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Review

Diabetes mellitus—Progress and opportunities in the evolving epidemic

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SUMMARY

Diabetes, a complex multisystem metabolic disorder characterized by hyperglycemia, leads to complications that reduce quality of life and increase mortality. Diabetes pathophysiology includes dysfunction of beta cells, adipose tissue, skeletal muscle, and liver. Type 1 diabetes (T1D) results from immune-mediated beta cell destruction. The more prevalent type 2 diabetes (T2D) is a heterogeneous disorder characterized by varying degrees of beta cell dysfunction in concert with insulin resistance. The strong association between obesity and T2D involves pathways regulated by the central nervous system governing food intake and energy expenditure, integrating inputs from peripheral organs and the environment. The risk of developing diabetes or its complications represents interactions between genetic susceptibility and environmental factors, including the availability of nutritious food and other social determinants of health. This perspective reviews recent advances in understanding the pathophysiology and treatment of diabetes and its complications, which could alter the course of this prevalent disorder.

INTRODUCTION

Diabetes mellitus has afflicted mankind for millennia.[1] From the time of the "early" descriptions of the malady to the present time, there has been an explosion in our understanding of the prevalence, pathophysiology, complications, and therapeutic options for the growing number of individuals worldwide who live with diabetes or are at increased risk for developing this disorder. Diabetes develops when there is insufficient insulin to stimulate the physiological disposal of glucose to promote the storage of energy in adipose tissue, muscle, and liver. The phenotypic spectrum of diabetes spans disorders of near total insulin deficiency, as occurs in type 1 diabetes (T1D), to relative insulin deficiency in the context of insulin resistance (IR) that characterizes type 2 diabetes (T2D). Although the diagnosis of diabetes is based on measuring blood glucose or glycated hemoglobin, the disorder should be considered a multisystem disorder that is associated with multiple comorbidities. Diabetes is broadly categorized as T1D, which develops on the basis of immune destruction of beta cells; T2D, which is associated with IR and relative beta cell insufficiency, diabetes syndromes specifically attributable to monogenic disorders, drug toxicity, or to pancreatic insufficiency; and diabetes of pregnancy (gestational diabetes). By far the largest numbers of individuals are affected by T2D, followed by T1D, which accounts for less than 5% of all cases. In 2021, the global prevalence of diabetes mellitus was estimated to be 6.1%, representing 529 million people, with prevalence estimates in certain regions as high as 12.3%. T2D accounts for 96% of cases, and greater than 50% of T2D is attributable to obesity. The trajectory of the diabetes pandemic is concerning, with an estimated 1.31 billion individuals projected to have diabetes by 2050, with prevalence exceeding 10% in two super-regions (16.8% in north Africa and the Middle East and 11.3% in Latin America and the Caribbean).[2] Other analyses suggest that the 2021 global prevalence already exceeds 10%.[3] Moreover, in 2021, an additional 464 million individuals were estimated to have impaired glucose tolerance and 298 million with impaired fasting glucose tolerance, collectively representing prediabetes.[4] Diabetes increases all-cause mortality largely from cardiovascular and renal disease and contributes

to multiple other morbidities, including blindness, limb loss, chronic pain, and disability.[5] Prediabetes also "clusters" with increased cardiovascular disease (CVD).[6] As such, the diabetes pandemic if left unchecked will continue to place significant burdens on public health.

Although elevated circulating glucose is a characteristic diabetes of any cause, T2D is a heterogeneous disorder with differences in outcomes in distinct population subgroups. Given the association between obesity and T2D, it has been argued that much of this burden could be preventable with increased focus on policy that would improve nutrition, increase physical activity, and reduce obesity. However, the heterogeneity of diabetes indicates that prevention and treatment strategies should ideally be tailored to maximize their efficacy in specific populations. Many fundamental questions remain regarding underlying mechanisms that increase the risk of diabetes in obesogenic environments and identification of targets that will reverse the metabolic abnormalities and reduce complications, particularly cardiorenal disease in individuals with established diabetes. Diabetes is a multisystem disorder driven by complex interactions between genetic predisposition and environmental variables that lead to metabolic dysfunction characterized by beta cell failure, organ-specific changes in insulin action, and inter-organ crosstalk that contribute to disease progression. Moreover, significant advances have been made in understanding the neurobiological basis of obesity and mechanisms arising from adipose tissue expansion, both of which are major risk factors for T2D.

Over the past 50 years, we have witnessed an explosion in knowledge addressing pathophysiology of T1D and T2D that is now revolutionizing approaches to diabetes treatment and prevention. Thus, any perspective on advances in the understanding of diabetes pathophysiology and treatment cannot be exhaustively comprehensive. We have structured this review on three broad areas to highlight recent advances in knowledge that inform the pathophysiology of T1D and T2D, prevalent organ-specific complications leading to cardiovascular and renal dysfunction, and recent advances in therapy. In addressing pathophysiology, we focus on key organs involved in diabetes pathophysiology namely the beta cell, brain, adipose tissue, skeletal muscle, and liver, and we discuss environmental determinants that contribute to diabetes prevalence, particularly in vulnerable populations. Although diabetes complications include retinopathy and neuropathy, which have been extensively reviewed,[7] in this perspective, we focus on cardiovascular and kidney disease that quantitatively represent major drivers of diabetes-related health care costs, morbidity, and mortality. Regarding diagnosis and treatment, we focus on potential roles of precision approaches to refine therapy, advances in the prevention and treatment of T1D, and the new era of therapeutics for T2D, which in addition to metabolic control are now impacting cardiorenal complications and reversing obesity.

