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Review Article

Antidiabetic Agents: Pathophysiology of Diabetes Mellitus and Therapeutic Approaches

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ABSTRACT

Diabetes mellitus is a heterogeneous group of chronic metabolic disorders characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action, or both. Its pathophysiology involves a complex interplay between genetic susceptibility, autoimmunity, insulin resistance, β-cell failure, chronic inflammation, oxidative stress, and environmental and lifestyle factors, ultimately leading to microvascular and macrovascular complications. Understanding these mechanisms provides the biological rationale for current and emerging antidiabetic therapies. This review summarizes the classification and pathophysiology of major diabetes subtypes, highlights key molecular and inflammatory pathways, and discusses pharmacological antidiabetic agents—including metformin, insulin secretagogues, thiazolidinediones, α-glucosidase inhibitors, DPP-4 inhibitors, GLP-1 receptor agonists, SGLT2 inhibitors, insulin, and newer multi-incretin agonists—in the context of underlying disease mechanisms and clinical outcome data. (1–3)

INTRODUCTION

Diabetes mellitus (DM) has reached pandemic proportions, with an estimated global prevalence exceeding 500 million adults and projections indicating a continued rise driven by ageing populations, urbanisation, obesity, and sedentary lifestyles. DM is a leading cause of blindness, end-stage kidney disease, non-traumatic lower-limb amputation and a major contributor to cardiovascular morbidity and mortality. (1,2) The burden is particularly high in low- and middle-income countries, where rapid epidemiological transition is not matched by health-system capacity, creating an urgent need for effective, affordable prevention and treatment strategies. (2,3)Contemporary understanding

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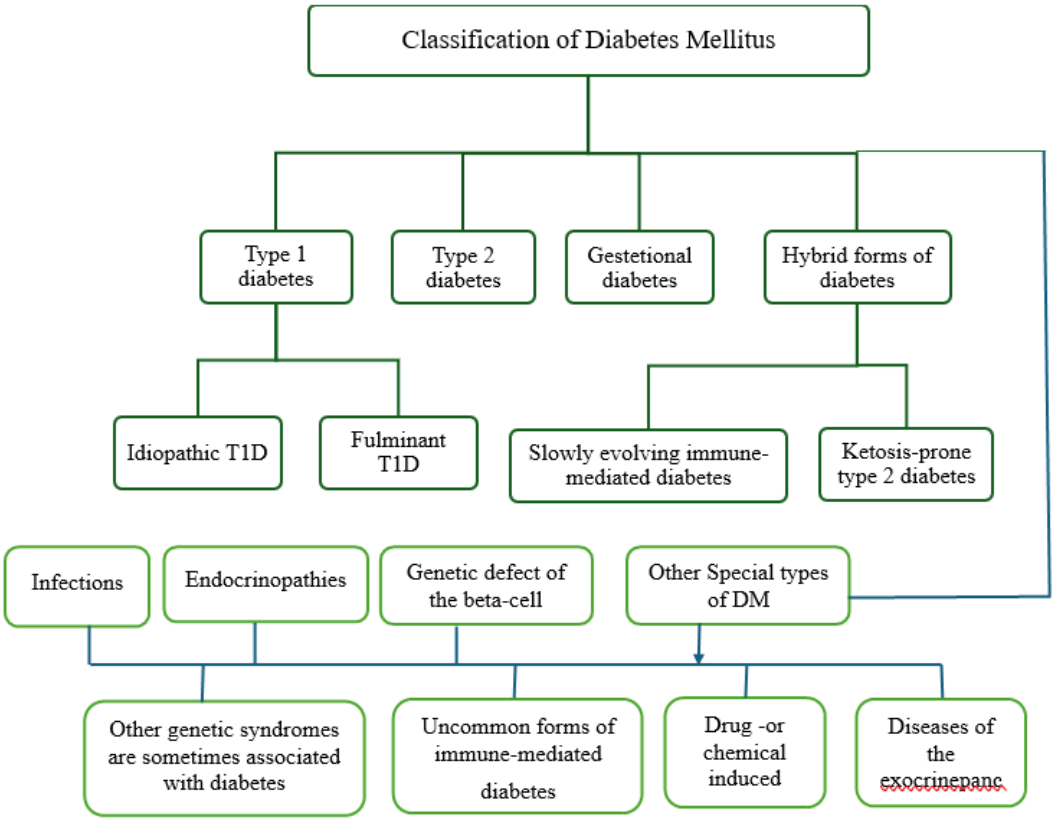
recognises DM as a systemic disorder of energy and nutrient handling rather than a purely glycaemic disease. Multiple organs—including pancreatic islets, adipose tissue, liver, skeletal muscle, gut, kidney, vasculature and immune system—participate in a dynamic network that regulates glucose homeostasis. Disruption of this network by genetic, environmental and behavioural factors leads to insulin resistance, progressive β-cell dysfunction, chronic low-grade inflammation and oxidative stress. (3–5) Knowledge of these interlinked mechanisms underpins rational use of antidiabetic agents and has shifted therapeutic goals from glucose normalisation alone to comprehensive cardiorenal risk reduction. (6,7)

