



Type 2 Diabetes Mellitus: From Insulin Resistance and β -Cell Failure to Management

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Abstract

Background: Type 2 diabetes mellitus (T2DM) is a heterogeneous metabolic disorder in which insulin resistance, progressive β -cell dysfunction, altered glucagon biology, adipose tissue dysfunction, ectopic lipid deposition, inflammation, and disturbed energy sensing interact over years before overt hyperglycemia appears. The therapeutic landscape has changed markedly, moving from a glucose-centered approach toward simultaneous control of glycemia, body weight, cardiovascular risk, kidney disease, and heart failure. Aim: To review the current pathophysiological framework of T2DM and connect it to contemporary pharmacological treatment, with particular attention to mechanisms that explain drug selection and organ protection. Methods: Evidence from major mechanistic studies, clinical trials, systematic reviews, and professional guidelines was integrated, with emphasis on insulin signaling, β -cell stress, incretin biology, renal glucose handling, AMPK-related pathways, and the clinical pharmacology of established and newer glucose-lowering agents. Results: T2DM develops through a network of defects involving impaired insulin receptor signaling, increased hepatic glucose production, reduced skeletal-muscle glucose uptake, lipotoxicity, glucotoxicity, mitochondrial and endoplasmic reticulum stress, and progressive loss of β -cell functional reserve. Metformin remains an effective and accessible foundation for many patients, while sodium-glucose cotransporter 2 inhibitors and glucagon-like peptide-1 receptor agonists have expanded treatment goals through cardiovascular and renal protection. Dual incretin agonism has further strengthened the role of weight-centered therapy. Sulfonylureas, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, and insulin retain important roles when selected according to phenotype, efficacy needs, hypoglycemia risk, cost, and comorbidity. Conclusion: Modern T2DM pharmacotherapy is best understood as mechanism-informed, patient-centered risk modification rather than sequential glucose lowering alone.

Keywords: Type 2 diabetes mellitus, Insulin resistance, β -cell dysfunction, Pharmacotherapy



Introduction

T2DM is the dominant form of diabetes worldwide and reflects a long interaction between inherited susceptibility, excess adiposity, dietary exposure, reduced physical activity, aging, sleep disruption, and several metabolic stressors. Hyperglycemia is the measurable clinical consequence, but the disease begins earlier, when insulin-sensitive tissues require progressively greater insulin concentrations to maintain normal glucose disposal. Once pancreatic β -cells can no longer compensate, fasting and postprandial glucose concentrations rise and the disease becomes clinically apparent. This framework explains why a single biochemical target cannot fully represent T2DM and why effective treatment increasingly addresses weight, cardiovascular disease, kidney disease, heart failure, and metabolic liver disease in parallel with glycemic control. [1]

Epidemiology and Clinical Burden

The prevalence of T2DM has increased with population aging, urbanization, obesity, and declining physical activity. The disease contributes substantially to premature cardiovascular disease, chronic kidney disease, neuropathy, retinopathy, liver disease, disability, and health-care expenditure. In many populations, diagnosis occurs after a prolonged asymptomatic phase, so vascular and metabolic injury may already be present when hyperglycemia is first recognized. This delay makes early risk identification and treatment of obesity, hypertension, dyslipidemia, smoking, and kidney disease essential components of diabetes care rather than secondary considerations. [2]

Insulin Resistance as an Early Metabolic Defect

Insulin resistance is characterized by a reduced biological response to insulin in skeletal muscle, liver, adipose tissue, and other insulin-responsive organs. In skeletal muscle, impaired insulin receptor substrate and PI3K/Akt signaling reduces GLUT4 translocation and limits glucose uptake. In the liver, insulin fails to adequately suppress gluconeogenesis and glycogenolysis, while in adipose tissue impaired antilipolytic signaling increases circulating free fatty acids. These changes reinforce each other: excess fatty acids promote ectopic lipid accumulation, diacylglycerol-protein kinase C signaling, inflammatory kinase activation, and inhibitory serine phosphorylation of insulin receptor substrates. [3]

β -Cell Compensation and Progressive Failure

During early insulin resistance, β -cells increase insulin secretion and may expand functional mass to maintain near-normal glucose concentrations. This compensation has limits. Persistent demand for insulin synthesis exposes β -cells to oxidative stress, endoplasmic reticulum stress, disturbed calcium handling, islet inflammation, and accumulation of islet amyloid polypeptide. β -cells are particularly vulnerable to oxidative injury because their antioxidant capacity is relatively modest. With time, first-phase insulin secretion becomes blunted, postprandial glucose rises, and later fasting hyperglycemia develops as β -cell reserve declines. [4]

