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Review Article

Current and Emerging Pharmacological Therapies for Type 2 Diabetes Mellitus: A Comprehensive Review

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Abstract

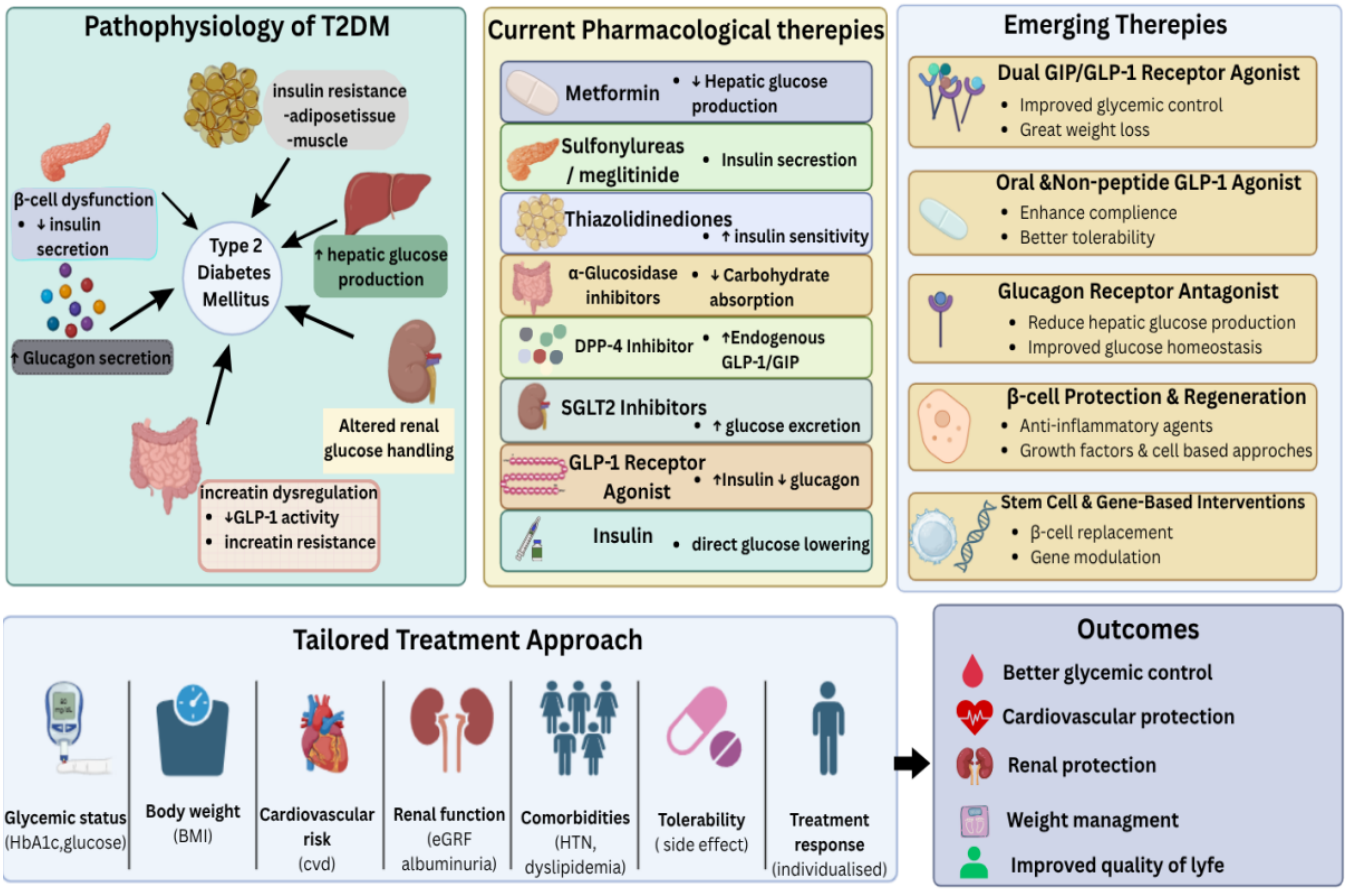
Type 2 diabetes mellitus (T2DM) is a progressive metabolic disorder characterised by insulin resistance, impaired pancreatic beta cell function, dysregulated glucagon secretion, altered incretin activity, increased hepatic glucose production and abnormal renal glucose handling. The growing burden of T2DM and its related cardiovascular, renal and metabolic complications has led to a change in focus from conventional glucose-lowering therapy to pharmacological strategies that address broader metabolic and clinical outcomes. This review provides a comprehensive overview of established and emerging pharmacological approaches for managing T2DM, emphasising their therapeutic targets, mechanisms of action, clinical applications, benefits and limitations. The review discusses established therapies, including metformin, sulfonylureas, meglitinides, thiazolidinediones, α-glucosidase inhibitors, dipeptidyl peptidase-4 inhibitors, sodium-glucose cotransporter-2 inhibitors, glucagon-like peptide-1 receptor agonists and insulin, in relation to their roles in contemporary diabetes management. The review also examines combination and fixed-dose therapies, as well as the importance of tailoring treatment to an individual's glycaemic status, body weight, cardiovascular risk, renal function, comorbidities, tolerability and treatment response. Recent therapeutic developments are also explored, including dual glucose-dependent insulinotropic polypeptide/glucagon-like peptide-1 receptor agonists, oral and non-peptide GLP-1 receptor agonists, glucagon receptor-targeted approaches, and strategies aimed at β-cell protection and regeneration. The potential of emerging approaches involving stem cell- and gene-based interventions to address the underlying pathophysiology of T2DM is also considered. Overall, the pharmacological management of type 2 diabetes mellitus (T2DM) is evolving towards strategies that are both mechanism-based and patient-centred, integrating glycaemic control with cardiovascular, renal, metabolic and weight-related outcomes. Further investigation of emerging therapies may expand the range of options available for long-term disease management.

Keywords: Type 2 diabetes mellitus, Insulin resistance, β-cell dysfunction, GLP-1 receptor agonists, SGLT2 inhibitors, Emerging therapeutics, β-cell regeneration.

Highlights:

- Reviews the evolving pharmacological landscape for the management of type 2 diabetes mellitus.
- Examines key molecular targets and mechanisms underlying established antidiabetic therapies.
- Highlights the transition from conventional glycaemic control to integrated cardiometabolic and renal risk management.
- Discusses emerging incretin-based strategies, including dual GIP/GLP-1 receptor agonists and oral GLP-1 therapies.
- Explores combination pharmacotherapy and β-cell-directed regenerative approaches as emerging avenues for diabetes management.

Graphical Abstract



1. Introduction

The occurrence of type 2 diabetes mellitus (T2DM) is rising in the developed and developing world and is a major public health problem globally. [1] Type 2 diabetes is the most common form of diabetes, accounting for more than 90% of all diabetes worldwide, and affecting hundreds of millions of people, according to the International Diabetes Federation.[2] A significant proportion of the affected individuals are undiagnosed and hence the microvascular and macrovascular complications of the disease are allowed to develop before appropriate management is started. Several factors are driving the increasing prevalence of type 2 diabetes, including population ageing, urbanisation, physical inactivity, poor eating habits and increasing rates of overweight and obesity. [3] These factors contribute to the increasing incidence of type 2 diabetes in the world in the next decades. This fact evidences the importance of better treatment options, early diagnosis, and effective prevention of this disease.[4]

The high prevalence of type 2 diabetes mellitus (T2DM) is especially observed in low- and middle-income countries where rapid changes in lifestyle, physical activity and eating habits have resulted in an increase in the number of complications associated with diabetes and have increased the burden on healthcare systems. Type 2 diabetes is strongly associated with poor glucose management, heart failure, increasing chronic renal disease and major cardiovascular events.[5] Diabetic kidney disease is a major contributor to the global rise in end-stage renal disease. The high cost to healthcare systems of managing diabetes further highlights the need for treatment options that provide not only adequate glycaemic control but also minimise the risk of cardiovascular and renal complications and provide long-term protection of key organs.

2. Pathophysiology of T2DM

The pathogenesis of type 2 diabetes mellitus (T2DM) is characterised by a complicated interaction of metabolic disorders involving several organs and physiological processes.[6] The genesis and progression of the disease are due to a number of interrelated abnormalities in glucose and energy metabolism, rather than only to diminished insulin secretion. These abnormalities, commonly referred to as the "ominous octet," include pancreatic β-cell dysfunction, impaired insulin action in peripheral tissues, increased hepatic glucose production, dysregulated glucagon secretion, altered incretin activity, enhanced renal glucose reabsorption, increased lipolysis, and abnormalities in central regulation of appetite and energy balance.[7] Taken together, these disorders increase the risk of microvascular and macrovascular complications, chronic hyperglycaemia, metabolic inflammation, and progressive β-cell failure.

a. Pancreatic Beta-Cell Exhaustion & Islet Dysfunction

The development of clinically apparent type 2 diabetes mellitus (T2DM) is directly correlated with progressive loss of pancreatic β-cell function and, ultimately, β-cell mass.[8] In the early stages of the disease, β cells try to compensate for peripheral insulin resistance by increasing insulin secretion and keeping blood glucose levels close to normal. However, prolonged exposure to high levels of glucose and free fatty acids leads to metabolic stress, a phenomenon referred to as glucolipotoxicity.[9] In pancreatic islets this situation contributes to increased oxidative stress, ER stress and inflammatory reactions, including activation of resident and infiltrating macrophages. With the progression of β-cell damage, the early phase of glucose-stimulated insulin secretion is impaired, leading to decreased insulin secretory capacity and increased β-cell death. These changes lead to a progressive loss of glycaemic control and progression from insulin resistance to established type 2 diabetes.[10]

b. Peripheral Insulin Resistance (Muscle and Adipose)