PATHOPHYSIOLOGY OF DIABETES—CURRENT STATE AND FUTURE PERSPECTIVES

This section will review lessons learned from human genetics approaches that seek to inform diabetes pathophysiology and review the pathophysiology of T1D. Specific contributions of the brain and nervous system, adipose tissue, skeletal muscle, and liver to T2D pathophysiology, particularly in humans, will be reviewed. We will then discuss the importance of environmental factors that play an important role in diabetes pathogenesis.

Genetics of T2D

At the end of the last century, our understanding of the genetic landscape for T2D, although not universally accepted, centered on the notion that only a handful of loci, each with a significant impact on an individual's risk for diabetes, would in concert with environmental risk factors, determine whether an individual developed diabetes. Two decades later, powered by hypothesis-free large-scale genome-wide association studies (GWASs), the genetic landscape now comprises of hundreds of variants, the vast majority with very small effect sizes.[8,9] Most T2D-associated variants do not directly alter protein function (i.e., change an amino acid) but rather alter their abundance by modifying regulatory elements in non-coding genomic sequences, which control gene expression.[8,9] Many of these elements work in temporal and spatial dependent manners, meaning they give rise to effects on gene expression in precise cell types and at defined developmental time points.[8,9] The greatest existing challenge and potential opportunity is to map these regulatory signals to relevant genes, often called "effector transcripts," which mediate their influence on diabetes risk. Their identification holds important clues not only into the mechanisms by which glucose homeostasis, diabetes progression, and risk of complications are altered in people with diabetes but also the potential to identify safe and effective targets for therapeutic development.

The emergence of single-cell resolution multi-omic datasets that provide information on whether a gene is expressed in specific cell types, whether chromatin is accessible to transcription factors, and whether promoters are in contact with enhancers provides a powerful strategy for connecting diabetes-associated variants to their effector transcripts.[10] When these data are coupled with high-throughput cellular phenotyping efforts that alter the expression of hundreds or thousands of genes, the disease relevance of altered gene expression linked to variants can be assessed at scale.[11]

Although each of these signals provides an opportunity for biological insight into the underlying pathophysiology of diabetes, unlike in monogenic forms of diabetes, there is currently no direct path to precision diagnostics or medicine. There has been considerable interest in overlaying genetic data for cardiometabolic and glycemic traits with those derived for T2D risk.[12,13] Shared signals provide important clues regarding underlying tissues and mechanisms through which variants alter the risk for diabetes or its complications. For example, genetic signals that are shared between T2D and proinsulin levels point to a mechanism of action in the pancreatic islet. Both "hard" and "soft" clustering approaches have been deployed by researchers to identify common processes, called clusters, which are defective in T2D (e.g., insulin action, beta cell function, dyslipidemia), and their clinical utility is being closely evaluated.[8,13] Since most genetic studies have been performed in European populations, efforts are urgently needed to perform similar

studies in more diverse populations to prevent health disparities arising from limited access to genetically informed diabetes care that addresses diabetes heterogeneity.

Key determinants of beta cell failure and strategies to enhance beta cell function

From the early 1990s, key components of the machinery coupling glucose metabolism to insulin secretion were demonstrated to be critical for glucose homeostasis through identification of mutations causing monogenic forms of diabetes.[14–16] Loss-of-function mutations in the key glycolytic enzyme glucokinase demonstrated the impact of effects of glycolysis on insulin secretion.[14] The discovery that transcription factors (HNF1A/HNF4A) first described in the liver are also crucial to the development and maintenance of the endocrine pancreas set the stage for a wealth of discoveries showcasing the importance of specific steps of pancreas and endocrine cell development that ultimately generate insulin-producing beta cells.[17,18] As the full allelic spectrum of variation in these genes has emerged, it is now recognized that rare fully penetrant mutations have large effects that manifest as diabetes early in life while alleles of more modest effect, which can either alter protein function or gene expression, also contribute to risk for T2D.[19]

Our mechanistic understanding of the various ways that beta cell function can be compromised has benefited from human genetic discoveries (Figure 1). Unexpected links between the exocrine- and endocrine pancreas demonstrated initially by rare mutations in the gene encoding for a digestive enzyme (carboxyl-ester lipase) and more recently by common variants associated with T1D and T2D, which alter levels of circulating exocrine pancreatic enzymes, support epidemiological and clinical evidence for links between pancreatic diseases such as pancreatitis and cystic fibrosis and endocrine cell dysfunction.[9,20] These observations provide opportunities to improve our understanding of the crosstalk between the endocrine and exocrine pancreas. Several lines of evidence now support a role for defective autophagy in maintaining beta cell functional mass.[11] Other genes that have emerged fall into expected categories of ion channels, cell cycle control, and transcription factors pointing to defects in function, proliferation, and development. Studies of human pancreas and islet tissue from cadaveric donors have also demonstrated differences in gene expression, islet composition, intra-islet crosstalk, and epigenetics supporting reduced beta cell mass, islet cell de-differentiation, and metabolic defects as contributing factors to diabetes pathogenesis.[21,22]

Given the importance of beta cell function in maintaining normal glucose tolerance, there is interest in strategies to enhance "functional beta cell mass" as a therapeutic approach for both T1D and T2D. Human genetics has supported the K_{ATP} channel (sulphonylureas) and glucokinase (glucokinase activators) as potential targets for improved insulin secretion. The demonstration that truncated protein variants in the *SLC30A8* gene, which is expressed almost exclusively in pancreatic beta cells, protect individuals from T2D has focused efforts on the development of antagonists against this zinc transporter ZnT8.[23] How loss of this channel promotes enhanced beta cell function remains poorly understood, but the lack of evidence from human genetics for adverse on-target effects makes this an attractive therapeutic pursuit. Undoubtedly the star of the show is the GLP-1 receptor (GLP-1R). Although of interest for decades before GWASs provided support for its efficacy as a therapeutic target, human genetics has provided concrete evidence to support its benefit in lowering circulating glucose and promoting desirable cardiometabolic effects.[24] The success of the GLP-1R agonists (GLP-1RAs) with positive effects beyond glycemic control, such as weight loss and reduced cardiovascular mortality, makes it challenging to develop new therapies exclusively targeting improved beta cell function. The growing success of the GLP-1 class also highlights the huge potential of therapeutics that target disease biology from multiple standpoints.