Glucotoxicity, Lipotoxicity, and Metabolic Memory

Chronic hyperglycemia aggravates insulin resistance and β -cell injury through advanced glycation products, reactive oxygen species, protein kinase C activation, hexosamine pathway flux, and altered gene regulation. Elevated free fatty acids exert parallel effects on mitochondria, endoplasmic reticulum, membrane signaling, and inflammatory pathways. When glucose and lipid excess coexist, glucolipotoxicity develops and accelerates β -cell dysfunction. Some of these molecular alterations persist after later improvement in glycemia, helping to explain the concept of metabolic memory and the value of early durable risk-factor control. [5]

Adipose Tissue as an Endocrine Organ

Adipose tissue dysfunction is central to T2DM. Hypertrophic adipocytes release excess fatty acids and develop local hypoxia, macrophage recruitment, and altered adipokine secretion. Reduced adiponectin and increased pro-inflammatory mediators such as TNF- α and interleukin-6 impair insulin signaling in liver and muscle. Visceral and ectopic fat are particularly important because they are closely linked to hepatic steatosis, dyslipidemia, and insulin resistance. This biology explains why weight reduction can improve glycemia beyond the numerical effect of caloric restriction and why pharmacological strategies



that reduce adiposity have become major components of diabetes treatment. [6]

Mitochondrial Dysfunction and Oxidative Stress

Mitochondria influence both insulin sensitivity and β -cell stimulus-secretion coupling. In insulin-resistant tissues, oversupply of glucose and fatty acids increases electron transport pressure and reactive oxygen species generation, while impaired mitochondrial flexibility limits the switch between substrates. In β -cells, mitochondrial ATP production is required for glucose-stimulated insulin secretion, so mitochondrial injury directly affects insulin release. Oxidative stress also activates stress kinases and inflammatory pathways that further inhibit insulin signaling, creating a feed-forward loop between metabolic overload and cellular dysfunction. [7]

Endoplasmic Reticulum Stress and the Unfolded Protein Response

The endoplasmic reticulum coordinates insulin biosynthesis and protein folding. Nutrient excess, free fatty acids, and increased proinsulin production can exceed folding capacity and activate the unfolded protein response. Initially, this response is adaptive: translation is reduced and chaperone systems increase. Persistent stress, however, activates pro-apoptotic mediators including CHOP and disturbs calcium homeostasis. ER stress is therefore positioned at the interface between β -cell secretory overload, inflammation, mitochondrial dysfunction, and apoptosis, making it a mechanistically attractive target even though direct ER-stress drugs have not yet become standard diabetes therapy. [8]

Inflammation and Innate Immune Signaling

Low-grade inflammation is not merely a consequence of obesity; it actively participates in insulin resistance. Nutrient excess, gut-derived signals, adipocyte stress, and cell injury activate innate immune pathways including toll-like receptor signaling and NF- κ B-related transcription. Inflammatory cytokines impair insulin receptor signaling and can promote β -cell dysfunction. This inflammatory-metabolic interface helps explain why several insulin-sensitizing interventions also reduce inflammatory markers, although broad anti-inflammatory therapy is not currently a routine glucose-lowering strategy. [9]

AMPK, Sirtuins, and Cellular Energy Sensing

AMP-activated protein kinase (AMPK) functions as a cellular energy sensor and coordinates glucose uptake, fatty-acid oxidation, mitochondrial biogenesis, and autophagy. Activation of AMPK promotes metabolic efficiency and can enhance GLUT4-related glucose disposal, while interactions with SIRT1 and PGC-1 α support mitochondrial adaptation. Metformin engages this network indirectly through changes in cellular energy status and hepatic metabolism. The AMPK-SIRT1-PGC-1 α axis is therefore useful for linking classical pharmacology with modern concepts of metabolic resilience, although the relative contribution of individual downstream pathways differs among tissues and drug exposures. [10]

The Incretin System and Enteroinsular Signaling

After oral nutrient intake, GLP-1 and glucose-dependent insulintropic polypeptide amplify glucose-dependent insulin secretion. GLP-1 also suppresses glucagon, slows gastric emptying, and reduces appetite through central and peripheral mechanisms. In T2DM the incretin effect is impaired, but pharmacological amplification remains effective. This led to two major strategies: inhibition of DPP-4 to prolong endogenous incretin action and administration of receptor agonists with much greater and more sustained pharmacological activity. The latter class has become particularly important because it can combine glucose lowering with meaningful weight reduction and cardiovascular benefit. [11]