The main tissue for glucose disposal postprandially is skeletal muscle and reduced insulin signalling in this tissue is a major characteristic of type 2 diabetes mellitus (T2DM).[11] Insulin resistance causes reduced translocation of glucose transporter 4 (GLUT4) to the cell surface and decreases glucose uptake by disrupting intracellular signalling involving insulin receptor substrate-1 (IRS-1) and the phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) pathway. Poor insulin action also results in decreased normal inhibition of lipolysis in adipose tissue, leading to enhanced release of free fatty acids (FFAs) into the circulation.[12] The persistent elevation of circulating FFAs promotes their deposition in non-adipose tissues such as the liver, pancreatic islets, and skeletal muscle, where lipid-derived metabolites can negatively influence insulin signalling and lower insulin sensitivity. Thus, changes in the metabolism of adipose tissue and skeletal muscle contribute to the development of type 2 diabetes and further aggravate systemic insulin resistance.[13]

c. Hepatic Overproduction & Alpha-Cell Dysregulation

Physiologically, the rise in circulating insulin after a meal suppresses hepatic glucose production and contributes to maintaining normal blood glucose levels.[14] In type 2 diabetes mellitus (T2DM) insulin sensitivity in the liver is decreased and the capacity of insulin to suppress gluconeogenesis and glycogenolysis is thus diminished. This leads to an inappropriately high hepatic glucose output, especially in the fasting state, which greatly contributes to chronic hyperglycaemia. This metabolic derangement is exacerbated by an exaggerated release of glucagon and inappropriate pancreatic α-cell activity.[15] Reduced intra-islet insulin-mediated regulation of glucagon secretion could lead to inappropriate or chronic hyperglucagonemia, which leads to activation of hepatic glucagon receptors and increased glucose production. Dysregulated glucagon signalling and hepatic insulin resistance therefore work together to induce fasting hyperglycemia and the development of type 2 diabetes.[16]

d. Impaired Gut Incretin Response

In healthy individuals, intestinal incretin hormones such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are involved in the regulation of postprandial insulin secretion.[17] These hormones are a major contributor to the normal postprandial insulin response and augment glucose-dependent insulin secretion. In type 2 diabetes mellitus (T2DM), the incretin response is impaired as shown by changes in GLP-1 activity and decreased pancreatic β cell responsiveness to GIP. Decreased incretin signalling leading to increased insulin production after food intake causes poor postprandial glucose control. Incretin signalling is also involved in satiety and appetite regulation and defective incretin signalling may thus contribute to the abnormalities in energy intake and metabolic homeostasis that develop in type 2 diabetes.[18]

e. Renal Maladaptation & Central Nervous System Deficits

In T2DM , the kidneys and central nervous system also play a role in the development and maintenance of hyperglycaemia. Increased expression or activity of sodium-glucose cotransporter 2 (SGLT2) in the proximal tubules of the kidney enhances glucose reabsorption and reduces urinary glucose excretion.[19] This increased renal conservation of glucose may account for the persistence of elevated blood glucose levels. Impaired insulin and leptin signalling may also affect the hypothalamic systems controlling hunger and energy balance in parallel. Such changes may dampen satiety signals, encourage overeating, and interfere with normal regulation of energy expenditure. The complex pathophysiology and progression of type 2 diabetes involve dysregulated central metabolic signalling and aberrant renal glucose management.[20]

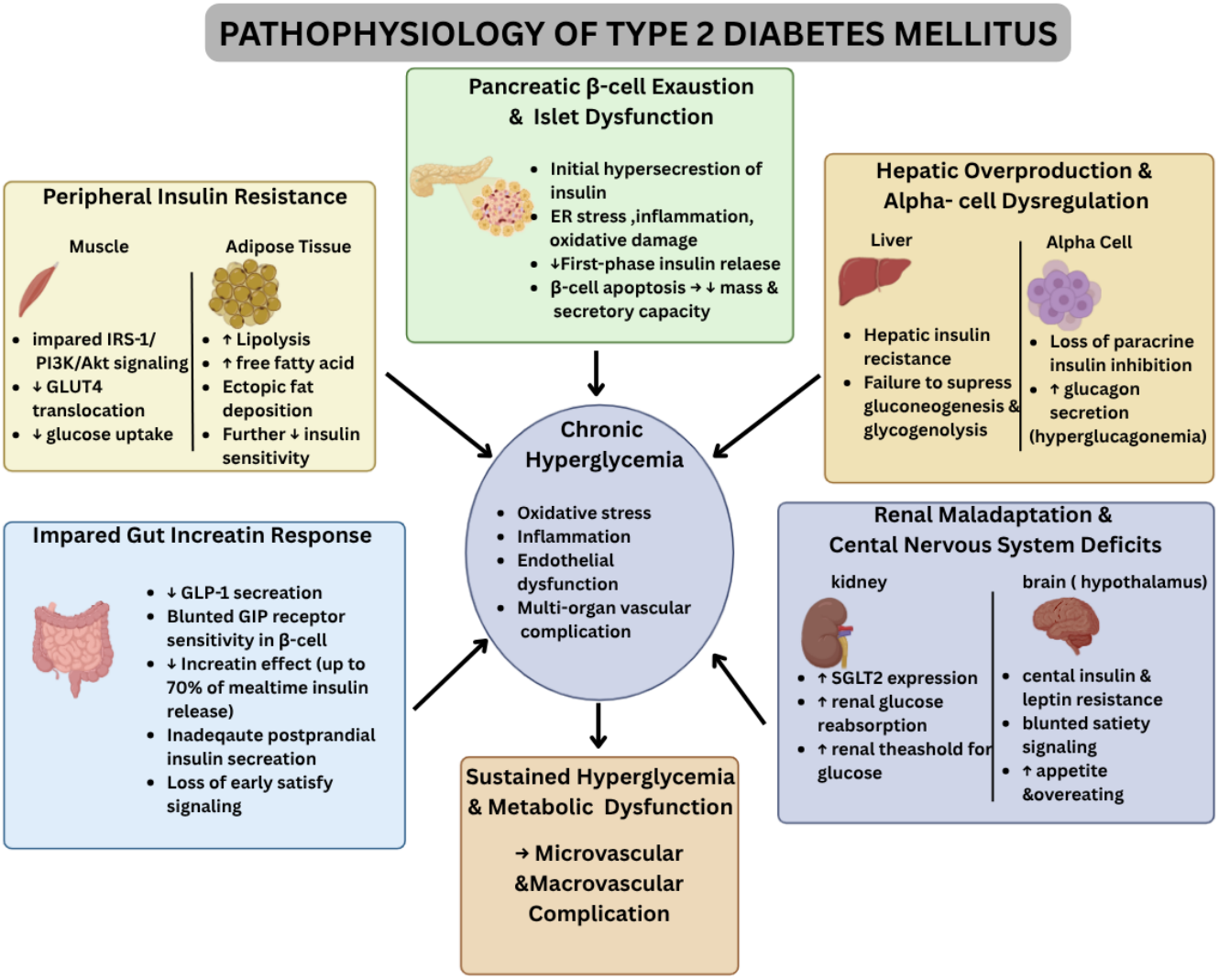


Figure_1: Pathophysiological Progression of β-Cell Dysfunction in Type 2 Diabetes Mellitus.

2.1 Evolution of Pharmacological Management

The treatment of type 2 diabetes mellitus (T2DM) has evolved considerably over the past few decades from a sole focus on glycaemic control to a more comprehensive strategy that encompasses metabolic, cardiovascular and renal outcomes.[21] In the past the main goals of drug treatment were to lower blood sugar and achieve target levels of glycated haemoglobin (HbA1c). Earlier therapies such as meglitinides, sulfonylureas and conventional insulin preparations were effective in reducing blood glucose but were often associated with side effects including hypoglycemia and weight gain.[22] Moreover, vigorous glucose reduction alone was not adequate to address the underlying risk for cardiovascular and renal disease. These limitations have helped in the development and adoption of newer therapy strategies that attempt to protect important organs and effectively control blood sugar levels while decreasing the likelihood of complications from diabetes.

The introduction of regulatory standards for cardiovascular outcome trials (CVOTs) assessing new glucose-lowering drugs has dramatically changed the therapeutic approach to type 2 diabetic mellitus (T2DM).[23] These trials showed that certain classes of treatment, especially glucagon-like peptide-1 (GLP-1) receptor agonists and sodium-glucose cotransporter 2 (SGLT2) inhibitors, can provide cardiovascular and renal benefits that are not limited to their effects on blood glucose. These agents have been associated with reductions in major adverse cardiovascular events (MACE), heart failure hospitalisations and progression of chronic renal disease in appropriate patient populations. Thus, contemporary diabetes management has moved to a more holistic, patient-centred approach, where therapeutic decisions are guided by body weight, metabolic status and cardiovascular and renal risk as well as glycaemic targets. This shift has promoted the use of therapies with broader cardiorenal and metabolic benefits in addition to effective glucose control.[24]

3. Therapeutic Targets in Type 2 Diabetes Mellitus

The multifactorial and multi-organ nature of type 2 diabetes mellitus (T2DM) has led to the identification of a number of molecular and physiological pathways that can be targeted therapeutically.[25] As knowledge of the causes of the illness has grown, drug development has

progressively moved beyond simply lowering blood glucose levels. Some of the physiological and molecular mechanisms of insulin resistance, β-cell dysfunction, abnormal glucagon signalling, altered renal glucose handling and disturbances in energy metabolism are emerging as targets of current therapeutic approaches. Along with treating the metabolic abnormalities that lead to the development of the condition and its complications, targeting these underlying mechanisms may provide a more holistic and effective approach to the management of type 2 diabetes.[26]

3.1 Insulin Resistance

Insulin resistance in peripheral tissues, especially skeletal muscle and adipose tissue, is one of the major causes of poor glucose disposal in type 2 diabetes mellitus (T2DM). Under physiological conditions, the greatest portion of postprandial glucose is taken up by skeletal muscle. In response to insulin, the phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) signalling cascade is activated that promotes effective glucose absorption by allowing the translocation of glucose transporter type 4 (GLUT4) from intracellular vesicles to the plasma membrane.[27]

In T2DM, chronic metabolic stress marked by increased circulating free fatty acids, oxidative stress and low-grade inflammation activates stress-responsive serine/threonine kinases, such as c-Jun N-terminal kinase (JNK) and protein kinase C (PKC). These kinases inhibit insulin receptor substrate-1 (IRS-1) by serine phosphorylation, which decreases downstream insulin signalling.[28] This disruption increases persistent hyperglycemia by impeding GLUT4 translocation consequently affecting glucose absorption in skeletal muscle.From a therapeutic point of view, the improvement of insulin sensitivity by targeting important nodes in the insulin signalling and energy metabolism pathways is promising. Thiazolidinediones increase insulin responsiveness by regulating lipid metabolism and adipocyte differentiation, through the activation of peroxisome proliferator-activated receptor-γ (PPAR-γ). Metformin, however, principally reduces blood sugar by stimulating AMP-activated protein kinase (AMPK) that enhances peripheral glucose utilisation and inhibits hepatic gluconeogenesis.[29]

3.2 *β*-Cell Dysfunction

Insulin resistance plays a key role in the metabolic dysfunction of type 2 diabetes mellitus (T2DM). However, continued hyperglycemia is mainly due to the progressive loss of pancreatic β-cell function. In early insulin resistance, β cells compensate through increased insulin secretion to preserve glucose homeostasis. [30] However, chronic exposure to high concentrations of glucose and free fatty acids leads to severe metabolic stress in beta cells, causing lipotoxicity and glucotoxicity. Increased demand for insulin production can trigger the unfolded protein response and endoplasmic reticulum (ER) stress, also excessive mitochondrial production of reactive oxygen species (ROS) is linked to sustained metabolic stress, which aggravates β-cell damage. Pancreatic β cells are extremely vulnerable to oxidative damage because they have a very weak antioxidant defence system. Chronic exposure to glucotoxic, lipotoxic and inflammatory environments may damage mitochondria, impair the production and secretion of insulin granules, and induce a progressive reduction of the release of glucose stimulated insulin especially in the first phases of insulin secretion. As the disease progresses, these metabolic disruptions may induce apoptosis, loss of cellular identity, and β-cell dysfunction, eventually resulting in a dramatic reduction in functional β-cell mass. Preservation of β-cell function has become a major goal in the treatment of type 2 diabetes. The incretin-based therapies, in particular the glucagon-like peptide-1 (GLP-1) receptor agonists and the dipeptidyl peptidase-4 (DPP-4) inhibitors, enhance glucose-dependent insulin secretion and may have other β-cell protective effects by reducing cellular stress and enhancing the pro-survival signalling. Thus, therapeutic approaches that reduce metabolic stress, while preserving β-cell viability and secretory function, may contribute to slowing the progressive decline in glucose homeostasis in type 2 diabetes.[31]