Pathophysiology of T1D

T1D accounts for 5%–10% of all diabetes cases and results from autoimmune-mediated destruction of pancreatic beta cells. The year 2021 marked the 100th anniversary of the discovery of insulin, an event that transformed T1D from a once fatal diagnosis into a chronic health condition. Over the ensuing 100 years, knowledge gains have facilitated remarkable advances in diabetes management, as well as the recent approvals of the first disease-modifying therapy and the first cell-based therapy for T1D.[25] However, despite these remarkable achievements, only about 20% of individuals with T1D are able to achieve optimal glycemic control,[26] and life expectancy for those with T1D remains 8–17.7 years shorter than those without diabetes, depending upon age at diagnosis.[27,28] We will briefly summarize current understanding of T1D pathophysiology to set the stage for subsequent discussion of how this knowledge has informed novel strategies for disease prevention and reversal.

GWASs have identified over 60 loci that contribute to T1D genetic risk, showing that T1D is highly heritable.[29] The ability to identify T1D genetic risk has facilitated a variety of natural history studies, including birth cohorts assembled through newborn screening and cross-sectional cohorts assembled through targeted autoantibody screening of affected families. Longitudinal assessment of these cohorts has provided insights into environmental associations, potential disease triggers, the trajectory of islet autoimmunity, and the identification of metabolic and immunologic phenotypes during disease evolution.[30–33] One of the most important observations informing the natural history of T1D came from a combined analysis of four birth cohorts from the US and Europe, which demonstrated that the presence of two or more islet autoantibodies led to a >80% risk of developing clinical T1D over 15 years of follow-up.[34] In 2005, this observation formed the basis for a new disease staging system, where stage 1 T1D is defined by the presence of two or more autoantibodies, stage 2 T1D is defined as multiple autoantibody positivity and dsyglycemia, and stage 3 T1D is defined by overt hyperglycemia based on American Diabetes Association standards.[35]

CNS and neural mechanisms

Extensive preclinical data highlight the essential role of the brain in the control of body weight and, in turn, the development of IR and obesity in susceptible individuals. The importance of the central nervous system (CNS) in the control of glycemia and