2. Classification of Diabetes Mellitus

Current classification distinguishes four major categories: type 1 diabetes (T1D), type 2 diabetes (T2D), gestational diabetes mellitus (GDM), and "other specific types," including monogenic forms, diseases of the exocrine pancreas, endocrinopathies, drug- or chemical-induced diabetes, infection-related diabetes and genetic syndromes associated with hyperglycaemia. (3,8) Hybrid phenotypes such as latent autoimmune diabetes in adults (LADA), latent autoimmune diabetes in youth (LADY) and ketosis-prone T2D further illustrate the biological continuum between classical T1D and T2D. (3,8,9)

Data-driven clustering approaches have proposed novel subgroups (e.g. severe autoimmune diabetes, severe insulin-deficient diabetes, severe insulin-resistant diabetes, mild obesity-related diabetes and mild age-related diabetes) based on age, BMI, insulin secretion, insulin resistance and autoantibody status. These clusters differ in risk of complications (e.g. kidney disease, retinopathy) and treatment requirements, suggesting that more granular phenotyping could improve prognostication and therapy individualisation. (3,10,11)



3. Pathophysiology of Diabetes Mellitus

3.1 Type 1 diabetes mellitus

T1D is characterised by autoimmune destruction of pancreatic β-cells leading to absolute insulin deficiency. Islet inflammation (insulitis) involves autoreactive $CD4^+$ and $CD8^+$ T cells, B cells, macrophages and dendritic cells infiltrating islets and targeting β-cell antigens such as insulin, GAD65 and IA-2. (3,12) Genetic susceptibility—most strongly linked to HLA class II alleles—is modified by environmental triggers such as viral infections, early-life diet and gut microbiota alterations, leading to breakdown of central and peripheral immune tolerance. (12,13)

The natural history of T1D typically progresses from genetic risk to islet autoimmunity (appearance of one or more autoantibodies), then dysglycaemia and finally overt hyperglycaemia once the majority of β-cell mass is lost. (12,13) Residual C-peptide secretion often persists for years after diagnosis ("honeymoon phase") and is associated with lower risk of hypoglycaemia and complications, emphasising the importance of preserving β-cell function in early disease. (12–14)

3.2 Type 2 diabetes mellitus

T2D is characterised by a combination of insulin resistance and relative insulin deficiency. In early stages, insulin resistance in liver, skeletal muscle and adipose tissue is compensated by hyperinsulinaemia; over time, β-cells fail to sustain the increased secretory demand, leading to fasting and postprandial hyperglycaemia. (4,5,11) Insulin resistance arises from ectopic lipid accumulation, chronic inflammation, mitochondrial dysfunction and defects in insulin signalling pathways, including serine phosphorylation of insulin receptor substrate (IRS) proteins and activation of stress kinases such as JNK and IKKβ. (4,5,11,15)

The "ominous octet" framework extends this view by recognising eight key pathophysiologic disturbances in T2D: impaired β-cell insulin secretion; increased hepatic glucose production; decreased peripheral glucose uptake; increased lipolysis; incretin deficiency/resistance; hyperglucagonaemia; increased renal glucose reabsorption; and central neurotransmitter dysfunction affecting appetite and energy balance. (4,15) This model provides a mechanistic rationale for targeting multiple organs and pathways using combination therapy rather than relying on monotherapy escalation. (4,6,15)

3.3 Gestational diabetes and hybrid forms

GDM results from the inability of maternal β-cells to compensate for physiological insulin resistance of pregnancy driven by placental hormones, weight gain and adipokine changes. (8,16) GDM is associated with increased risk of pre-eclampsia, caesarean delivery, macrosomia and neonatal complications, and confers a high lifetime risk of subsequent T2D and cardiovascular disease in both mother and offspring. (8,16,17)

