetes Mellitus (T1DM and T2DM) [69].

b. GLP-1 Agonists:

- GLP-1 agonists or analogues are injectable treatments for T2DM [70, 71, 72].
- Analogues were designed by substituting the alanine residue at the N-terminal of GLP-1 with amino acids like threonine, glycine, and serine, making them more stable against DPP-Ⅳ [73].
- Exenatide was the first GLP-1 analogues, resistant to DPP-Ⅳ, with 53% similarity to human GLP-1. It is available as Bydureon®(weekly) and Byetta®(twicw daily).
- Other GLP-1 analogues include Lixisenatide (Lyxumia®), Dulaglutide (Trulicity®), and Liraglutide (Victoza®) [75].

c. Mechanism of Action and Side Effects:

- GLP-1 agonists increase insulin secretion and inhibit glucagon release, lowering blod glucose levels and reducing HbA1c levels [76].
- Side effects may include diarrhea, nausea, vomiting, headaches, dizziness, increased sweating, indigestion, constipation, and loss of appetite [76].

d. Clinical Recommendations:

- GLP-1 receptors agonists are recommended as add-on therapy for patients not achieving Hb1Ac targets with metformin alone [77].
- They are suggested as first-line therapy for patients unable to tolerate or contraindication for metformin, due to their low risk of hyperglycemia [76].
- In combination therapy, GLP-1 agonists can be used with metformin and/or Sodium-glucose co-transporter 2 (SGLT-2) inhibitors for patients with persistent hyperglycemia [79].
- Combining GLP-1 agonists with basal insulin may delay the need for mealtime insulin, reducing the risk of hypoglycemia and mitigating weight gain associated with insulin use [79, 80].

e. DPP-Ⅳ Inhibitors:

- DDP-Ⅳ exists as both a membrane-bound serine protease and a soluble form in plasma [81].
- Dipeptidyl peptidase-Ⅳ (DPP-Ⅳ) inhibitors increase GLP-1 activity by inhibiting its degradation [82].
- Inactivation of DPP-Ⅳ increases the half of GLP-1 [82].
- Several DPP-Ⅳ inhibitors are available with high oral bioavailability, such as Sitagliptin, Vildagliptin, Saxagliptin, Linagliptin, Alogliptin, Gemigliptin, Anagliptin, Tenegliptin, Trelagliptin, and Omarigliptin [83].

**7. Sodium glucose co-transporter 2 antagonists/ inhibitors**

a. Mechanism of Glucose Re-absorption in the Proximal Convoluted Tubule (PCT):

Glucose re-absorption in the PCT involves both passive transport via facilitative glucose transporter (GLUT) and active co-transport via sodium glucose co- transporter (SGLT) [84].

b. Functions of SGLT2 inhibitors:

SGLT2 inhibitors target the SGLT2 present in the PCT, inhibiting glucose re-absorption and promoting glucose excretion in urine.

c. Effect on Blood Glucose Levels:

Increased excretion of glucose in urine helps maintain blood glucose levels and other glycaemic parameters [85].

d. Available SGLT2 Inhibitors:

The category includes Canagliflozin, Dapagliflozin, Empagliflozin, Ipragliflozin, Luseogliflozin, and Tofogliflozin [86].

e. Clinical Use:

SGLT2 inhibitors can be employed in monotherapy or in combination with metformin, sulfonylurea, thiazolidinediones, or insulin as adjunct therapy [87].

❖ **Single-drug Therapy For Managing Type 2 Diabetes Mellitus (Mono-Therapy for T2DM):-**

a. Objectives:

- Aim to reduce glycosylated hemoglobin (HbAlc) by 0.5 to1.5% [88].
- Emphasize control of postprandial glucose levels, especially when HbAlc reaches below 7% [89].

b. First-Line Treatment Choices:

- Metformin is the preferred initial drug for monotherapy in T2DM.

c. Alternative Options:

If metformin is contraindicated or causes complications:

- Other available hypoglycemic agents are considered as the primary treatment for T2DM [89, 90].