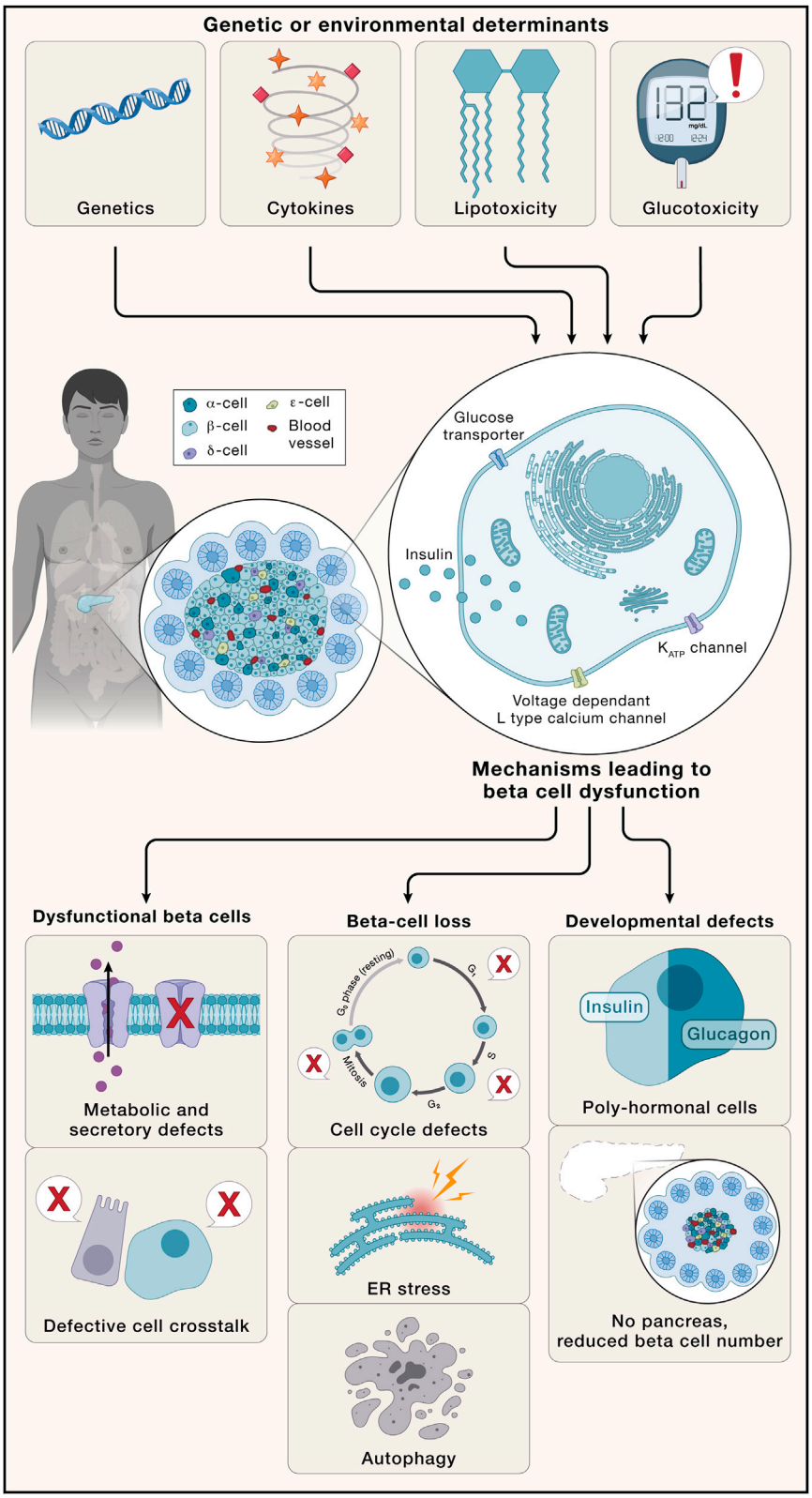


Figure 1. Schematic representation of the potential ways in which pancreatic beta cells are damaged through environmental and genetic factors

Upper arrows represent genetic or environmental determinants. Lower arrows represent mechanisms leading to beta cell dysfunction. Diabetes can arise due to abnormal beta cell development, loss of functional beta cell mass, or through defects in beta cell function. Figure was prepared in BioRender.

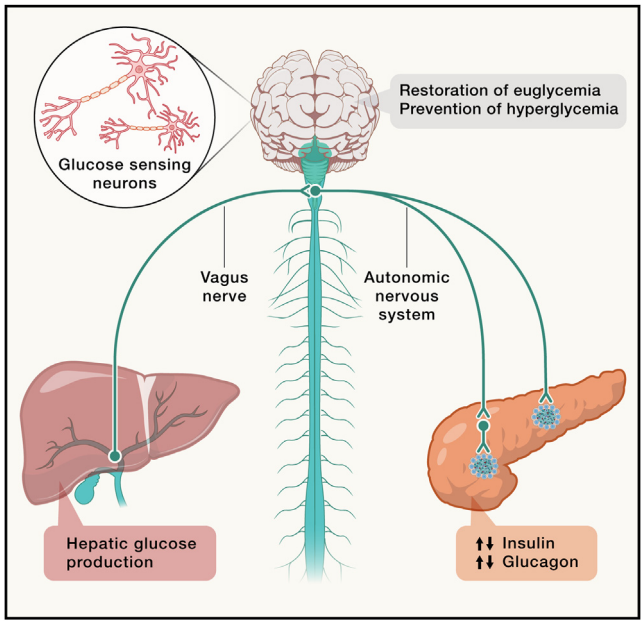


Figure 2. Schematic representation of the interactions between the brain and periphery that may regulate systemic glucose homeostasis

Outputs of glucose-sensing neurons a transmitted via the brain stem and the autonomic nervous to modulate hepatic glucose production and insulin and glucagon release by the liver.

the pathophysiology of T2D is discussed, with an emphasis on insights from human studies. Obesity is an important risk factor for developing T2D. There is broad acceptance that regulation of appetite and energy expenditure, key factors in obesity pathogenesis are centrally regulated, with important contributions from gut- and adipose-derived hormones such as ghrelin and leptin, for example, and potential contributions of alterations in gut microbiota. Much progress has been made in mapping the neural circuits predominantly in the hypothalamus and brain stem that regulate these processes, and these concepts have been extensively reviewed.[36] More recently, there has been growing attention on elucidating the role of the central and autonomic nervous system in integrating body weight regulation and glucose metabolism and specifically the role of the brain in the maintenance of optimal circulating glucose concentrations.[37] Most of these insights have derived from studies in animal models. For example, both vagal and CNS circuits are essential for nutrient sensing, linking ingestion of fat or sugar to dopamine release and over-eating in preclinical studies[38] (Figure 2). This section will focus on recent insights derived mainly from human studies linking central mechanisms to glycemic regulation and T2D and the implications of these observations for therapy.

The central and autonomic nervous systems play important roles in the maintenance of normoglycemia in humans and animals, through the regulation of hepatic glucose production (HGP) and via counterregulatory mechanisms that restore normal glucose levels in response to hypoglycemia (Figure 2). Pancreatic islets are extensively innervated with nerve fibers originating from the hypothalamus, and manipulation of brain glucose levels in the arcuate nucleus of the mouse hypothalamus can lower insulin secretion and impair glucose tolerance.[39] Intriguingly, insulin receptors within tanacytes also contribute to regulation of systemic IR in mice.[40] Intranasal administration of insulin to healthy men undergoing a 2 h. hyperglycemic clamp augmented insulin secretion in a subset of study subjects, with a strong hypothalamic response to insulin as judged by brain changes quantified using functional magnetic resonance imaging (MRI) in response to insulin.[41] In the context of this short-term experimental paradigm, there appears to be inter-individual variation governing the relative importance of brain insulin action for glucose-stimulated insulin secretion. Furthermore, inter-individual differences in brain insulin availability have been described, and brain insulin transport is diminished in subjects with IR and with increased age. Additionally, cerebrospinal insulin levels and brain responses to exogenous insulin are also lower in individuals with obesity.[42]