LADA and LADY represent slowly progressive autoimmune diabetes that clinically resembles T2D at onset but is characterised by islet autoantibodies (typically GAD antibodies) and eventual insulin dependence. (3,9) Ketosis-prone T2D presents with severe hyperglycaemia and ketoacidosis but often enters remission after initial insulin therapy; intermittent β-cell failure driven by glucose toxicity and variable insulin resistance is postulated. (3,9,18)

3.4 β-cell dysfunction and failure

β-cell dysfunction in T2D reflects both functional impairment and loss of mass. Chronic exposure to hyperglycaemia (glucotoxicity) and elevated free fatty acids (lipotoxicity) induces endoplasmic reticulum stress, mitochondrial dysfunction, oxidative damage and activation of pro-apoptotic pathways in β-cells. (4,5,19) Increased production of islet amyloid polypeptide (IAPP) and formation of amyloid deposits in islets further contribute to β-cell apoptosis. (19,20)

Genetic factors modulate β-cell resilience; many T2D susceptibility loci identified by genome-wide association studies affect β-cell development, function or survival. (11,20) Environmental exposures such as heavy metals (e.g. arsenic), endocrine disruptors and certain drugs can also impair β-cell function, partly via oxidative stress and mitochondrial injury. (3,19,21)

3.5 Insulin resistance and organ crosstalk

Insulin resistance is driven by a network of organ interactions. In adipose tissue, hypertrophic adipocytes and infiltrating macrophages secrete pro-inflammatory cytokines (TNF-α, IL-6, MCP-1) and adipokines (reduced adiponectin, increased resistin) that impair insulin signalling in muscle and liver. (3,5,8) In skeletal muscle, accumulation of intramyocellular lipids and diacylglycerol activates novel protein kinase C isoforms, leading to serine phosphorylation of IRS and reduced insulin-stimulated glucose transport. (4,5,11,15)

The liver in insulin-resistant states exhibits increased gluconeogenesis and hepatic glucose output, frequently accompanied by non-alcoholic fatty liver disease (NAFLD) and steatohepatitis (NASH), which further perpetuate systemic inflammation and dyslipidaemia. (3,11,22) The kidney contributes via increased SGLT2-mediated glucose reabsorption, raising the renal threshold for glycosuria and sustaining hyperglycaemia. (4,15,23) The central nervous system integrates hormonal and nutrient signals; hypothalamic inflammation and leptin/insulin resistance disrupt appetite and energy expenditure, promoting obesity and worsening insulin resistance. (5,11,15)

3.6 Inflammation and oxidative stress

Chronic low-grade inflammation is now recognised as a hallmark of both T1D and T2D. In T2D, obesity-associated metaflammation in adipose tissue and liver activates NF-κB and JNK pathways, increasing the production of TNF-α, IL-1β, IL-6 and other mediators that blunt insulin action and damage β-cells. (3,5,8,24) Circulating levels of inflammatory markers such as high-sensitivity C-reactive protein, IL-6 and TNF-α correlate with incident T2D and cardiovascular risk, and may partially mediate the link between obesity and diabetes. (5,24,25)

Oxidative stress results from excess production of reactive oxygen species (ROS) and/or impaired antioxidant defences. Hyperglycaemia increases mitochondrial superoxide generation and drives activation of multiple damaging pathways: polyol and hexosamine flux, protein kinase C activation, formation of advanced glycation end products (AGEs) and AGE–receptor (RAGE) signalling, all of which promote endothelial dysfunction and tissue injury. (3,5,19,26) β-cells are particularly vulnerable due to low expression of antioxidant enzymes, so sustained oxidative stress accelerates β-cell failure and progression of both T1D and T2D. (19,26,27)

3.7 Environmental toxins, gut microbiota and metabolic regulation

Chronic exposure to environmental toxins such as arsenic, cadmium and persistent organic pollutants has been linked to increased risk of insulin

resistance and T2D, potentially via increased oxidative stress, disruption of mitochondrial function, interference with insulin signalling and depletion of protective micronutrients like selenium. (3,21,28) In parallel, accumulating evidence highlights the role of gut microbiota in glucose metabolism: dysbiosis, altered short-chain fatty acid production and increased intestinal permeability allow translocation of lipopolysaccharide and other microbial products, triggering low-grade endotoxaemia and systemic inflammation. (3,8,29)