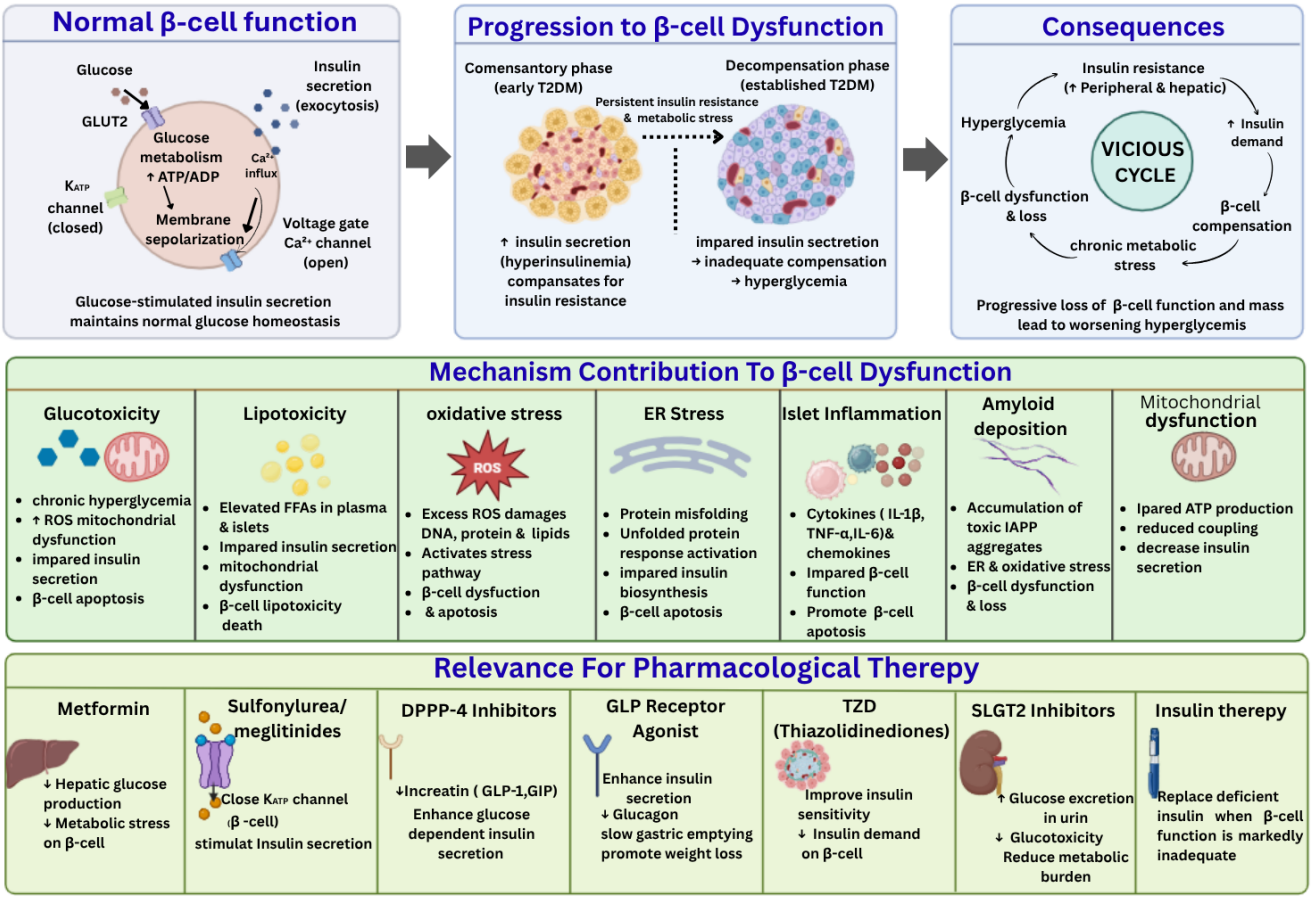


Figure_2: Integrated Pathophysiology of Type 2 Diabetes Mellitus: Insulin Resistance, β-Cell Dysfunction, and Metabolic Dysregulation

3.3 Incretin Pathway

The incretin axis is a key component of the gut-pancreas axis that regulates insulin secretion in response to food intake. The two major incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are mainly secreted by intestinal L cells and K cells, respectively. Following a meal, GLP-1 and GIP bind to and activate their own G protein-coupled receptors on pancreatic β cells, leading to intracellular signalling pathways involving exchange protein directly activated by cAMP 2 (EPAC2), protein kinase A (PKA) and cyclic adenosine monophosphate (cAMP).[32] Activation of these pathways results in improved postprandial glucose homeostasis and increased glucose-dependent insulin secretion. GLP-1 additionally has extra-pancreatic effects that may reduce food intake and facilitate weight management such as delayed gastric emptying and increased satiety. In type 2 diabetes mellitus (T2DM), the incretin effect is compromised by a decrease in GIP-mediated insulinotropic responses and alterations in GLP-1 activity, resulting in insufficient postprandial insulin secretion and suboptimal glucose control. The identification of incretin signalling as a major therapeutic target in type 2 diabetes has been prompted by these physiological changes. GLP-1 receptor agonists are direct GLP-1 receptor activators that augment glucose-dependent insulin secretion and exert additional effects on appetite and body weight, whereas dipeptidyl peptidase-4 (DPP-4) inhibitors prevent rapid enzymatic degradation of endogenous incretin hormones thus increasing their action . More recently, the therapeutic arena has been broadened by dual and multi-receptor agonists that target complementary incretin pathways with potential benefit for glycaemic control, weight loss and other metabolic outcomes. [33]

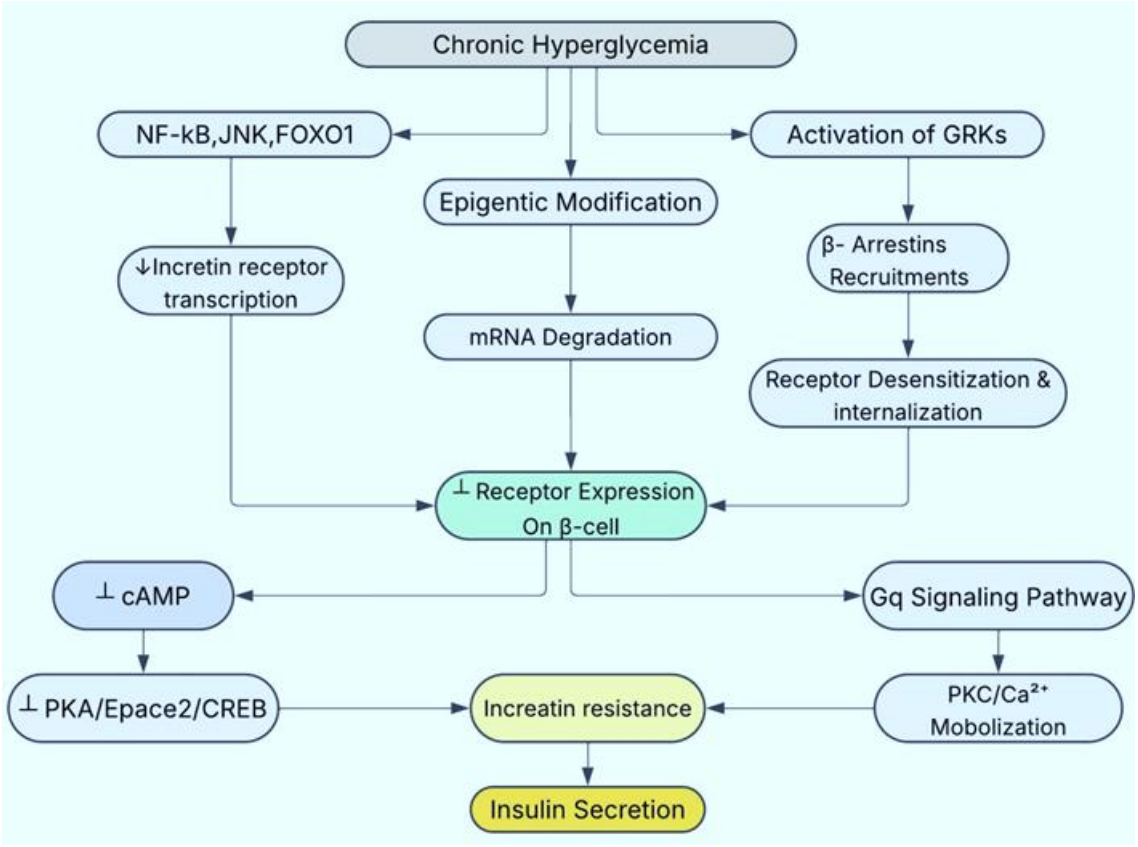


Figure_3: Molecular Mechanisms Underlying Incretin Resistance and Impaired Insulin Secretion in Type 2 Diabetes Mellitus

3.4 Renal Glucose Transport

The kidneys play a major role in glucose regulation through glomerular filtration and tubular reabsorption. In normal physiological conditions, urinary glucose loss is minimal since most of the glucose filtered by the glomeruli is reabsorbed by the proximal tubules. The majority of glucose reabsorption by the kidney is mediated by sodium-glucose cotransporter 2 (SGLT2), which is localised mainly in the early proximal tubule.[34] The rest is through sodium-glucose cotransporter 1 (SGLT1). An augmented renal glucose re-absorption capacity is associated with persistent hyperglycaemia in type 2 diabetes mellitus (T2DM) that favours glucose retention and contributes to the maintenance of hyperglycaemia. Pharmacological inhibition of SGLT2 lowers plasma glucose by increasing urine glucose excretion and decreasing glucose reabsorption through an insulin-independent mechanism. SGLT2 inhibitors have important cardiovascular and renal benefits in addition to glycaemic control, such as reducing intraglomerular pressure and, in appropriate patients, slowing the progression of chronic kidney disease. Targeting renal glucose reabsorption is a key therapeutic strategy in modern T2DM therapy, because SGLT2 inhibitors combine glucose-lowering action with greater cardiorenal protection.[35]

3.5 Hepatic Glucose Production

The liver is a key regulator of fasting blood glucose, providing glucose by glycogenolysis and gluconeogenesis. High insulin levels generally promote the synthesis and storage of glycogen and inhibit glucose production in the liver, especially after meals. This metabolic control is disturbed in type 2 diabetes mellitus (T2DM) by hepatic insulin resistance, which results in inappropriate continuing gluconeogenesis and glycogenolysis in spite of increased amounts of circulating insulin.[36] Nevertheless, some insulin-mediated pathways, especially those involving de novo lipogenesis via sterol regulatory element-binding protein-1c (SREBP-1c), may still be partially active. In addition, increased expression and activity of key gluconeogenic enzymes, including glucose-6-phosphatase (G6Pase) and phosphoenolpyruvate carboxykinase (PEPCK), augment hepatic glucose production and play an important role in fasting hyperglycemia . Thus, pharmacological strategies aimed to reduce excessive hepatic glucose production are an important part of the management of type 2 diabetes. The primary treatment, metformin, inhibits hepatic gluconeogenesis via pathways that include mitochondrial energy metabolism and AMP-activated protein kinase (AMPK)-dependent and -independent pathways. New approaches include glucagon receptor antagonism as a means of directly modulating aberrant hepatic glucose production.[37]