Brain insulin action, studied in humans following intranasal insulin administration, also contributes to regulation of whole-body insulin sensitivity and HGP.[42] Interestingly, hypothalamic insulin action is linked to control of peripheral insulin sensitivity in women predominantly during the follicular but not the luteal phase of the menstrual cycle.[43] The therapeutic potential for targeting the brain to correct the metabolic defects associated with diabetes is exemplified by studies using administration of fibroblast growth factor-1 (FGF-1). A single intracerebroventricular (icv) injection of FGF-1 produces sustained remission of experimental diabetes in mice and rats through weight loss-independent enhancement of glucose clearance.[44] Similar results, principally sustained remission of diabetes, were described using intranasal or icv administration of FGF-4 in mice.[45] The feasibility of using FGF administration to produce sustained diabetes remission in older mice, rats, and monkeys (and perhaps 1 day in humans) is an important area for further research.

Whether structural and functional defects in the brain contribute to the development of diabetes is an active area of investigation. MRI detects evidence for hypothalamic gliosis in the medial basal hypothalamus of individuals with higher body mass index (BMI), yet individuals with hypothalamic gliosis were also found to have higher insulin levels and IR determined by homeostatic model assessment of IR (HOMA-IR), independent of BMI.[46] Detection of hypothalamic gliosis by MRI was found to predict the subsequent development of IR over a 1-year period of follow-up.[46] Interestingly, the extent of hypothalamic gliosis may be reversed in some but not all subjects after bariatric surgery; however, the importance of these directional changes for associated improvements in glucose control is difficult to ascertain.[47]

Whether the brain is important for the glucose-lowering and metabolic activities of some medicines used for the treatment of T2D in humans is uncertain. The dopamine receptor D2 agonist bromocriptine reduces body weight and improves insulin sensitivity and was approved for use in T2D in 2009, although it is not widely prescribed. GLP-1RAs, introduced in 2005, reduce gastric emptying, food intake, body weight, and systemic inflammation through mechanisms requiring CNS GLP-1Rs.[48,49] Whether CNS GLP-1Rs are required for glucose control is less

clear, as GLP-1RAs directly increase insulin and somatostatin and reduce glucagon secretion through islet GLP-1Rs on α, β, and δ cells independent of CNS GLP-1R activity. Interestingly, administration of the sodium-glucose cotransporter 2 inhibitor (SGLT-2i) empagliflozin for 8 weeks to subjects with prediabetes increased hypothalamic insulin responsiveness as assessed by intranasal insulin administration and concomitant functional MRI.[50] Whether these emerging CNS effects of SGLT2i contribute to one or more of the pleiotropic actions of SGLT2i in people with T2D is unclear and requires more careful scrutiny. Several current and investigational agents being developed for the treatment of T2D and obesity exert a subset of actions through the CNS. These include tirzepatide acting through both glucose-dependent insulinotropic polypeptide receptor (GIPR) and the GLP-1R,[51] as well as glucagon and amylin-containing GLP-1-based therapeutics. Indeed, the principal metabolic actions of amylin agonism, including reduction of gastric emptying, food intake, and glucagon secretion, all require CNS amylin receptor signaling.

There is ongoing interest in the link between T2D and higher rates of neurodegeneration and impairment of cognitive function.[52] Brain insulin responsiveness, assessed following intranasal insulin administration and MRI, is impaired with increasing age in multiple brain regions of healthy subjects.[53] The application of ^{1}H magnetic resonance spectroscopy to study brain metabolites in male and female patients with T2D (HbA1c > 7.5%, mean age 47.4) versus age- and sex-matched controls revealed elevated brain glucose, taurine, *myo*-inositol, and miscellaneous choline-containing compounds in the CNS of people with T2D.[54] Individuals with poorly controlled T2D also exhibit impaired cerebral glucose transport that may be partially reversible with even short-term (12 week) periods of intensification of diabetes therapy and improved glucose control.[55] Interestingly, a randomized trial of intranasal insulin administration once daily for 24 weeks to male and female subjects 50–85 years of age with T2D increased cerebral blood flow and improved several parameters of cognitive function as well as walking speed.[56] GLP-1RAs have also exhibited neuroprotective properties in preclinical studies and reduce the rates of incident dementia in clinical trials and in real-world studies.[57,58] Oral semaglutide is currently being studied in two phase 3 trials for the treatment of people ages 55–85 with early Alzheimer's disease with or without T2D. Taken together, these observations portend ongoing interest in exploring mechanisms in humans linking CNS mechanisms, diabetes pathogenesis, and response to current and novel therapeutics. Whether more brain-penetrant GLP-1 medicines will exhibit greater neuroprotection without higher rates of adverse events (AEs) is not known. Given the overlapping prevalence of neurodegenerative disorders with T2D and the increases of each with aging, identifying shared pathways could lead to additional treatment options that could tackle both disorders.

Adipose tissue dysfunction and lipid mediators of IR

A major driver of T2D is obesity and increased adipose tissue mass.[59] Adipocytes are distinct from other cells in their ability to store lipids. Up to 80% of white adipocyte tissue mass can be composed of lipid droplets, an organelle containing a phospholipid monolayer, and a core of triglycerides and cholesterol esters. The energy storage capacity of adipocytes allows them to play a central role in communicating energy availability as an endocrine organ. Disruption of energy homeostasis by caloric excess leads to IR in adipocytes; these cells expand and swell reaching maximal capacity by hypertrophic growth that induces tissue hypoxia. Adipocyte hypertrophy increases the surface-to-volume ratio that correlates with adipocyte IR and reduced production of the insulin-sensitizing adipokine adiponectin. Adipocyte hypertrophy also increases inflammatory cytokine production, leading to increased infiltration of pro-inflammatory immune cells and systemic inflammation.[60] Metabolically, adipose tissue IR increases lipolysis elevating circulating free fatty acids (FFAs).[61] Thus, adipose tissue expansion is not only a manifestation of tissue-specific IR but also a driver of systemic IR by altering adipokine release, promulgating inflammatory cytokines, and increasing FFA delivery to other organs.