Microbial metabolites such as imidazole propionate and trimethylamine-N-oxide (TMAO) modulate insulin signalling, hepatic gluconeogenesis and vascular function, linking diet, gut microbiota and cardiometabolic disease. (8,29) These insights have sparked interest in microbiota-targeted interventions, although their role in routine diabetes management remains investigational. (8,29,30)

3.8 Chronic complications

Prolonged hyperglycaemia, dyslipidaemia, hypertension and oxidative/inflammatory stress converge to damage microvascular and macrovascular beds. Persistent exposure leads to characteristic lesions in retina (diabetic retinopathy), kidney (diabetic nephropathy) and peripheral nerves (diabetic neuropathy), as well as accelerated atherosclerosis causing coronary artery disease, stroke and peripheral arterial disease. (3,26,31) Landmark trials have shown that improved glycaemic control substantially reduces microvascular complications, while multifactorial management including blood pressure control and lipid-lowering therapy is critical for macrovascular risk reduction. (7,26,31,32)

Table 1.Etiology, Pathophysiology and Clinical Outcomes of Major Forms of Diabetes Mellitus

Type	Etiology	Pathophysiology	Outcome
Type 1 Diabetes Mellitus (T1DM)	Genetic susceptibility (HLA class II); environmental triggers (viral infections, diet, microbiota)	Autoimmune β-cell destruction mediated by $CD4^+$/$CD8^+$ T cells and autoantibodies (insulin, GAD65, IA-2) → insulitis → absolute insulin deficiency	Persistent hyperglycaemia; risk of ketoacidosis; lifelong insulin dependence; chronic micro- and macrovascular complications
Type 2 Diabetes Mellitus (T2DM)	Obesity, genetic predisposition, sedentary lifestyle, ageing	Insulin resistance in liver, muscle and adipose tissue + progressive β-cell failure due to glucotoxicity, lipotoxicity, inflammation and defective insulin signalling (IRS, JNK, IKKβ)	Fasting and postprandial hyperglycaemia; progressive disease requiring combination therapy; chronic vascular complications
Gestational Diabetes Mellitus (GDM)	Pregnancy-induced insulin resistance (placental hormones, adipokines, weight gain)	Inadequate β-cell compensation during pregnancy → transient hyperglycaemia	Maternal and fetal complications; high future risk of T2DM and cardiovascular disease
Hybrid forms (LADA, LADY, KPD)	Autoimmune predisposition with metabolic stress	Slow autoimmune β-cell loss with initial T2DM-like presentation; intermittent β-cell failure in KPD	Eventual insulin dependence; variable remission and relapse
β-cell dysfunction and failure	Chronic hyperglycaemia, elevated FFAs, genetic susceptibility, toxins	Glucotoxicity, lipotoxicity, ER stress, oxidative damage, IAPP amyloid deposition → apoptosis	Progressive loss of insulin secretion; worsening glycaemic control

Insulin resistance (organ crosstalk)	Obesity-related inflammation, ectopic fat deposition	Adipokine imbalance, cytokine release, PKC activation, ↑ hepatic glucose output, ↑ renal glucose reabsorption	Sustained hyperglycaemia; increased insulin demand
Inflammation & oxidative stress	Obesity, hyperglycaemia, immune activation	NF-κB/JNK activation; ROS overproduction; AGE–RAGE signalling	Endothelial dysfunction; β-cell damage; vascular complications
Environmental toxins & gut dysbiosis	Arsenic, cadmium, pollutants; altered gut microbiota	Oxidative stress, mitochondrial dysfunction, endotoxaemia, altered microbial metabolites	Increased insulin resistance; cardiometabolic risk
Chronic complications	Long-standing hyperglycaemia, dyslipidaemia, hypertension	Microvascular and macrovascular damage via oxidative and inflammatory pathways	Retinopathy, nephropathy, neuropathy, CAD, stroke, PAD

4. Therapeutic Approaches: General Principles

Management of DM is multifaceted, combining lifestyle intervention, pharmacologic glucose-lowering therapy and comprehensive cardiovascular risk reduction. International guidelines recommend individualisedglycaemic targets—often around HbA1c 7% for many non-pregnant adults—with more stringent or relaxed goals depending on age, comorbidities, risk of hypoglycaemia and patient preference. (6,7,33) Early achievement and maintenance of near-normal glycaemia confer long-term benefits ("metabolic memory") on microvascular and, to some extent, macrovascular outcomes. (31,32,34)