3.6 Glucagon Signaling

Glucagon is a 29-amino acid peptide hormone secreted by pancreatic α cells, and is a key counter-regulatory hormone to insulin to maintain glucose homeostasis. Normally a drop in blood sugar causes the release of

glucagon which leads to the activation of glucagon receptors on hepatocytes through a G protein coupled signalling cascade including cyclic adenosine monophosphate (cAMP) and adenylate cyclase. This signalling improves glucose availability by stimulating hepatic glycogenolysis and gluconeogenesis during fasting or hypoglycaemia.[38] In type 2 diabetes mellitus (T2DM), however, α-cell control becomes inappropriate, and inappropriate glucagon release may occur even in the presence of elevated blood glucose concentrations due to decreased intra-islet communication, including insufficient insulin-mediated suppression of glucagon secretion. Prolonged or excess glucagon activity increases hepatic glucose production and is also involved in postprandial hyperglycemia and fasting. Thus, therapeutic regulation of glucagon signalling provides a new approach to the management of type 2 diabetes. GLP-1 receptor agonists may reduce inappropriate glucagon secretion in a glucose-dependent manner. Dual- and multi-receptor agonists with additional glucagon receptor activity are under investigation, and may be useful in improving glucose metabolism, increasing energy expenditure and reducing hepatic steatosis.[39]

3.7 Inflammation and Oxidative Stress

Type 2 diabetes is characterised by systemic, low-grade inflammation (also called "metainflammation") that originates in nutrient-saturated visceral adipose tissue. Local hypoxia in hypertrophic adipocytes leads to cell death and the release of danger-associated molecular patterns. This drives tissue macrophage infiltration and polarisation from an anti-inflammatory "M2" to a pro-inflammatory "M1" phenotype. The activated macrophages and hypertrophic adipocytes produce a high amount of pro-inflammatory cytokines such as Tumour Necrosis Factor-alpha ("TNF"-α), Interleukin-6 ("IL-6") and Interleukin-1 beta ("IL-1" β). [40] These cytokines enter systemic circulation and interfere with insulin signalling in peripheral organs. This inflammatory cascade is directly related to systemic oxidative stress, in which hyperglycemia induces mitochondrial electron leakage to produce excess superoxide radicals. This imbalance of excess generation of reactive oxygen species over cellular antioxidant defences damages the endothelial cells and accelerates the development of microvascular and macrovascular complications.[41]

4. Current Pharmacological Therapies

The pharmacological treatment of type 2 diabetic mellitus (T2DM) encompasses a variety of oral and injectable glucose lowering medications that operate through different molecular and physiological pathways. The decisions on which treatments to use are increasingly driven not only by an agent's ability to achieve and maintain glycaemic control, but also by its effects on body weight, cardiovascular outcomes and renal function. Therefore, in patients with relevant comorbidities or risk factors, modern therapeutic approaches aim at individualised treatment and the use of drugs with proven cardiovascular and renal benefits. This larger strategy represents a shift from the conventional, glucose-centric management to holistic care aimed at reducing diabetes-related complications and improving long-term clinical outcomes.[42]

4.1 Biguanides

Mechanism of Action

Metformin is a well-known biguanide and remains the first-line drug for type 2 diabetic mellitus (T2DM). Its main action in lowering blood sugar is to suppress excessive hepatic glucose output.[43] At the cellular level, metformin can partially inhibit mitochondrial respiratory-chain complex I, which can change the energy state of the cell and increase the AMP-to-ATP ratio. Together, these changes reduce hepatic gluconeogenesis through AMP-activated protein kinase (AMPK) signalling and other AMPK-independent pathways. In addition, metformin decreases the expression and activity of the rate-limiting enzymes of gluconeogenesis, namely glucose-6-phosphatase (G6Pase) and phosphoenolpyruvate carboxykinase (PEPCK). In addition, it has been suggested that metformin modulates the hepatic redox state and restricts the conversion of gluconeogenic substrates, such as lactate and glycerol, to glucose by inhibiting mitochondrial glycerol-3-phosphate dehydrogenase. Metformin also increases peripheral insulin sensitivity and glucose utilisation in addition to its effects on the liver. Changes in intestinal glucose metabolism and gut microbiota may also contribute to its metabolic effects. When combined, these activities do not directly increase insulin secretion but improve overall glycaemic management and decrease hepatic glucose production.[44]

4.2 Sulfonylureas

Mechanism of Action

Oral insulin secretagogues, such as sulfonylureas (eg, glibenclamide, gliclazide, and glimepiride) help lower blood sugar by increasing secretion of insulin from pancreatic β-cells.[45] They essentially work by binding to the sulfonylurea receptor 1 (SUR1), a regulatory component of the ATP-sensitive potassium (K_ATP) channels on the β-cell membrane. Binding of these drugs results in closure of the K_ATP channels, reducing potassium efflux and depolarising the membrane. This depolarisation opens voltage dependent calcium channels, increasing calcium entry into the β-cell and causing exocytosis of insulin-containing granules. The longer contact with the target receptor of sulfonylureas is often associated with a more sustained stimulation of insulin secretion than is observed with meglitinides. Crucially, their risk of hypoglycaemia is increased by the fact that their insulin secretory effect is not strictly dependent on the current blood glucose content. Long-term insulin stimulation, especially when used over a long period of time, may also encourage weight gain.[46]

4.3 Meglitinides

Mechanism of Action

Meglitinides are short-acting oral insulin secretagogues that primarily act to reduce postprandial hyperglycemia through stimulating the release of insulin from

pancreatic β-cells. Examples of such drugs are repaglinide and nateglinide.[47] They bind to specific sites on the regulatory subunit SUR1 and modulate the ATP-sensitive potassium (K_ATP) channels of the β-cell membrane. This interaction causes the K_ATP channels to close. This results in reduced potassium outflow and depolarisation of the membrane. This depolarisation causes the opening of voltage dependent calcium channels and calcium ions enter the β-cells . This causes an increase in intracellular calcium which in turn increases the exocytosis of insulin-containing secretory granules and increases insulin production. The short-acting insulinotropic effects of meglitinides are explained by their binding to and dissociation from their target channels within a relatively short time span. Their pharmacological properties enable them to decrease persistent stimulation of insulin secretion and at the same time to restrain postprandial increases in glucose. However, adequate functional pancreatic β-cell mass is required for their efficacy.[58]

4.4 Thiazolidinediones

Mechanism of Action

Thiazolidinediones (TZDs), such as pioglitazone and rosiglitazone, are potent and selective ligands for the nuclear hormone receptor peroxisome proliferator-activated receptor-gamma (PPAR-γ), which is expressed primarily in adipose tissue and, to a lesser extent, in liver and skeletal muscle. Binding of a ligand causes a conformational change that allows heterodimerisation of PPAR-γ with the retinoid X receptor (RXR). This complex binds to certain peroxisome proliferator response elements (PPREs) in DNA and changes the transcription of genes involved in the metabolism of fats and carbohydrates. TZDs promote adipocyte differentiation, resulting in a shift in fat storage from hepatocytes, skeletal muscle and visceral depots to subcutaneous adipose tissue. Decreased ectopic fat deposition results in restored systemic insulin sensitivity, increased GLUT4 expression, increased circulating adiponectin levels and decreased systemic pro-inflammatory cytokines such as TNF-α.[49]

4.5 *α*-Glucosidase Inhibitors

Mechanism of Action

Alpha-glucosidase inhibitors (AGIs) such as acarbose, voglibose and miglitol are a class of oral antidiabetic agents that act primarily by reducing postprandial blood glucose by decreasing the breakdown and absorption of dietary carbohydrates in the small intestine.[50]These drugs reversibly inhibit the intestinal brush-border α-glucosidase enzymes (e.g., sucrase, maltase, isomaltase, glucoamylase) involved in the final stages of carbohydrate digestion. The inhibition of these enzymes decreases the breakdown of complex carbohydrates and disaccharides into absorbable monosaccharides (especially glucose). That means glucose is absorbed into the blood more slowly, so there's less need for insulin and less spike in blood sugar after meals. AGIs have little inherent risk of hypoglycemia and do not generally promote weight gain when used alone, as they do not directly stimulate pancreatic β-cells or increase circulating insulin levels. Thus, the amount they lower blood sugar depends mainly on how many carbohydrates are in the meal.[51]

4.6 DPP-4 Inhibitors

Mechanism of Action

Sitagliptin, linagliptin, saxagliptin and alogliptin are the dipeptidyl peptidase-4 (DPP-4) inhibitors or gliptins. They work by blocking the enzyme dipeptidyl peptidase-4 (DPP-4), which rapidly degrades glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), increasing the activity of endogenous incretins.[52] In physiological conditions, active GLP-1 and GIP are rapidly inactivated by DPP-4-mediated cleavage leading to very short half-lives in circulation. Pharmacologic inhibition of this enzyme increases the availability and duration of action of natural incretin hormones. DPP-4 inhibitors have been shown to improve postprandial and overall glycaemic control through increased glucose-dependent insulin secretion from pancreatic β cells and decreased inappropriate glucagon secretion from α cells. DPP-4 inhibitors are generally associated with a low risk of hypoglycaemia in the absence of insulin or insulin secretagogues, due to a glucose-dependent effect on insulin secretion. They are useful as an oral treatment option for patients where hypoglycemia and weight gain are a crucial therapeutic consideration as they are generally weight neutral.[53]

4.7 SGLT2 Inhibitors

Mechanism of Action

Empagliflozin, dapagliflozin, canagliflozin, and sotagliflozin are all sodium-glucose cotransporter 2 (SGLT2) inhibitors, or gliflozins. These drugs lower blood glucose in an insulin-independent manner by decreasing renal glucose reabsorption in the proximal tubule. SGLT2 is predominantly expressed in the apical membrane of early proximal tubular segments and is responsible for the majority of glucose reabsorbed by the kidneys. Pharmacological inhibition of SGLT2 reduces blood glucose levels via a reduction in the renal threshold for glucose reabsorption and an increase in urinary glucose excretion.[54] SGLT2 inhibitors also decrease salt reabsorption, leading to natriuresis and osmotic diuresis, which may reduce blood pressure, plasma volume and cardiac preload and afterload. Increased sodium delivery to the macula densa also favours reversal of tubuloglomerular feedback and hence decreases intraglomerular pressure. These haemodynamic and metabolic effects account for the cardiovascular and renal benefits of SGLT2 inhibitors, such as a reduced risk of heart failure hospitalisation and a slower progression of chronic kidney disease in eligible patient populations.

4.8 GLP-1 Receptor Agonists

Mechanism of Action

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are a class of pharmacological substances that include semaglutide, dulaglutide, liraglutide, and lixisenatide,

and are designed to mimic native GLP-1 but with a substantially prolonged duration of action.[55] Structural changes (i.e., substitution of amino acids or conjugation of a fatty acid side-chain) increase the resistance of these peptide analogues to rapid degradation by dipeptidyl peptidase-4 (DPP-4). In some medicines these changes also enhance binding to circulating albumin. Activation of GLP-1 receptors on pancreatic α cells reduces inappropriate glucagon secretion (especially postprandial) whereas activation of GLP-1 receptors on pancreatic β cells increases glucose-dependent insulin secretion. Furthermore, GLP-1 receptor activation slows gastric emptying, thus decreasing the rate of glucose entry into the circulation and improving postprandial glucose excursions. Furthermore, GLP-1 receptor signalling within the CNS regulates neural pathways that are involved in appetite and satiety, which leads to a reduction in appetite and food intake. [56] GLP-1 RAs are a key component of the current pharmacologic management of type 2 diabetes, due to their synergistic effects that not only control blood glucose levels but also induce clinically meaningful weight loss.