Increased circulating FFAs induce IR in adipocytes, liver, and skeletal muscle in part through increased production of diacylglycerides (DAGs) and ceramides[61–64] (Figure 3). Increased levels of DAGs and ceramides in human plasma are observed in prediabetes and have been proposed as a diagnostic marker of metabolic health.[65] DAGs and ceramides directly drive IR through the activation of phosphatases. Mechanistic experiments in mice and cells demonstrated that DAGs bind protein kinase C ε (PKCε) isozymes at the plasma membrane, leading to inhibitory phosphorylation of the insulin receptor that limits its kinase activity and impairs insulin signaling.[66] This regulation is stereospecific, with sn-1,2 DAGs having higher affinity for PKCε and localization to the plasma membrane, while sn-1,3 and sn-2,3 DAGs have higher localization to the lipid droplet and the endoplasmic reticulum (ER). Excess FFAs in T2D also increase the production of ceramides, especially long-chain C16 and C18.[67] Ceramides activate protein kinase C ζ (PKCζ) for inhibitory phosphorylation of Akt or protein phosphatase 2A (PP2A) to remove activating phosphorylation of Akt, leading to impaired insulin signaling.[68] Induction of IR is specific to ceramides, as other sphingolipids such as dihydroceramides or sphingomyelin fail to induce IR or to inhibit lipolysis in mouse models.[69] As DAG and ceramide levels increase in skeletal muscle and liver, selective IR exacerbates ectopic lipid deposition, further accelerating diabetes pathophysiology.

Another way in which obesogenic adipose tissue drives IR is through decreased release of fatty acid esters of hydroxy fatty acids (FAHFAs).[70] FAHFAs are a class of complex lipids with an ester linkage of two fatty acids that have been shown to improve insulin sensitivity and are decreased with T2D. FAHFAs exert their activity in part by binding to G-protein-coupled receptors in key metabolic tissues to regulate insulin sensitivity, adipogenesis, and energy expenditure in mice.[71] Recent work in mice demonstrated that adipose triglyceride lipase (ATGL) that regulates lipolysis may act as a synthase for FAHFAs, providing a potential link between FAHFAs and lipolysis in T2D through altered ATGL function.[72] The convergence of multiple adipose-derived signals in the obesogenic state drives a feedforward cycle that worsens systemic IR. Adipocyte IR, characterized by impaired glucose uptake has been mechanistically linked to altered release of insulin-sensitizing adipokines and complex lipids, which impact insulin action elsewhere. These changes particularly in liver and skeletal muscle

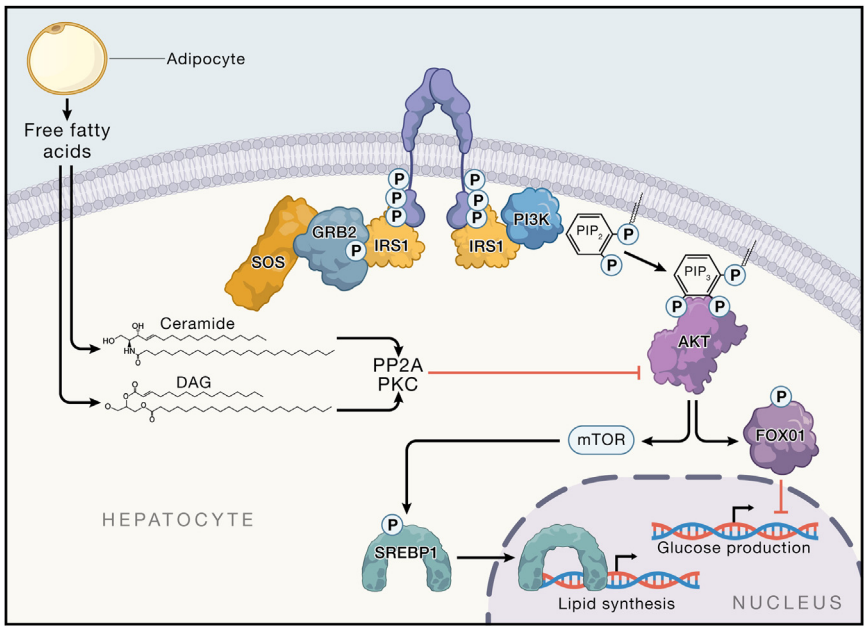


Figure 3. Lipid-mediated disruption of insulin signaling

In type 2 diabetes (T2D) and the metabolic syndrome, basal lipolysis is increased, leading to elevated circulating free fatty acids. These free fatty acids directly inhibit insulin signaling in several tissues including hepatocytes and skeletal muscle. Once taken up into these cells, these free fatty acids are processed into ceramides and DAGs (diacylglycerides), which activate PP2A (protein phosphatase 2A) and protein kinase C (PKC) to inhibit AKT (protein kinase B, or Akt) and mTOR. Decreased insulin signaling in hepatocytes increases glucose production through inhibition of forkhead box protein O1 (FOXO1) contributing to elevated blood glucose levels. The insulin-induced mTOR-mediated lipogenesis through sterol regulatory element binding protein 1 (SREBP1) remains intact despite impaired insulin signaling via AKT, leading to fatty liver. In skeletal muscle cells (not shown) similar signaling defects contribute to impaired translocation of glucose transporters.