Renal Glucose Handling and SGLT2

The kidney contributes to hyperglycemia by reabsorbing most filtered glucose through sodium-glucose cotransporter 2 in the proximal tubule. SGLT2 inhibition lowers the renal threshold for glucose and produces glucosuria through an insulin-independent mechanism. The resulting modest osmotic diuresis, natriuresis, reduction in intraglomerular pressure, and changes in substrate utilization have clinical effects extending well beyond HbA1c lowering. Large outcome trials established reductions in heart-failure hospitalization and progression of chronic kidney disease, which has moved SGLT2 inhibitors from purely glucose-lowering drugs to cardio-renal medicines. [12]



Diagnosis and Glycemic Assessment

Diagnosis is based on validated thresholds for fasting plasma glucose, 2-hour glucose during a 75-g oral glucose tolerance test, HbA1c, or random plasma glucose in a patient with classic symptoms. HbA1c is convenient because it reflects average glycemia over several weeks, but interpretation may be altered by conditions affecting erythrocyte turnover or hemoglobin structure. Once diabetes is diagnosed, glycemic targets should be individualized rather than applied mechanically, taking into account age, comorbidity, hypoglycemia risk, life expectancy, treatment burden, and the potential value of tighter control. [13]

Lifestyle Intervention and Weight Reduction

Nutrition, physical activity, sleep, smoking cessation, and structured diabetes education remain foundational because they influence insulin sensitivity, body weight, blood pressure, lipid profile, and treatment adherence. A sustained loss of 5–10% of initial body weight can substantially improve metabolic control, while larger losses may produce remission in selected patients with relatively recent T2DM. Resistance training adds benefit to aerobic activity by improving muscle glucose disposal. Lifestyle treatment should therefore accompany pharmacotherapy rather than be treated as a preliminary phase that ends when medication starts. [14]

Metformin

Metformin remains one of the most widely used glucose-lowering drugs because it is effective, inexpensive, weight neutral or modestly weight reducing, and has a low intrinsic risk of hypoglycemia. Its principal clinical action is suppression of excessive hepatic glucose production, with additional effects on gut metabolism and peripheral insulin sensitivity. Pharmacologically, metformin alters cellular energy handling and can activate AMPK-dependent and AMPK-independent pathways. Gastrointestinal intolerance is common, vitamin B12 deficiency may develop with long-term exposure, and dose adjustment or avoidance is required in advanced renal impairment because of concern about lactic acidosis. [15]

Sulfonylureas and Meglitinides

Sulfonylureas stimulate insulin secretion by binding to the SUR1 component of ATP-sensitive potassium channels in pancreatic β -cells, causing membrane depolarization and calcium-dependent insulin exocytosis. They lower glucose effectively and remain useful where cost is a major constraint, but their action is largely glucose independent and therefore carries risks of hypoglycemia and weight gain. Meglitinides act on the same channel complex with shorter pharmacokinetics and greater emphasis on prandial insulin release. These agents retain practical value, but their position has narrowed as drugs with lower hypoglycemia risk and organ-protective effects have become available. [16]

Thiazolidinediones

Thiazolidinediones activate peroxisome proliferator-activated receptor- γ and improve insulin sensitivity in adipose tissue, liver, and muscle. Redistribution of lipid away from ectopic sites and increased adiponectin contribute to their metabolic effects. Pioglitazone can produce durable glycemic improvement and has potential benefit in selected patients with steatotic liver disease, but fluid retention, weight gain, fracture risk, and concern in heart failure limit broad use. Their pharmacology illustrates an important principle in T2DM: improving insulin sensitivity can be powerful, but tissue-specific adverse effects may determine clinical usefulness. [17]

DPP-4 Inhibitors

DPP-4 inhibitors increase endogenous GLP-1 and GIP concentrations by slowing enzymatic degradation. Their glucose-lowering effect is modest, but they are orally administered, generally weight neutral, and have a low risk of hypoglycemia when not combined with insulin or secretagogues. They are particularly useful when simplicity and tolerability are priorities. Cardiovascular outcome trials demonstrated overall cardiovascular safety for the class, although heart-failure signals with some agents require attention. DPP-4 inhibitors should not be combined with GLP-1 receptor agonists because the combination adds little pharmacological benefit. [18]