4.9 Insulin Therapy

Mechanism of Action

Insulin exerts its metabolic effects by binding to the extracellular α-subunits of the transmembrane receptor tyrosine kinase insulin receptor, which is most widely expressed in the liver, skeletal muscle and adipose tissue. Ligand binding causes conformational changes leading to activation of the intrinsic tyrosine kinase activity of the receptor and autophosphorylation of intracellular β-subunits.[57] The activated receptor then phosphorylates insulin receptor substrate proteins, mainly IRS-1 and IRS-2, which are crucial signalling intermediates for downstream metabolic pathways. One of the main mechanisms involved is the phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) cascade. Upon IRS activation, PI3K produces phosphatidylinositol-3,4,5-trisphosphate (PIP3) which activates Akt. Akt enhances cellular glucose uptake in skeletal muscle and adipose tissue by stimulating the translocation of the glucose transporter 4 (GLUT4) to the plasma membrane. In the liver, Akt stimulates glycogen synthesis by inhibiting glycogen synthase kinase-3 (GSK-3) and inhibits forkhead box O1 (FOXO1)-dependent transcription of gluconeogenic enzymes such as phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase). Insulin also promotes storage of food by inhibiting lipolysis in adipose tissue and stimulating protein synthesis via mammalian target of rapamycin (mTOR)-related signalling. These combined processes enable the body to use and store glucose and to promote the synthesis of proteins and fats and, in effect, to change the metabolism of the entire body into an anabolic and energy-storing state.[58]

Table no. 01: Summary of established pharmacological therapies for type 2 diabetes mellitus [59-61]

Drug class	Mechanism of action	Clinical efficacy	Advantages	Limitations
Biguanides	Reduces hepatic gluconeogenesis, primarily through effects on cellular energy metabolism and AMPK-related pathways; also improves peripheral insulin sensitivity and glucose utilization.	HbA1c reduction: **~1–1.5%**	Effective, inexpensive, extensive clinical experience; minimal hypoglycemia when used alone; generally weight-neutral or associated with modest weight loss.	Gastrointestinal adverse effects; vitamin B12 deficiency with prolonged use; dose limitations in renal impairment; rare lactic acidosis.
Sulfonylureas	Bind to SUR1 on pancreatic β-cell KATP channels, causing channel closure, membrane depolarization, Ca^{2+} influx, and insulin release.	HbA1c reduction: **~1–1.5%**	Rapid and effective glucose lowering; inexpensive; widely available.	Hypoglycemia; weight gain; efficacy decreases with progressive β-cell dysfunction; insulin secretion is relatively glucose-independent.
Meglitinides	Bind to β-cell KATP-channel components and stimulate rapid insulin secretion, particularly around meals.	HbA1c reduction: **~0.5–1.0%**	Rapid onset and short duration; useful for postprandial glucose control; flexible meal-related dosing.	Hypoglycemia and weight gain; multiple daily dosing; less convenient than several newer therapies.

Thiazolidinediones (TZDs)	Activate PPAR-γ, modifying transcription of genes involved in glucose and lipid metabolism and increasing insulin sensitivity in adipose tissue, skeletal muscle, and liver.	HbA1c reduction: **~0.8–1.2%**	Durable glucose-lowering effect; improves insulin sensitivity; low intrinsic hypoglycemia risk when used alone; inexpensive generic options.	Weight gain; edema/fluid retention; increased heart-failure risk; fracture risk; slow onset of action.
α-Glucosidase Inhibitors	Inhibit intestinal brush-border α-glucosidases, delaying carbohydrate digestion and glucose absorption and thereby reducing postprandial glucose excursions.	HbA1c reduction: **~0.5–0.8%**	Primarily targets postprandial hyperglycemia; low risk of hypoglycemia when used alone; generally weight-neutral.	Flatulence, abdominal discomfort, and diarrhea; frequent dosing; relatively modest glucose-lowering efficacy; gastrointestinal tolerability can limit adherence.
DPP-4 Inhibitors	Inhibit DPP-4, preventing degradation of endogenous GLP-1 and GIP. Increased incretin activity enhances glucose-dependent insulin secretion and suppresses glucagon secretion.	HbA1c reduction: **~0.5–0.8%**	Weight-neutral; low risk of hypoglycemia; oral once-daily administration; generally well tolerated.	Modest glucose-lowering efficacy; cost may be higher than metformin or sulfonylureas; limited weight-loss effect; should not generally be combined with GLP-1 receptor agonists.
SGLT2 Inhibitors	Inhibit SGLT2 in the proximal renal tubule, reducing glucose and sodium reabsorption and increasing urinary glucose excretion.	HbA1c reduction: **~0.5–1.0%**	Weight loss; low hypoglycemia risk when used without insulin/insulin secretagogues; cardiovascular and renal benefits in appropriate high-risk populations.	Genital mycotic infections; volume depletion; increased risk of euglycemic ketoacidosis in susceptible patients; efficacy decreases with declining renal function.
GLP-1 Receptor Agonists	Activate GLP-1 receptors, increasing glucose-dependent insulin secretion, reducing glucagon secretion, slowing gastric emptying, and increasing satiety.	HbA1c reduction: **~1.0–2.0%**, depending on agent and dose	Strong glucose-lowering efficacy; substantial weight loss with several agents; low intrinsic hypoglycemia risk; cardiovascular benefit demonstrated for selected agents.	Gastrointestinal adverse effects, particularly nausea and vomiting; injectable administration for most agents; higher cost; contraindications/precautions in selected patients.
Insulin Therapy	Replaces endogenous insulin, promoting glucose uptake in skeletal muscle and adipose tissue, suppressing hepatic glucose production	**Potentially unlimited;** highly effective reduction of hyperglycemia and HbA1c when appropriately titrated.	Most potent glucose-lowering therapy; essential when there is severe insulin deficiency or marked hyperglycemia; can be used at any stage of T2DM	Hypoglycemia; weight gain; injections and glucose monitoring; treatment complexity; risk of dosing errors and adherence difficulties.

5. Combination Pharmacotherapy

5.1 Injectable Combination Therapy

Injectable combination treatment is the parenteral administration of two or more active therapeutic drugs by subcutaneous, intravenous or intramuscular injection. This approach is particularly important for biologic and macromolecular drugs such as proteins, peptides and monoclonal antibodies with potentially low oral bioavailability or significant gastrointestinal degradation. Thus, parenteral administration ensures consistent systemic exposure and enables rapid or regulated drug delivery depending on the route. Hence, injectable combination therapies have become important in a number of therapeutic areas including endocrinology, oncology and treatment of severe infections. One important example is the fixed-ratio combination of basal insulin and glucagon-like peptide-

1 receptor agonists (GLP-1 RAs) in type 2 diabetes mellitus. In these combinations, GLP-1 RA enhances glucose-dependent insulin secretion, suppresses glucagon release and constrains postprandial glucose excursions, while basal insulin primarily improves fasting glycaemic control by reducing excessive hepatic glucose synthesis. These medications work together to improve overall glycaemic control and reduce the weight gain often seen with insulin therapy.[62] Injectable combination regimens in oncology can utilise monoclonal antibodies that target different immune checkpoints such as programd cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) to enhance antitumor immune responses via complementary mechanisms. In some severe systemic infections, intravenous combinations of antimicrobial drugs such as an aminoglycoside and an antipseudomonal β-lactam may be used to give complementary antibacterial activity and broader antimicrobial coverage. Overall, when oral administration is contraindicated or when systemic exposure to multiple drugs is desired, injectable combination therapy offers an effective approach to combine drugs with different mechanisms.[63]

5.2 Fixed-Dose Combinations

Fixed dose combinations (FDCs) are pharmaceutical formulations containing two or more active pharmaceutical ingredients (APIs) in specific doses or ratios in a single dosage form. Depending on the formulation, FDCs can be prepared as co-formulated liquid preparations, capsules with multiparticulate systems or conventional or bilayer tablets. Creation of the interactions between APIs or excipients may influence the stability, manufacturability and drug release of the product.[64] Thus, a comprehensive evaluation of the physicochemical compatibility of the various components is necessary. It is therefore important to identify possible incompatibilities during formulation development such as Maillard reactions, eutectic formation or other solid-state interactions. A number of formulation and manufacturing strategies may be used to minimise interactions and achieve the desired drug-release profiles such as multilayer compression, separation by inert excipient barriers and the application of functional polymeric coatings to multiparticulate systems. In the clinic, FDCs can make drug treatment easier by reducing the number of pills or injections a person has to take and by simplifying how often the drug is taken. Development of a single-dose treatment that combines several medicines may help improve treatment adherence by reducing the likelihood of patients taking only one part of a recommended combination regimen. However, a disadvantage of FDC therapy is the reduced flexibility for the individual dose control. If adverse effects, change in therapeutic response or alteration of organ function e.g. deterioration of renal function necessitate this, it may not be possible to alter the dose of a single drug without changing the complete formulation. In such cases the FDC may need to be replaced by its constituent parts to allow for greater dose optimisation. Therefore, while FDCs can offer important benefits in terms of convenience and compliance, their use should be assessed in light of the need for dose titration and patient specific therapeutic requirements.[65]

5.3 Rational Sequencing of Therapy

The term "rational sequencing of pharmacological therapy" refers to an evidence-based approach, involving initiation, escalation, switching or termination of therapy according to the evolution of type 2 diabetes mellitus (T2DM), in relation to treatment response, relevant biomarkers, comorbidities and specific patient features.[66] If proper glycaemic control is not achieved, treatment can be optimised by adding drugs with complementary mechanisms of action rather than increasing the dose of a single drug until the maximum tolerated dose is reached. The response to treatment should be assessed at appropriate intervals, usually within a few months of the start of therapy or a change in therapy, to determine whether the desired therapeutic goals are being achieved on the current regimen. If sufficient control is not achieved, intensification of treatment should be done immediately rather than continuing an ineffective regimen for an extended period.