❖ **Multi-drug Regimen for Managing Type 2 Diabetes Mellitus (Combination Therapy for T2DM):-**

a. Effectiveness of Combination Therapy:

- Consider whether combining medications will effectively control glycemic parameters, especially when mono-therapy fails [92, 93].
- Aim to delay the deterioration of β-cells to maintain glycemic control [94].

b. Improvement of Diabetic Conditions:

- Evaluate if combining different medications can modify β-cell function and improve the pathophysiology of diabetes [95].

c. Patient Compliance and Acceptance:

- Assess patient compliance based on factors such as acceptance, dosing frequency, and safety of the combination therapy [96].

d. Cost considerations:

- Evaluate the affordability of the combination therapy for the patient, considering the cost of the medication involved [97].

e. Risk-to-Benefit Ratio:

- Determine if the risk-to-benefit ratio of the combination therapy is acceptable for the patient [98].

f. Assessment of Primary and Secondary End Points:

- Analyze whether combination therapy addresses primary and secondary endpoints effectively, potentially overcoming issues associated with single therapy or add-on insulin, such as weight gain and hypoglycemia [92].

❖ **Innovative Drug Delivery System Targeting Type 2 Diabetes Mellitus (T2DM):-**

Traditional drug delivery systems encounter limitations such as ineffective dosage, altered effects due to metabolism, and lack of specificity [99, 100]. Novel Drug Delivery Systems (NDDS) address these challenges by offering reduced dosing frequency, improved bioavailability, and targeted therapeutic efficacy while minimizing side effects [101].

a. Classification of NDDS for T2DM Treatment

NDDSs explored for treating Type 2 Diabetes Mellitus (T2DM) include:

1. PARTICULATE SYSTEM: Particulate systems, comprising miniaturized structures, facilitate intracellular drug transport and receptor recognition, making them promising carriers for anti-diabetic drugs [8]. Further, it divided as:

- Microparticulate System: Microparticle-based therapy enables targeted drug release at specific sites, maintaining plasma drug concentration and enhancing dissolution of insoluble drugs through a larger surface-to-volume ratio [102].
- Nanoparticulate System: Nanoparticles, categorized as polymeric, metallic, lipid-based, or biological, offer higher intracellular uptake and enhanced mucoadhesion, delivering drugs via cellular uptake pathways [103, 104,105].

2. VESICULAR SYSTEM: Vesicular systems, resembling lipid bilayer structures, offer controlled release, improved stability, and reduced toxicity. Liposomes (uni-lamellar or multi-lamellar) and niosomes enhance oral bioavailability and reduce dosing frequency [106-109].
3. SELF NANO-EMULSIFYING DRUG DELIVERY SYSTEM (SNEDDS):

SNEDDS, an oil-in-water nano-emulsion, enhances solubility, and oral bioavailability of poorly water-soluble drugs, providing a controlled release pattern [110,111,112].

4. TRANSDERMAL DRUG DELIVERY SYSTEM (TDS):

TDS, a non-invasive and patient-compliant alternative, overcomes first-pass metabolism issues and offers an option for delivering hydrophilic drugs and macromolecules with permeation enhancers [113].

## V. CONCLUSION

The increasing prevalence of sedentary lifestyles and the corresponding rise in obesity rates have led to a surge in diabetes cases, necessitating a significant demand for anti-diabetic medications. This trend has spurred companies to allocate more resources towards research and development to create targeted formulations. Nanotechnology holds immense promise in revolutionizing therapeutic approaches in our daily lives. Extensive research into nano-formulations has yielded substantial advancements in nanoparticulate drug delivery systems for anti-diabetic medications. However, ensuring the long-term safety and addressing ethical concerns associated with nano-formulations, alongside complying with the latest FDA regulations, are imperative to enhance their efficacy and safety. Active targeting strategies, such as functionalizing suitable ligands or employing combinational drug therapy involving multiple anti-diabetic drugs, present promising avenues for regulating glucose levels over extended durations. These

ongoing technological breakthroughs in nanotechnology offer compelling prospects for the development of efficient glucose-lowering therapeutic modalities in the foreseeable future.

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