GLP-1 Receptor Agonists and Dual Incretin Agonism

GLP-1 receptor agonists provide glucose-dependent insulin secretion, glucagon suppression, delayed gastric emptying, reduced appetite, and clinically meaningful weight loss. Several agents also reduce major adverse cardiovascular events in people with T2DM at high cardiovascular risk. The development of dual GIP/GLP-1 receptor agonism has further increased the achievable reductions in HbA1c and body weight. These drugs have shifted the therapeutic hierarchy because weight management is now treated as a disease-modifying goal rather than an optional benefit. Gastrointestinal adverse effects are common during dose escalation, and treatment selection should incorporate tolerability, access, and individual comorbidity. [19]

SGLT2 Inhibitors as Cardio-Renal Drugs

SGLT2 inhibitors have a comparatively modest glucose-lowering effect at reduced glomerular filtration, yet their cardiovascular and renal benefits remain clinically important. They reduce heart-failure events in patients with and without diabetes and slow chronic kidney disease progression across a range of albuminuria. Adverse effects include genital mycotic infection, volume depletion in susceptible patients, and rare euglycemic diabetic ketoacidosis. Temporary interruption is appropriate during major surgery, prolonged fasting, or severe acute illness. Their modern use is driven more by cardiorenal phenotype than by the magnitude of HbA1c reduction alone. [20]

Insulin Therapy

Progressive β -cell failure means that many people with long-standing T2DM eventually require insulin. Basal insulin is commonly introduced first because it targets fasting hyperglycemia with less complexity than full basal-bolus therapy. When postprandial control is inadequate, prandial insulin or a GLP-1-based strategy may be added. Insulin has no ceiling effect for glucose lowering, but weight gain and hypoglycemia remain important limitations. Contemporary guidance therefore favors GLP-1-based therapy before insulin in many patients without severe hyperglycemia and encourages continuation of organ-protective agents when insulin is started, unless contraindications exist. [21]

Person-Centered Drug Selection

Modern treatment algorithms no longer require a rigid sequence of metformin followed by progressively stronger glucose-lowering drugs. In people with established or high risk of atherosclerotic cardiovascular disease, heart failure, or chronic kidney disease, SGLT2 inhibitors and/or GLP-1 receptor agonists with proven outcome benefit should be considered independently of baseline HbA1c and, in many situations, independently of metformin use. For patients without these comorbidities, treatment can be chosen according to glycemic potency, weight goals, hypoglycemia risk, adverse effects, cost, route of administration, and patient preference. [22]

Prevention of Microvascular and Macrovascular Complications

Reducing hyperglycemia remains essential for prevention of retinopathy, nephropathy, and neuropathy, particularly when good control is achieved early in the disease course. Macrovascular risk reduction requires a broader strategy including blood-pressure control, lipid lowering, smoking cessation, antiplatelet therapy when indicated, and preferential use of glucose-lowering agents with cardiovascular benefit. The distinction between 'diabetes treatment' and 'cardiovascular prevention' has therefore become increasingly artificial; pharmacological care is now organized around integrated risk reduction. [23]

Therapeutic Gaps and Future Directions

Important gaps remain despite the expansion of available drugs. Treatment access is unequal, long-term adherence is difficult, and many patients remain exposed to therapeutic inertia. Precision pharmacology is likely to develop around clinical phenotypes, genetic architecture, β -cell reserve, obesity biology, kidney function, liver disease, and cardiovascular risk rather than a single universal sequence. Additional interest surrounds combination incretin approaches, agents targeting glucagon biology, β -cell preservation, inflammation, mitochondrial stress, and metabolic liver disease. The major challenge is to translate mechanistic sophistication into affordable, durable, and safe care. [24]



Conclusion

T2DM is a progressive metabolic disease produced by the interaction of insulin resistance, β -cell dysfunction, abnormal adipose biology, ectopic lipid exposure, inflammation, and impaired cellular energy handling. Its pharmacological management has moved beyond a glucose-only model. Metformin remains important, but GLP-1-based therapies and SGLT2 inhibitors have changed treatment by linking glycemic control to weight reduction and cardiovascular and renal protection. Drug selection should therefore be guided by the patient's dominant clinical risks, treatment goals, safety profile, access, and preferences. The strongest long-term strategy combines early metabolic control with sustained weight management and aggressive reduction of cardiovascular and kidney risk.

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