In the modern T2DM care, treatment selection based on a patient-centered and comorbidity approach is increasingly important.[67] Hence, the presence of cardiovascular disease, heart failure, chronic renal disease, obesity and other clinically important diseases influences the choice of further medication in addition to glycated haemoglobin (HbA1c) or other markers of glycaemic management. For example, sodium-glucose co-transporter 2 (SGLT2) inhibitors are particularly beneficial in patients with heart failure or chronic kidney disease because of demonstrated cardiovascular and renal benefits, while glucagon-like peptide-1 receptor agonists (GLP-1 RAs) could be the initial treatment of choice when important treatment goals include weight loss or reduced cardiovascular risk. Crucially, when reassessing the treatment plan on a regular basis, glycaemic control, organ function, side effects, adherence and new contraindications should all be considered. This continuous assessment allows prompt escalation, switching or de-escalation of therapy during the course of type 2 diabetes and encourages the continuation of an effective and customised therapeutic approach.[68]

6. Emerging Pharmacological Therapies

Modern pharmaceutical approaches for Type 2 Diabetic Mellitus (T2DM) are increasingly targeting multiple interconnected metabolic pathways rather than one particular molecular target. Multi-receptor agonists and co-agonists are in particular development to simultaneously target complementary endocrine pathways regulating body weight, energy metabolism, appetite and glucose homeostasis. These drugs combine the effects of several hormonal pathways into one therapeutic strategy and may improve glycaemic control and metabolic health better than traditional single-target medicines. These approaches constitute a crucial

step toward the development of future T2DM treatments.[69]

6.1 Dual GIP/GLP-1 Receptor Agonists

A major advance in incretin-based therapy of type 2 diabetes mellitus (T2DM) is the application of dual glucose-dependent insulinotropic polypeptide (GIP)/glucagon-like peptide-1 (GLP-1) receptor agonists. These substances have the combined metabolic actions of two endogenous gut-derived hormones important in postprandial glucose control by activating both the GIP and GLP-1 receptors. Incretins GIP and GLP-1 are important mediators of the incretin effect in physiological conditions by potentiating glucose-dependent insulin secretion after food intake. Dual-receptor agonists are designed to activate both signalling pathways to exert complementary effects on body weight, energy homeostasis and glucose metabolism compared with selective GLP-1 receptor agonists. Activation of the GLP-1 receptor, particularly in the postprandial state, suppresses inappropriate glucagon secretion and enhances glucose-dependent insulin secretion from pancreatic β cells. GLP-1 receptor signalling also decreases food intake and promotes weight loss by slowing gastric emptying and influencing central neuronal circuits related to hunger and satiety . In contrast, the activation of the GIP receptor is involved in the metabolism of adipose tissue and induces insulin secretion in a glucose-dependent manner . GIP signalling may enhance insulin sensitivity in adipose tissue and may help to control and store excess nutrients more effectively. It also helps to regulate energy balance and, in cases of low blood glucose, may contribute to the liberation of glucagon.[70]

a) Tirzepatide

Tirzepatide is a synthetic 39-amino acid peptide with dual agonism on glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) receptors. Its structure has been modified to provide sustained stimulation and extended activity to both incretin pathways.[71]

Pharmacokinetics: Following subcutaneous administration, tirzepatide is absorbed slowly with peak plasma concentrations achieved in 8 to 72 hours and with an absolute bioavailability of approximately 80%. Drug exposure is comparable after injection into the upper arm, thigh, or abdomen and steady-state concentrations are usually obtained after about four weeks of once-weekly dosing. Tirzepatide is highly bound to serum albumin and has an apparent volume of distribution of ~10.3 L, mainly because of the presence of the C20 fatty-acid side chain, which leads to prolonged systemic exposure. Tirzepatide is not significantly metabolised by CYP450 enzymes. Tirzepatide is metabolised primarily via proteolysis of the peptide backbone, oxidation of the fatty-acid moiety, and hydrolysis. Excretion of metabolites occurs both by renal and faecal routes. Its low clearance of approximately 0.06 L/h and elimination half-life of approximately 5 days support weekly dosing. Overall exposure is not significantly affected by age, gender, body weight, renal or hepatic impairment. However, tirzepatide may temporarily affect the absorption of oral medications, particularly oral hormonal contraceptives, when treatment is initiated and during dose escalation due to the slowing of stomach emptying.[72]

6.2 Oral GLP-1 Receptor Agonists

The advent of oral GLP-1 receptor agonists represents a major advance in incretin-based medicine and provides an alternative to injectable GLP-1 receptor agonists. However, oral administration of peptide-based GLP-1 therapies is problematic since these molecules can be degraded by intestinal and gastric proteolytic enzymes, may be unstable in the gastrointestinal environment and typically have poor absorption across the intestinal mucosa due to their hydrophilic nature and large molecular size. Recent advances have focused on the development of orally active small-molecule GLP-1 receptor agonists that overcome the limitations of peptide delivery, and the improvement of gastrointestinal absorption of peptide-based GLP-1 receptor agonists through proprietary formulation technologies.[73]

6.2.1 Absorption-Enhanced Peptide Co-Formulation (SNAC Technology)

One of the most proven ways for oral delivery of peptide-based GLP-1 receptor agonists is co-formulation with a permeation-enhancing excipient, sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC). SNAC locally raises the pH of the stomach after the breakdown of the tablets in the stomach, thereby inhibiting the activity of acid-sensitive proteolytic enzymes such as pepsin and reducing peptide breakdown. Additionally, SNAC transiently interacts with the gastric mucosal membrane and increases the membrane fluidity. This allows the intact peptide to pass through cells into the systemic circulation without serious damage to the epithelial tight junctions. However, the oral bioavailability of peptide formulations remains very low, typically in the range of 0.4-1.0% despite these absorption enhancing properties. Certain conditions are required to improve the absorption of the drug . For example , the pill should be taken on an empty stomach after waking up with a small amount of plain water and no food ,drink , or other oral drugs for at least half an hour after dosing . This approach has now enabled oral delivery of peptide based GLP-1 receptor agonists but the low bioavailability and tight administration requirements still constitute major drawbacks .[74]

6.2.2 Non-Peptide Small-Molecule GLP-1 Receptor Agonists

To overcome some of the limitations of oral peptide-based formulations such as poor bioavailability and strict dosage requirements, small-molecule non-peptide GLP-1 receptor agonists have been developed. An example of this new type is the synthetic, low-molecular-weight drug orforglipron, which enhances downstream cyclic adenosine monophosphate (cAMP)-dependent signalling and directly activates the human GLP-1 receptor . These compounds do not have peptide bonds and are therefore less susceptible to degradation

by gastrointestinal proteolytic enzymes such as pepsin, trypsin and chymotrypsin, unlike peptide agonists. Furthermore, their small molecular size and chemical stability are compatible with oral absorption and systemic exposure. Therefore, small-molecule GLP-1 receptor agonists may offer effective once-daily oral treatment without the strict fasting, water-volume or post-dose administration restrictions, compared to some oral peptide formulations. This simplified dose profile may enhance treatment convenience, and perhaps improve long-term adherence, for patients requiring incretin-based therapy.[75]

6.3 Glucagon Receptor-Based Therapies

Targeting the glucagon receptor (GCGR) for therapeutics has great potential for next-generation metabolic therapeutics. Historically, glucagon has been viewed as a counter-regulatory hormone that increases blood glucose, but its physiological effects include regulation of energy expenditure, hepatic lipid metabolism and hunger. This enhanced knowledge of glucagon biology has aided in the design of treatment strategies to modulate GCGR signalling through either selective receptor antagonism or co-activation of glucagon and other metabolic hormone receptors. The possible use of these strategies in the treatment of metabolic diseases such as the metabolic dysfunction-associated steatohepatitis (MASH) is under investigation with the aim to increase hepatic lipid metabolism, decrease body weight, and improve glucose homeostasis. Research on manipulation of glucagon receptor signalling is important to increase the number of therapy options for type 2 diabetes and related metabolic diseases.[76]

Pharmacological Rationale and Physiological Mechanisms

The glucagon receptor (GCGR) is a class B G protein-coupled receptor that is expressed mainly in liver, but is also expressed in other tissues such as kidney, heart, and central nervous system. GCGR is the primary receptor by which glucagon mediates its metabolic activities. Hepatocyte GCGR activation induces hepatic lipids utilisation, and may also decrease intrahepatic fat storage by inducing fatty acid oxidation and inhibiting pathways involved in lipid synthesis. Glucagon signalling may also improve thermogenic processes and increase whole-body energy expenditure in combination with suitable metabolic therapies and might be helpful in decreasing body weight.Conversely, selective activation of GCGR is expected to increase blood glucose levels via increased hepatic glycogenolysis and gluconeogenesis. This potential hyperglycaemic effect has led to the creation of multi-receptor agonists that combine glucagon action with GLP-1 and/or GIP receptor signalling. GLP-1 and GIP pathway activation increases glucose-dependent insulin production and may counteract the glucose-raising effects of glucagon. The aim of this complementary pharmaceutical approach is to enhance glycaemic control, while maintaining the positive effects of glucagon on lipid metabolism, energy expenditure and hepatic steatosis. Therefore, glucagon-containing multi-agonists are being investigated as potential treatment options for obesity, type 2 diabetes and associated metabolic diseases.[77]

6.4 β-Cell-Protective and Regenerative Therapies

Key aspects of diabetes mellitus include pancreatic β-cell dysfunction, metabolic stress and a progressive loss of functional β-cell mass, all of which lead to a worsening glycaemic control. Hence, novel therapeutic approaches aim to induce restoration of β-cell mass or to ensure survival and function of the remaining β cells. Immunomodulatory therapies have been explored to diminish autoimmune destruction of pancreatic β cells in type 1 diabetes mellitus.[78] For example, teplizumab, an anti-CD3 monoclonal antibody directed against activated T cells, has demonstrated the potential to prevent progression to clinical stage 3 type 1 diabetes in high-risk subjects with preservation of endogenous insulin secretion. Furthermore, the use of anti-inflammatory agents, such as Janus kinase (JAK) inhibitors like baricitinib, are being investigated for their ability to mitigate cytokine-induced cellular stress and downstream pathways contributing to β-cell damage and death. Besides the classic glucose-lowering medication, β-cell preservation and regeneration are interesting avenues for disease-modifying therapy, however many of these approaches are still in research.

To overcome the limited regenerative potential of mature human pancreatic β cells, pharmacological strategies are being explored to promote controlled β-cell proliferation and restore insulin-producing capacity. Inhibition of dual-specificity tyrosine-phosphorylation-regulated kinase 1A (DYRK1A) with compounds such as harmine may promote β-cell cycle progression via modification of cell-cycle regulatory pathways involving nuclear factor of activated T cells (NFAT) and cyclin-dependent kinase inhibitors such as p16 and p18. Preclinical data suggest that combining GLP-1 receptor agonists and DYRK1A inhibitors may lead to increased β-cell proliferation compared to either strategy alone.Another possible approach is cellular reprogramming or trans differentiation, in which non-β pancreatic cells are converted to β-like cells that secrete insulin. The possibility of using key transcription factors involved in pancreatic β-cell identity and maturation, including musculoaponeurotic fibrosarcoma oncogene homolog A (MAFA), neurogenin-3 (NGN3) and pancreatic and duodenal homeobox 1 (PDX1), to trigger this conversion has been examined. Laboratory studies have centred on reprogramming glucagon-producing α cells into insulin-producing β-like cells, a possible non-transplant strategy to restore endogenous insulin secretion. Pharmacological β-cell proliferation and cellular reprogramming are promising approaches for future disease-modifying treatments in diabetes, although these approaches are largely experimental.[79]

6.5 Stem Cell-Based Therapy

Stem cell-based therapies are now being developed as a viable disease-modifying strategy for diabetes, with the aim of restoring functional insulin-producing β-cell mass rather than just lowering glucose. This approach may be most useful for patients with type 1 diabetes

mellitus and advanced type 2 diabetes mellitus with significant β-cell dysfunction. A major disadvantage of traditional islet transplantation is the lack of available, suitable donor tissue of consistent quality. Progress in stem cell biology has provided an alternative by allowing the creation of insulin-producing cells from induced pluripotent stem cells (iPSCs) and human embryonic stem cells (hESCs). Stepwise differentiation with specific growth factors and small-molecule regulators is used to direct differentiation of pluripotent stem cells through definitive endoderm and pancreatic progenitor stages to insulin-producing β-like cells or stem cell-derived islet clusters. These cells are capable of acquiring important features of native pancreatic β cells including glucose sensing and regulated insulin production, although their functional maturation and long-term performance may differ from that of endogenous human islets. Therefore, stem cell derived islet replacement is studied extensively as a potential regenerative therapy. However, before being broadly applicable in the clinic, major challenges such as immunological rejection, graft survival, maturation, safety, and long-term glucose responsiveness need to be overcome.[80]

The clinical translation of stem cell-derived islet (SC-islet) therapy has progressed substantially, with intraportal transplantation of allogeneic cells demonstrating promising outcomes in patients with type 1 diabetes mellitus and reduced hypoglycemia awareness. Clinical trials have demonstrated that zimislecel (VX-880) restores endogenous C-peptide secretion, improves glycaemic management, reduces the frequency of severe hypoglycaemic episodes and has enabled some recipients to become insulin-independent. However, repeated autoimmune β-cell death and immune-mediated graft rejection are major barriers to widespread use. Current strategies focus on immune-protective encapsulation and genome editing to minimise the need for long-term immunosuppression. They are developing systems for semi-permeable macro- and microencapsulation to restrict access by immune cells but allow interchange of nutrients, glucose, oxygen and insulin.In addition, CRISPR/Cas9-based modification is being explored to generate hypoimmune cells by introducing immunomodulatory molecules and disrupting antigen-presentation pathways. Risks of teratoma formation from residual pluripotent cells, graft hypoxia and inflammatory responses after transplantation, selection of optimal implantation sites, and development of scalable production procedures conforming to good production Practices (GMP). To be safe and repeatable for clinical implementation these problems need to be solved.