Therapeutic decisions now explicitly incorporate cardiorenal comorbidities. For people with T2D and established atherosclerotic cardiovascular disease (ASCVD), heart failure or chronic kidney disease (CKD), agents with proven cardiovascular and renal benefit—primarily SGLT2 inhibitors and GLP-1 receptor agonists—are prioritised regardless of baseline HbA1c or metformin use. (6,7,23,33,35) Lifestyle measures (medical nutrition therapy, physical activity, weight management, smoking cessation) remain fundamental at every stage and exert favourable effects on insulin sensitivity, inflammation and vascular health. (2,6,33,36)

5. Antidiabetic Agents and Their Pathophysiologic Targets

5.1 Metformin

Metformin, a biguanide, is widely recommended as first-line pharmacologic therapy for T2D in the absence of contraindications. It primarily reduces hepatic gluconeogenesis and hepatic glucose output, improves hepatic and peripheral insulin sensitivity, and increases intestinal glucose utilisation partly via alterations in gut microbiota and stimulation of GLP-1 secretion. (4,15,23,37) Metformin activates AMP-activated protein kinase (AMPK) and may exert anti-inflammatory and antioxidant effects, contributing to vascular protection beyond glycaemic control. (23,37,38)

Clinically, metformin lowers HbA1c by about 1–1.5%, is weight-neutral or mildly weight-reducing and carries a very low risk of hypoglycaemia. The UKPDS suggested macrovascular benefits in overweight patients treated early with metformin compared with conventional therapy. (31,32,39) Gastrointestinal intolerance is common but often manageable with gradual dose escalation or extended-release formulations; concerns about

lactic acidosis necessitate caution in advanced CKD, liver failure or conditions associated with tissue hypoxia. (37,39)

5.2 Insulin secretagogues: sulfonylureas and meglitinides

Sulfonylureas (e.g. glibenclamide, glipizide, gliclazide, glimepiride) and meglitinides (repaglinide, nateglinide) stimulate insulin secretion by binding to the sulfonylurea receptor (SUR1) subunit of the ATP-sensitive potassium channel on β-cells, causing channel closure, depolarisation, calcium influx and insulin exocytosis. (4,7,10,37) Sulfonylureas provide potent HbA1c reductions at low cost and have long been widely used, particularly in resource-limited settings. (37,40)

However, these agents increase the risk of hypoglycaemia and weight gain and may accelerate β-cell exhaustion by driving non-physiological insulin secretion irrespective of ambient glucose. (10,40,41) Meglitinides have shorter action and predominantly target postprandial hyperglycaemia with somewhat lower hypoglycaemia risk, but require multiple daily dosing. (10,37,41) In modern algorithms, sulfonylureas are generally reserved for patients where cost is the overriding concern, and used with caution in older individuals and those at high hypoglycaemia risk. (6,7,33)

5.3 Biguanides

Metformin, the only biguanide approved in the United States, represents first-line pharmacotherapy for T2D through multiple mechanisms improving insulin sensitivity.[23][29][35] Metformin decreases hepatic gluconeogenesis by impairing mitochondrial function in hepatocytes, reducing glucose absorption in the gastrointestinal tract through effects on brush border glucose transporters, and enhancing glucose uptake and oxidation in skeletal muscle through AMPK-mediated improvements in insulin signaling.[32][35]

Metformin monotherapy decreases fasting plasma glucose by 60-70 mg/dL and HbA1c by 1.5-2%, with additive effects when combined with other antidiabetic agents.[35][106] Metformin demonstrates an excellent safety profile with negligible hypoglycemia risk as monotherapy, though gastrointestinal disturbances including diarrhea, nausea, and dyspepsia occur in approximately 30% of patients during initiation, manageable through gradual dose escalation and extended-release formulations.[103][106] Rare but serious lactic acidosis predominantly occurs in patients with severe renal insufficiency, necessitating renal function monitoring and contraindication in advanced chronic kidney disease.