are quantitatively the major drivers of increased glucose levels in diabetes.[73]

Skeletal muscle IR is characterized by an early reduction in insulin-mediated glycogen synthesis,[74] impaired insulin-mediated GLUT4 translocation to the plasma membrane, and reduced glucose oxidation.[61] Over time the skeletal muscle IR contributes to skeletal muscle atrophy, diminished exercise capacity, and reduced mitochondrial mass and bioenergetics.[75] Hepatic IR manifests primarily as increased HGP secondary to impaired suppression by insulin of gluconeogenic genes while promoting lipid accumulation. Hyperglycemia per se also exacerbates IR in adipose tissue, skeletal muscle, and liver through increased flux of glucose through the hexosamine biosynthesis pathway to generate uridine diphosphate-N-acetyl glucosamine (UDP-GlcNAc), the precursor to N- and O-linked glycosylation. O-linked glycosylation of insulin signaling proteins including Akt further induces IR.[76] Thus, shared pathophysiology converges to impair insulin action in adipose tissue, skeletal muscle, and liver to perturb metabolic homeostasis in T2D.

Adipose tissue remodeling in obesity is an important driver of systemic IR, inflammation, and aberrant systemic homeostasis of glucose and lipids. Future work is necessary to understand inter-tissue communication, including novel mediators such as exosomes, mechanisms that govern the mobilization of lipids between tissues and organelles, and functional exploration of uncharacterized lipids that will further elucidate lipid dysregulation in T2D and the complex pathophysiological ramifications of these pathways in perpetuating IR.

T2D and MASLD

Hepatic metabolic dysfunction is increasingly recognized in many patients with T2D and also contributes to the pathophysiology of impaired glucose homeostasis and cardiovascular complications of diabetes. Obesity provokes twin abnormalities in liver, increasing both hepatic glucose and lipid production. T2D is a well-established risk factor for the excess triglyceride accumulation that defines the recently renamed metabolic dysfunction-associated steatotic liver disease (MASLD),[77] which is now the leading cause of chronic liver disease in the United States.[78] MASLD ranges in severity from simple steatosis, a prevalent and reversible state,[79] to the inflammatory changes that mark metabolic dysfunction-associated steatohepatitis (MASH) and predispose to fibrosis,[80] the major contributor to mortality in affected patients.[81] Why some individuals develop more severe complications is unknown, but the "multiple-hit" hypothesis[82] that lipid-laden hepatocytes induce aberrant non-parenchymal cell (NPC) activation best explains the progression along this pathogenic continuum. GLP-1-based pharmacotherapy may be helpful in early-stage disease but does not alter disease pathology in the setting of advanced fibrosis.[83] With available livers for transplantation already limiting, metabolic liver disease represents a growing and significant unmet need in a population living with high rates of obesity.

The primary hit—Hepatic lipid accumulation

Increased liver triglycerides in patients with T2D[84] are multifactorial,[85] but a hallmark is excess *de novo* lipogenesis (DNL).[86] DNL is regulated by both the hormonal and nutrient state. In the healthy liver, post-prandial insulin action is transduced via a signaling cascade to Akt, a critical node in determining insulin action.[87] PI3K-mediated Akt-Thr^{308} phosphorylation prompts mTORC2-mediated phosphorylation at Akt-Ser^{473},[87] which within minutes,[88] leads to FoxO1 inactivation to repress HGP. Later, Akt phosphorylates tuberous sclerosis complex 2 (TSC2) to increase mTORC1 signaling,[89] leading to increased sterol regulatory element binding protein 1c (SREBP-1c) activity at lipogenic promoters (Figure 3).[89] In the insulin-resistant liver, Akt-mediated FoxO1 phosphorylation is attenuated, leading to increased HGP and hyperglycemia, but somehow, insulin's ability to promote DNL persists[90] (Figure 3). Recent work has evaluated mechanisms of this paradox.[91] Patients with MASLD show reduced levels of the Akt-Ser^{473} phosphatase PH domain and

leucine-rich repeat protein phosphatase 2 (PHLPP2), due to carbohydrate response element binding protein (CHREBP)-induced expression of its degradation machinery.[92] As mice lacking hepatocyte PHLPP2 show excess DNL,[93] these data suggest that Akt must be appropriately stimulated but also inactivated in a timely fashion to maintain normal hepatic physiology.

Coupled with chronic hyperinsulinemia in many subjects with T2D, these data suggest a revision of the bifurcation model of insulin signaling[90] that shifts focus toward kinetics of insulin action. Inhibition of FoxO1 to repress glucose production represents early insulin action,[94] but an extension of Akt activity induces a "late" lipogenic response.[95] Other potential cell-autonomous mechanisms for excess DNL also contribute,[96] as do adipose[97] and gut signals,[97–99] leading to excess hepatic lipids in patients with T2D. These mechanistic findings are consistent with meta-analyses showing excess liver fat is associated with incident T2D even when adjusted for BMI/adiposity and other potential confounders.[100] Hence, beyond shared risk factors, T2D and MASLD likely increase their respective risks in a bi-directional manner.[96,101]