6.6 Gene Therapy

Gene therapy is a novel approach to modifying disease in diabetes, targeting underlying pathogenic pathways rather than simply symptomatic glycaemic control. [81] A major strategy for type 1 diabetes mellitus (T1DM) is to transfer therapeutic genes to non-pancreatic tissues such as intestinal cells or hepatocytes to allow regulated insulin production and release. Recombinant adeno-associated viral (rAAV) vectors have been used to deliver genes encoding insulin, and glucose-responsive promoters have been investigated for regulation of insulin expression in response to fluctuations in blood glucose levels. Engineered insulin constructs can have appropriate proteolytic processing sequences to aid in the production of biologically active insulin since non-endocrine tissues lack the specialised prohormone-processing machinery of pancreatic β-cells. Beside insulin replacement, cytoprotective and antioxidant factors such as B-cell lymphoma 2 (Bcl-2), glucagon-like peptide-1 (GLP-1), superoxide dismutase, and nuclear factor erythroid 2-related factor 2 (Nrf2) have been expressed to protect pancreatic β-cells from apoptosis, oxidative stress, endoplasmic reticulum stress, and inflammatory injury. Approaches using the transfer of immunomodulatory genes, including the local expression of immunoregulatory molecules and the genetic modification of regulatory T cells to enhance immunological tolerance to pancreatic islet antigens, have also been explored to decrease autoimmune β-cell destruction. Although the preclinical results are encouraging, clinical application of gene therapy for diabetes has yet to be achieved. Potential for immune responses to vectors and transgenes, heterogeneity in gene expression, difficulty in achieving tissue-specific delivery, and the risk of hypoglycemia and inappropriate insulin production are all issues to be addressed. Other challenges include long-term safety, vector stability, large-scale production and regulatory issues. Further improvements in non-integrating delivery platforms, including lipid nanoparticles and tissue-targeted viral vectors, and more precise glucose-responsive regulatory systems may enhance the safety and therapeutic potential of gene therapy for diabetes.

7. Clinical Challenges in Diabetes Pharmacotherapy

The drug treatment of diabetes mellitus is associated with a number of clinical problems besides the achievement of adequate glycaemic control. While the reduction of blood glucose continues to be an important therapeutic goal, effective long-term care requires consideration of cardiovascular and renal protection, metabolic health, medication safety, and the uniqueness of the patient. When choosing and maintaining a suitable therapy, the risk of side effects, comorbidities, complexity of treatment, patient adherence and accessibility have to be balanced. These variables may play an important role in the results of the treatment, and they indicate the need for tailored and thorough approaches to the medication of diabetes.[82]

7.1 Hypoglycemia

Hypoglycemia is a significant side effect that may impair optimal glycaemic control, especially in patients on insulin or insulin secretagogues such as meglitinides and sulfonylureas. In addition to producing autonomic symptoms, a major fall in blood glucose may produce neuroglycopenia, decreased neurologic function, loss of consciousness, seizures, and other dangerous sequelae if the fall is severe or prolonged. Repeated episodes of hypoglycaemia may also impair the natural counter-

regulatory response, and thus increase the risk for recurrent severe episodes and hypoglycaemia unawareness. Severe hypoglycaemia may worsen heart problems in vulnerable people, especially those with existing cardiovascular disease. Thus glycaemic efficacy and individual risk of hypoglycaemia should be considered in the choice of a drug. Agents such as sodium-glucose cotransporter-2 (SGLT2) inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) generally have a low intrinsic risk of hypoglycaemia, as their glucose-lowering effects are largely glucose dependent. However, when these drugs are used in combination with insulin or insulin secretagogues, the risk may be increased, highlighting the need for individual dose adjustments and regular monitoring.[83]

7.2 Weight Management

Weight control is an important part of diabetes treatment. Being overweight can worsen insulin resistance and metabolic regulation. Traditional treatments such as insulin, sulfonylureas, and thiazolidinediones may also cause weight gain by increasing energy storage, reducing urine glucose excretion, and fluid retention. Newer incretin-based therapies (including GLP-1 receptor agonists and the GIP/GLP-1 receptor dual agonist tirzepatide) can improve glycaemic control and induce clinically relevant weight loss through effects on gastric emptying, appetite suppression and increased satiety, as compared to older incretin-based therapies. The triple GIP/GLP-1/glucagon receptor agonist retatrutide is also under investigation for its ability to improve metabolic outcomes and to hasten reductions in body weight. Therefore, weight effects should be taken into account when selecting a drug, especially in overweight or obese patients.

7.3 Polypharmacy

Polypharmacy is common in type 2 diabetes patients as many of these patients require multiple drugs to control their diabetes and associated conditions like hypertension, dyslipidaemia, chronic renal disease and cardiovascular disease. Combination therapy may be required to meet therapeutic goals. However, multiple drug use can increase the risk of drug-drug interactions, adverse effects and drug related problems.[84] Other factors that could affect drug exposure in vulnerable patients include changes to renal drug excretion and hepatic drug metabolism, especially cytochrome P450 enzymes. This makes regular medication reviews and individualised selection of treatment essential to reduce unnecessary therapy and enhance the safety and effectiveness of diabetes care.

7.4 Drug Adherence

Poor adherence to antidiabetic therapy continues to be one of the major impediments to long-term glycaemic management. Factors that can impact a patient's desire to stay on a therapy include a heavy medication burden, complex dosing or titration schedules, resistance to injectable therapies, side effects of therapy such as nausea and vomiting, and the often asymptomatic nature of the early stages of diabetes. To improve compliance and durability, treatment regimens can be made simpler. The advent of once-weekly injectable therapy, once-daily oral fixed-dose combinations, and longer-acting basal insulin formulations has resulted in decreased dosing frequency and treatment complexity. Although patient education, tolerability, affordability and customised treatment planning remain important for effective diabetic management, these strategies may enhance convenience and drive better long-term adherence.[85]

7.5 Cost-Effectiveness and Accessibility

Many of the newer antidiabetic agents such as SGLT2 inhibitors, GLP-1 receptor agonists and combination GIP/GLP-1 agonists are often more expensive than traditional treatment but offer substantial glycaemic, cardiovascular and renal benefits. They can be prohibitively expensive, particularly in low and middle-income countries. These treatments, however, may also have long-term health and economic benefits by reducing diabetes-related complications, hospitalisations, cardiovascular events and progression of kidney disease. They need to be made more accessible and affordable to be used more widely in control of diabetes.

7.6 Special Populations

Individualised diabetes care is required for patients with hepatic or renal impairment and in pregnancy.[86] SGLT2 inhibitors and GLP-1 receptor agonists may provide additional renal and cardiovascular benefits when indicated, but reduced drug clearance in chronic kidney disease may require dose adjustment or avoidance of certain drugs. In patients with hepatic impairment, special attention must be paid to the selection of medications to minimise the risk of drug accumulation and hepatic side effects. Insulin is generally the drug of choice in pregnancy because it provides good glycaemic control and does not cross the placenta to any clinically significant degree. The safety of many modern antidiabetic drugs in pregnancy and lactation is not yet established.[87]

8. Comparative Evaluation of Current and Emerging Therapies

The therapeutic landscape for type 2 diabetes mellitus (T2DM) has shifted progressively from conventional glucose-lowering strategies to a broader metabolic approach that addresses hyperglycaemia, excess body weight, and associated cardiometabolic complications. Current and emerging pharmacological agents differ considerably in terms of their molecular mechanisms, potency in lowering glucose levels, effects on body weight, cardiovascular and renal benefits, and overall safety and tolerability. These differences are important for tailoring treatment to the clinical needs and risk profile of each patient.[88]

Table 2: Comparative pharmacological profiles, therapeutic effects, and clinical outcomes of established and emerging pharmacotherapies for type 2 diabetes mellitus.[89- 92]

Drug Class	Mechanism of Action	HbA_{1c} Reduction	Body Weight Effect	Cardiovascular Outcomes	Renal Outcomes	Major Adverse Effects & Risks	Therapeutic Objectives
Biguanides*(Metformin)*	Decreases hepatic gluconeogenesis; enhances AMPK activation	Moderate (1.0 – 1.5%)	Neutral / Slight loss	Neutral to mild secondary benefit	Neutral; hold if eGFR < 30	GI distress (diarrhea, nausea), Vitamin B12 deficiency	Reduce hepatic glucose production
SGLT2 Inhibitors*(Empagliflozin, Dapagliflozin)*	Inhibits renal glucose reabsorption in proximal tubule	Moderate (0.7 – 1.0%)	Mild to Moderate loss (2 – 4 kg)	Major benefit (↓ 3-point MACE, ↓ HF hospitalization)	Major benefit (↓ CKD progression, ↓ ESRD)	Mycotic genital infections, volume depletion, euglycemic DKA	Increase urinary glucose excretion
GLP-1 RAs*(Injectable Semaglutide, Dulaglutide)*	Activates GLP-1R; glucose-dependent insulin secretion, slows gastric emptying	High (1.2 – 1.8%)	Moderate to High loss (5 – 10%)	Major benefit (↓ 3-point MACE)	Moderate benefit (↓ persistent macroalbuminuria)	GI symptoms (nausea, vomiting), rare pancreatitis	Enhance glucose-dependent insulin secretion
Dual GIP/GLP-1 RAs*(Tirzepatide)*	Biased dual co-agonist at GIP and GLP-1 receptors	Very High (2.0 – 2.6%)	Profound loss (15 – 22.5%)	Positive overall impact; pending dedicated CVOTs	Promising nephroprotective profiles	Dose-dependent GI distress, nausea, diarrhea	Improve glycaemic control and weight loss
Triple Agonists*(Retatrutide - Emerging)*	Tri-agonist engaging GIP, GLP-1, and Glucagon receptors	Extreme (> 2.0%)	Exceptional loss (> 24%)	Under evaluation; marked clearance of liver fat	Under evaluation; reduced metabolic renal stress	GI side effects, transient pulse rate increases	Target multiple metabolic pathways
Oral GLP-1 RAs*(Oral Semaglutide, Orforglipron)*	Enteral activation of GLP-1R (via SNAC enhancer or small molecule)	High (1.0 – 1.5%)	Moderate loss (4 – 8%)	Comparable class benefit (MACE reduction)	Comparable class benefit	GI distress, requires strict administration (SNAC)	Provide oral incretin-based therapy
DPP-4 Inhibitors*(Sitagliptin, Linagliptin*	Prevents degradation of endogenous incretins (GLP-1/GIP)	Mild to Moderate (0.5 – 0.8%)	Neutral	Neutral (CV safety demonstrated)	Neutral	Rare joint pain, rare pancreatitis	Enhance endogenous incretin action