5.4 Thiazolidinediones (TZDs)

TZDs (pioglitazone, rosiglitazone) are peroxisome proliferator-activated receptor-γ (PPAR-γ) agonists that improve insulin sensitivity in adipose tissue, skeletal muscle and liver. They promote adipocyte differentiation, favor lipid storage in subcutaneous rather than visceral depots, increase adiponectin and reduce pro-inflammatory cytokine expression, thereby ameliorating lipotoxicity and insulin resistance. (4,7,10,42) TZDs may preserve β-cell function by reducing glucolipotoxic stress and improving islet insulin content. (19,42)

Pioglitazone has shown benefits on surrogate cardiovascular outcomes and secondary endpoints in some high-risk populations, although results have been heterogeneous. (42,43) Clinical use is limited by side effects: weight gain, fluid retention

and oedema, increased risk of heart failure in susceptible individuals, and increased fracture risk, particularly in women. (7,10,43) Regulatory concerns about bladder cancer with pioglitazone further constrained use, although later analyses have been mixed. (43)

5.5 α-Glucosidase inhibitors

α-Glucosidase inhibitors (acarbose, miglitol, voglibose) delay carbohydrate digestion in the proximal small intestine by inhibiting brush-border α-glucosidase enzymes, thereby attenuating postprandial glucose excursions. (4,7,10) They are weight-neutral and carry a low risk of hypoglycaemia when used without insulin or secretagogues, making them suitable for patients with predominantly postprandial hyperglycaemia and in some ethnic populations with high carbohydrate intake. (7,10,44)

The main limitations are modest HbA1c efficacy and frequent gastrointestinal adverse effects (flatulence, abdominal discomfort, diarrhoea) due to fermentation of undigested carbohydrates in the colon, which reduce long-term adherence. (10,44) Consequently, α-glucosidase inhibitors occupy a niche role in contemporary practice. (44)

5.6 DPP-4 inhibitors

Dipeptidyl peptidase-4 (DPP-4) inhibitors (sitagliptin, vildagliptin, saxagliptin, linagliptin, alogliptin, among others) increase endogenous incretin levels (GLP-1 and GIP) by inhibiting their enzymatic degradation. (4,7,13,45) This leads to glucose-dependent enhancement of insulin secretion, suppression of glucagon, modest improvement in fasting and postprandial glucose and potential preservation of β-cell mass and function. (13,45,46)

DPP-4 inhibitors are weight-neutral, have a very low risk of hypoglycaemia and are orally administered once daily, making them attractive add-on options, especially in frail or elderly patients. (7,33,45) Cardiovascular outcome trials have demonstrated CV safety but not consistent CV benefit; a signal for increased heart failure hospitalisation with saxagliptin has led to caution in patients with existing heart failure. (45,46,47) Rare adverse events include pancreatitis and joint pain, though causal links remain debated. (45,47)

5.7 GLP-1 receptor agonists

GLP-1 receptor agonists (GLP-1RAs)—including exenatide, liraglutide, dulaglutide, semaglutide, lixisenatide and others—are analogues of GLP-1 resistant to DPP-4 degradation. They enhance glucose-dependent insulin secretion, suppress glucagon, slow gastric emptying and promote satiety, resulting in robust HbA1c reduction and clinically meaningful weight loss. (4,13,19,48) In addition to glycaemic effects, GLP-1RAs improve multiple cardiometabolic parameters such as blood pressure, lipid profile and markers of inflammation and endothelial function. (19,25,48)

Large cardiovascular outcome trials—including LEADER (liraglutide), SUSTAIN-6 and PIONEER-6 (semaglutide), REWIND (dulaglutide), EXSCEL (exenatide) and HARMONY OUTCOMES (albiglutide)—have demonstrated significant reductions in major adverse cardiovascular events in high-risk T2D populations, with some agents also showing renal benefits (slower decline in eGFR and reduced albuminuria). (25,35,48,49) Consequently, GLP-1RAs with proven CV benefit are recommended for T2D patients with ASCVD or at high CV risk, particularly when weight reduction is also a priority. (6,7,33,35)

The main adverse effects are gastrointestinal (nausea, vomiting, diarrhoea) which typically diminish over time; rare concerns include pancreatitis and gallbladder disease. Most GLP-1RAs are injectable (daily or weekly), although oral semaglutide offers an alternative for selected patients. (13,48,49)

5.8 SGLT2 inhibitors

Sodium–glucose cotransporter-2 (SGLT2) inhibitors (empagliflozin, canagliflozin, dapagliflozin, ertugliflozin, among others) reduce renal glucose reabsorption in the proximal tubule, promoting glucosuria and modest osmotic diuresis. They lower HbA1c, body weight and blood pressure with a minimal intrinsic risk of hypoglycaemia. (4,7,23,50) By reducing intraglomerular pressure and tubular workload, SGLT2 inhibition also exerts favourablehaemodynamic and metabolic effects in the kidney. (23,35,50)