Sulfonylureas*(Glimepiride, Gliclazide)*	Closes pancreatic K_{ATP} channels; drives insulin release	High (1.0 – 1.5%)	Weight gain (1 – 3 kg)	Neutral to potential risk if severe hypoglycemia	Neutral	High risk of hypoglycemia, weight gain	Increase insulin secretion
Exogenous Insulins*(Basal & Bolus)*	Direct activation of insulin receptor; drives peripheral glucose uptake	Unlimited (titration dependent)	Weight gain (3 – 6 kg)	Neutral	Neutral	High risk of hypoglycemia, weight gain, injection site reactions	Replace/augment insulin deficiency

9. Ongoing and Late-Stage Clinical Trials of Emerging Antidiabetic Therapies:

The development of emerging pharmacological interventions for type 2 diabetes mellitus (T2DM) is moving beyond the management of glycaemia alone towards the comprehensive treatment of metabolic and cardiometabolic abnormalities. Recent late-stage clinical programmes are investigating multi-receptor agonists and orally available glucagon-like peptide-1 (GLP-1) receptor agonists, as well as long-acting basal insulin formulations. As well as changes in glycated haemoglobin (HbA1c), these studies are evaluating weight loss, the durability of the therapeutic response, tolerability, hypoglycaemia, adherence to treatment and, where applicable, cardiovascular and renal outcomes. [93]

Retatrutide is an investigational, once-weekly, triple receptor agonist which simultaneously targets the glucose-dependent insulinotropic polypeptide (GIP), glucagon-like peptide-1 (GLP-1) and glucagon receptors. It represents an emerging therapeutic strategy that modulates complementary metabolic pathways with a single pharmacological agent. The ongoing TRANSEND-T2D clinical programme is evaluating retatrutide in various T2DM patient groups, including those with inadequate glycaemic control despite background glucose-lowering treatment and individuals with renal impairment. These studies are expected to provide further information regarding retatrutide's effects on glycaemia and weight, its safety profile, and its potential utility across clinically relevant patient populations.[94]

Orforglipron is a non-peptide GLP-1 receptor agonist administered orally, providing an alternative to injectable, peptide-based incretin therapy. Its small-molecule characteristics allow it to be taken orally while retaining pharmacological activity at the GLP-1 receptor. Phase III clinical trials have investigated the use of orforglipron in various populations with type 2 diabetes mellitus (T2DM) and in different treatment settings, with a particular focus on reducing HbA1c levels, changes in body weight, tolerability and overall safety. Further clinical studies are examining its therapeutic effects in overweight or obese individuals, including those with and without T2DM. Together, these studies are helping to evaluate the potential of oral GLP-1 receptor agonism as a more convenient approach to managing metabolic diseases.[95]

Another area of clinical development involves extended-duration basal insulin formulations, which are being developed to provide prolonged and consistent insulin exposure with fewer administration requirements. Such formulations may help to reduce the frequency of insulin administration while maintaining adequate basal glycaemic control. Clinical investigations are therefore evaluating parameters such as HbA1c, fasting glycaemia, hypoglycaemic events, treatment adherence, and overall safety. While reduced dosing frequency may decrease treatment burden, further comparative and long-term clinical evidence is required to confirm the therapeutic benefits and optimal clinical application of these formulations compared to existing basal insulin therapies. Overall, the current landscape of clinical development reflects a broader shift in type 2 diabetes mellitus (T2DM) pharmacotherapy, moving away from conventional glucose-lowering approaches and towards interventions that can address several interconnected aspects of the disease, including hyperglycaemia, excess body weight, treatment burden, and cardiometabolic risk. However, the successful translation of these investigational therapies into routine clinical practice requires robust evidence regarding therapeutic persistence, long-term safety, treatment adherence and discontinuation, cardiovascular and renal outcomes, tolerability, accessibility, and cost-effectiveness. Ultimately, such evidence will determine their appropriate place within the evolving therapeutic framework of T2DM. [96]

Table 3: Selected ongoing and late-stage clinical trials of emerging pharmacological therapies for type 2 diabetes mellitus

Investigational therapy	Target/mechanism	Trial/program	Phase	Population/comparator	Major endpoints	Status
Retatrutide	GIP/GLP-1/glucagon receptor agonist	TRANSEND-T2D-2 (NCT06260722)	III	T2DM inadequately controlled with metformin ± SGLT2 inhibitor; comparator: semaglutide	HbA1c, body weight, safety	Active, not recruiting; estimated completion Jan 2027*
Retatrutide	GIP/GLP-1/glucagon receptor agonist	TRANSEND-T2D-3	III	T2DM with moderate/severe renal impairment	Efficacy and safety in renal impairment	Clinical development*
Orforglipron	Oral non-peptide GLP-1 receptor agonist	ACHIEVE programme	III	Adults with T2DM receiving different background therapies	HbA1c, body weight, safety and tolerability	Multiple Phase III studies completed; development continues*
Orforglipron	Oral non-peptide GLP-1 receptor agonist	NCT06972472	III	Overweight/obesity with or without T2DM	Glycaemic and weight-related outcomes	Ongoing; estimated completion Aug 2027*
Weekly basal insulin candidates	Extended-duration insulin replacement	Phase III programmes	III	Insulin-naïve or insulin-treated T2DM	Glycaemic control, adherence, hypoglycaemia	

10. Conclusion

The management of type 2 diabetes mellitus (T2DM) has evolved from a conventional emphasis on reducing blood glucose levels to a more comprehensive approach that encompasses a range of metabolic objectives. These objectives include the regulation of body weight and the mitigation of cardiovascular and renal risks. Whilst established antidiabetic medications remain pivotal within clinical management protocols, the selection of these medications is contingent upon a multifaceted set of considerations. These include, but are not limited to, their therapeutic efficacy, their impact on body weight, the risk of hypoglycaemia, their tolerability, the presence of associated comorbidities, and the overall treatment burden.

The advent of novel therapeutic modalities, most notably dual GIP/GLP-1 receptor agonists, oral GLP-1 receptor agonists, glucagon-based approaches, and longer-acting insulin formulations, has further diversified the available treatment options. Concurrently, strategies directed towards the preservation and restoration of β-cells, including regenerative approaches, stem-cell-derived islet therapies, and gene-based interventions, are being explored to address the progressive decline in β-cell function associated with T2DM. However, further clinical investigation is required to establish the long-term efficacy, safety, tolerability, treatment persistence, cardiovascular and renal effects, accessibility, and cost-effectiveness of most of these emerging approaches.

It is evident that advancements in the field of T2DM pharmacotherapy are indicative of a gradual transition towards more individualised and mechanism-oriented treatment strategies. Future therapeutic development should aim not only to achieve sustained glycaemic control but also to preserve β-cell function, manage excess body weight, reduce diabetes-related complications, minimise treatment-related risks, and support long-term adherence. The incorporation of emerging therapies into standard clinical practice is contingent upon the existence of robust long-term clinical evidence and a meticulous consideration of individual patient requirements, economic considerations, and the equitable distribution of effective treatments.

List of abbreviations:

AGIs- Alpha-Glucosidase Inhibitors

Akt- Protein Kinase B

AMP- Adenosine Monophosphate

AMPK - AMP-Activated Protein Kinase

API(s)- Active Pharmaceutical Ingredient(s)

ATP- Adenosine Triphosphate

Bcl-2- B-Cell Lymphoma 2

cAMP- Cyclic Adenosine Monophosphate

CNS- Central Nervous System

CRISPR/Cas9- Clustered Regularly Interspaced Short Palindromic Repeats/CRISPR-Associated Protein 9

CTLA-4- Cytotoxic T-Lymphocyte-Associated Antigen 4

CVOTs- Cardiovascular Outcome Trials

CYP450- Cytochrome P450

DPP-4- Dipeptidyl Peptidase-4

DYRK1A- Dual-Specificity Tyrosine-Phosphorylation-Regulated Kinase 1A

EPAC2- Exchange Protein Directly Activated by cAMP 2

ER- Endoplasmic Reticulum

FDCs- Fixed-Dose Combinations

FFA/FFAs- Free Fatty Acid(s)

FOXO1- Forkhead Box O1

G6Pase- Glucose-6-Phosphatase

GCGR- Glucagon Receptor

GIP- Glucose-Dependent Insulinotropic Polypeptide

GIP/GLP-1- Glucose-Dependent Insulinotropic Polypeptide/Glucagon-Like Peptide-1

GLP-1- Glucagon-Like Peptide-1

GLP-1- Glucagon-Like Peptide-1 Receptor Agonists

GLUT4- Glucose Transporter Type 4

GMP- Good Manufacturing Practices

GSK-3- Glycogen Synthase Kinase-3

HbA1c - Glycated Haemoglobin

hESCs- Human Embryonic Stem Cells

IL-1β- Interleukin-1 Beta

IL-6- Interleukin-6

iPSCs- Induced Pluripotent Stem Cells

IRS-1- Insulin Receptor Substrate-1

IRS-2- Insulin Receptor Substrate-2

JAK- Janus Kinase

JNK- c-Jun N-Terminal Kinase

KATP- ATP-Sensitive Potassium Channel

M1- Pro-inflammatory Macrophage Phenotype

M2- Anti-inflammatory Macrophage Phenotype

MACE- Major Adverse Cardiovascular Events

MAFA- Musculoaponeurotic Fibrosarcoma Oncogene Homolog A

MASH- Metabolic Dysfunction-Associated Steatohepatitis

mTOR- Mammalian Target of Rapamycin

NFAT- Nuclear Factor of Activated T Cells

NGN3- Neurogenin-3

Nrf2- Nuclear Factor Erythroid 2-Related Factor 2

PD-1- Programmed Cell Death Protein 1

PDX1- Pancreatic and Duodenal Homeobox 1

PEPCK- Phosphoenolpyruvate Carboxykinase

PI3K- Phosphatidylinositol 3-Kinase

PIP3- Phosphatidylinositol-3,4,5-Trisphosphate

PKA- Protein Kinase A

PKC- Protein Kinase C

PPAR-γ- Peroxisome Proliferator-Activated Receptor-γ

PPREs- Peroxisome Proliferator Response Elements

rAAV- Recombinant Adeno-Associated Virus

ROS- Reactive Oxygen Species

RXR- Retinoid X Receptor

SC-islet- Stem Cell-Derived Islet

SGLT1 - Sodium-Glucose Cotransporter-1

SGLT2 - Sodium-Glucose Cotransporter-2

SNAC- Sodium N-(8-[2-Hydroxybenzoyl]) Amino Caprylate

T1DM - Type 1 Diabetes Mellitus

T2DM - Type 2 Diabetes Mellitus

TNF-α- Tumour Necrosis Factor-Alpha

TZDs- Thiazolidinediones

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