Multiple landmark trials—EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI 58, CREDENCE, DAPA-CKD, EMPA-KIDNEY, DAPA-HF and EMPEROR-Reduced/Preserved—have consistently shown that SGLT2 inhibitors markedly reduce hospitalisation for heart failure, slow CKD progression and, in several studies, reduce cardiovascular and all-cause mortality across a broad range of patients, including those without diabetes. (23,35,50–52) These benefits appear only partly explained by glucose lowering and likely involve improved haemodynamics, myocardial and renal energy metabolism, reduced inflammation and fibrosis. (35,50,52)

Adverse effects include genital mycotic infections, volume depletion, hypotension, and a small absolute risk of diabetic ketoacidosis—often euglycaemic—particularly in patients with marked insulin deficiency or during acute illness or peri-operative periods. (50,51) Canagliflozin has been associated with an earlier signal of increased amputations, though subsequent analyses have been less definitive; careful risk assessment and foot care are advised. (50,51)

5.9 Insulin therapy

Insulin is essential for survival in T1D and is required in many patients with advanced T2D to achieve glycaemic targets when endogenous insulin secretion becomes inadequate. Physiological replacement typically combines basal insulin to control fasting and between-meal glucose with prandial (bolus) insulin to cover meal-related excursions. (6,7,33,34) Modern basal insulin analogues (glargine, detemir, degludec) provide more predictable pharmacokinetics and lower hypoglycaemia risk than NPH, while rapid-acting analogues improve postprandial control compared with regular insulin. (34,53)

The Diabetes Control and Complications Trial (DCCT) and its long-term follow-up, the Epidemiology of Diabetes Interventions and Complications (EDIC) study, provided definitive evidence that intensive insulin therapy in T1D reduces the risk of retinopathy, nephropathy and neuropathy by 35–76% and confers durable cardiovascular benefits decades later. (31,32,34,53) In T2D, more intensive insulin-based regimens reduce microvascular complications, but macrovascular outcomes depend on patient selection and overall risk-factor management. (31,32,34)

Insulin therapy is limited by risks of hypoglycaemia and weight gain, as well as the need for injections and self-monitoring of blood glucose or continuous glucose monitoring (CGM). (6,33,53) Advances such as insulin pumps, hybrid closed-loop systems and CGM have improved glycaemic control and quality of life, especially in

T1D. (34,53,54) Combining insulin with agents that mitigate weight gain and hypoglycaemia (e.g. GLP-1RAs, SGLT2 inhibitors) is increasingly common in T2D. (35,48,54)

Table 2. Mechanisms of Action and Clinical Considerations of Antidiabetic Agents

Drug Class	Representative Drugs	Mechanism of Action	Therapeutic Advantages	Major Limitations
Insulin & Insulin Analogs	Regular insulin, Insulin glargine, Insulin lispro	Enhances glucose uptake in muscle and adipose tissue, suppresses hepatic gluconeogenesis and lipolysis	Essential in T1DM, effective in advanced T2DM, flexible dosing	Hypoglycemia, weight gain, injection requirement
Sulfonylureas & Meglitinides	Glibenclamide, Glipizide, Repaglinide	Closure of K^+-ATP channels → membrane depolarization → Ca^{2+} influx → insulin release	Rapid glucose lowering, cost-effective	Hypoglycemia, β-cell exhaustion, weight gain
Biguanides	Metformin	Decreases hepatic gluconeogenesis, improves peripheral insulin sensitivity, reduces intestinal glucose absorption	First-line therapy, weight neutral, cardiovascular benefit	GI intolerance, lactic acidosis (rare)
Thiazolidinediones (TZDs)	Pioglitazone, Rosiglitazone	Enhances insulin sensitivity by regulating adipokine expression and fatty acid metabolism	Improves insulin resistance, durable glycemic control	Weight gain, edema, heart failure risk
Alpha-Glucosidase Inhibitors	Acarbose, Miglitol	Delays carbohydrate digestion and glucose absorption in intestine	Controls postprandial hyperglycemia	Flatulence, abdominal discomfort
DPP-4 Inhibitors	Sitagliptin, Vildagliptin	Inhibits incretin degradation → ↑ GLP-1 & GIP → glucose-dependent insulin secretion	Low hypoglycemia risk, weight neutral	Moderate efficacy, cost
GLP-1 Receptor Agonists	Exenatide, Liraglutide	Enhances glucose-dependent insulin secretion, suppresses glucagon, delays gastric emptying	Weight loss, β-cell protection, CV benefit	Injectable, GI adverse effects
SGLT-2 Inhibitors	Empagliflozin, Canagliflozin	Reduces renal glucose reabsorption → glucosuria	Cardioprotective, renoprotective, weight loss	Genital infections, dehydration

6. Emerging and future therapies

Newer agents aim to address multiple pathophysiologic defects simultaneously. Dual GIP/GLP-1 receptor agonists (e.g. tirzepatide) have produced unprecedented reductions in HbA1c and body weight compared with GLP-1RAs or basal insulin alone, reflecting synergistic incretin effects on insulin secretion, appetite regulation and energy expenditure.

(11,13,55) Ongoing cardiovascular and renal outcome trials will clarify their role in high-risk populations. (55)

Other investigational strategies include multi-incretin agonists, glucagon/GLP-1 co-agonists, small-molecule GLP-1 receptor agonists, agents targeting inflammation (e.g. IL-1 antagonists), oxidative stress and specific signaling nodes such as protein tyrosine phosphatase 1B (PTP1B). (2,5,14,55) Cell-based therapies—including islet transplantation, stem cell-derived β-cells and immune-modifying regimens—offer the prospect of disease-modifying or curative approaches in T1D, although significant scientific, logistical and economic challenges remain. (12,14,56)

7. Diabetes Prevention and Lifestyle Interventions

The Diabetes Prevention Program (DPP) landmark study demonstrated that intensive lifestyle intervention including diet modification targeting 7% weight loss and 150 minutes weekly moderate-intensity exercise reduced T2D progression by 58% compared with 31% reduction with metformin monotherapy in individuals with impaired glucose tolerance.(12)(15) Lifestyle modifications remained superior to pharmacotherapy during extended follow-up, establishing lifestyle intervention as first-line prevention in prediabetic populations.(10)(16)Additional preventive pharmacotherapies show efficacy in T2D delay: acarbose reduced annual diabetes incidence to 2.0% versus 11.6% in control subjects in the Chinese Diabetes Prevention Program, while metformin reduced incidence to 4.1%, demonstrating intermediate efficacy between placebo and lifestyle intervention.(18) GLP-1 agonists and SGLT2 inhibitors demonstrate emerging evidence for diabetes prevention in high-risk populations, though lifestyle intervention remains superior and preferred initial approach.(86)(12)(18)

8. CONCLUSIONS

Diabetes mellitus arises from the convergence of insulin resistance, β-cell dysfunction, autoimmunity, chronic low-grade inflammation, oxidative stress, environmental exposures and organ crosstalk involving adipose tissue, liver, skeletal muscle, pancreas, gut, kidney, vasculature and the immune system. (3–5,8,11,14) The uploaded review by Antar and colleagues underscores the central role of inflammatory and oxidative mediators, environmental toxins and organ-specific complications in the natural history of diabetes, providing a rich pathophysiologic framework for identifying therapeutic targets. (3)

Modern antidiabetic therapy increasingly reflects this mechanistic understanding. Rather than focusing solely on glucose normalisation, treatment strategies are now designed to address multiple pathophysiologic defects and to prevent or delay cardiovascular and renal complications. Metformin remains the cornerstone for many patients with T2D, while GLP-1 receptor agonists and SGLT2 inhibitors with proven outcome benefits are prioritised in those with ASCVD, heart failure or CKD. (6,7,23,33,35,48,50) Combination therapy is often required to simultaneously target hepatic glucose production, peripheral insulin resistance, β-cell dysfunction and renal glucose handling. (4,6,15,23)

Looking ahead, more refined phenotyping—through clinical clustering, genetics, biomarkers and digital phenotypes—may allow tailoring of therapy to individual pathophysiologic profiles, maximising benefit and minimising harm. (10,11,14,55) Integrating lifestyle interventions, pharmacological agents with pleiotropic cardiorenal protective effects and, eventually,

disease-modifying immunologic or cell-based therapies holds promise for transforming the prognosis of people living with diabetes worldwide. (2,12,14,36,56)

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