Hepatocyte-NPC interactions drive MASH pathogenesis

Individuals with T2D often show excess hepatic lipids in imaging tests. What is less clear is which of these individuals will progress to clinically meaningful liver disease, or the time course or inciting factors that initiate this progression. Similarly, GWASs in subjects with T2D and MASLD have exposed common risk alleles in genes that regulate body weight (i.e., *FTO*) or hepatic lipid accumulation (i.e., *PNPLA3*, *TM6SF2*, and *APOB*),[102,103] but these same risks do not translate well to prediction algorithms of disease progression to MASH. Thus, patients with T2D and MASLD may have hepatocytes that intrinsically store but cannot handle excess lipid without cellular injury and/or non-genomic risks that determine hepatocyte-NPC communication, which culminate in inflammation and fibrosis. To distinguish between these hypotheses, investigators have relied on modeling MASH in mice. Traditional high-fat diets (HFDs) induce IR, liver steatosis, and modest inflammation but not fibrosis.[104] Once popular methionine-choline-deficient (MCD) diets that induce liver injury have largely fallen out of favor due to significant anorexia and progressive weight loss. While HFD-MCD hybrid diets were eventually developed,[105] many of these diets fail to mimic obesity and IR that characterizes human disease.[106] To fill the resultant gap, protocols were developed combining fructose-containing drinking water with diets rich in saturated fat, sucrose, and sufficient cholesterol to "humanize" the model, as commonly used strains of mice only absorb a small portion of dietary cholesterol.[107–109] These nutrient-dense diets result in obesity, IR, and all three cardinal features of MASH—hepatic steatosis, inflammation, and fibrosis—and eventually hepatocellular carcinoma (HCC),[110] and thus represent the current state-of-the-art in MASH modeling[111] and are particularly important to mimic comorbid T2D and MASH.

This innovation has enabled better understanding of how hepatocyte-NPC interactions determine heterogeneity in disease trajectory. For example, while hepatocyte IR has long been considered causal to the fasting hyperglycemia that often heralds T2D,[112] recent studies have re-positioned hepatocytes also as causal determinants, not simple bystanders, in liver inflammation and fibrosis. For example, hepatocytes show a surprisingly large endocrine contribution to NPC infiltration and activation through elaboration of chemotactic[113] and fibrogenic[114] cytokines, even in the absence of detectable hepatocyte injury.[114] Upstream determinants of this hepatocyte response include processes that are increased in individuals with T2D and MASLD, such as re-activated Notch signaling[115,116] that increases both HGP[117] and DNL.[118] Understanding dynamics of these hepatocyte signals may have translational implications, given the ability to target hepatocyte pathways with relative specificity, using GalNAc-modified anti-sense oligonucleotides or siRNA, and potentially, *in vivo* base editing.

Despite recent advances, many open questions remain. Key directions for the field include:

Role of hyperinsulinemia and non-hormonal factors in co-incident T2D/MASLD. IR in T2D prompts compensatory hyperinsulinemia.[112] Data from humans show a positive relationship between plasma insulin levels and hepatic DNL,[119] corroborating animal studies suggesting that inappropriate timing of insulin action may be causal to MASLD. Intriguingly, blocking insulin secretion with octreotide decreased DNL markers and liver triglyceride in rats.[120] This concept is now being tested in non-diabetic individuals using diazoxide (NCT05729282); whether these results will extrapolate to individuals with T2D is unknown. Other hormones (i.e., glucagon) clearly contribute as well, not only by forcing glycogen breakdown but also by reducing hepatic lipids. Similarly, fructose[121] and cholesterol[109] may affect hepatic lipid production. Finally, whether non-nutrient and non-hormone determinants of HGP, such as sympathetic outflow to the liver,[122] similarly co-regulate lipid production is less well understood.

Spatial determinants of MASH. The liver is a heterogeneous tissue, with differing oxygen tension and nutrient states across the hepatic lobule, leading to "zonation" of metabolic functions such as gluconeogenesis and lipogenesis.[78] Similarly, MASH can be characterized as primarily pericentral or periportal—especially in pediatric populations—with zonal subtypes associated with different degrees of metabolic and liver pathology.[123] For reasons that are yet unclear, periportal disease is more likely in patients with metabolic syndrome and T2D.[124] Similarly unknown is whether these different patterns reflect a continuum of disease. Understanding this biology may lead to trials in pericentral or periportal disease with therapeutics that target zonated pathways (i.e., Notch, farnesoid X receptor [FXR], thyroid hormone receptor [TR], and peroxisome proliferator-activated receptor [PPAR]).

Fibrosis regression pathways. Despite greater understanding of pro-inflammatory and fibrotic pathways in liver, relatively less attention has been paid to how fibrosis is cleared and how hepatocyte pathways may affect fibrosis resolution. We speculate the existence of commensurate "fibrosis-off" signals for all the recently discovered hepatocyte-determined "fibrosis-on" signals and that a systematic approach for discovery of regression pathways will have similar impact on liver fibrosis as current work in vascular lesion resolution in atherosclerosis,[125] with possible translational implications. Novel therapeutic targets may be of particular value in individuals with T2D, who are partially resistant to the weight loss and downstream hepatic benefits, of incretin therapy.

Bi-directional hepatocyte-NPC crosstalk. Although we highlight the role of hepatocytes as orchestrators of obesity-induced chronic liver injury, NPC populations simultaneously affect hepatocyte health. For example, hepatic stellate cells are an important source of hepatocyte growth factor (HGF), an important determinant of hepatocyte regeneration in reaction to injury,[126] but whether these cells regulate hepatocyte metabolic processes deranged in T2D requires further study. Similarly, increased recruitment of immune cells contributes to altered hepatic insulin sensitivity, which may explain the modest beneficial effects of anti-inflammatory agents in individuals with T2D.[127]

Genetic adaptation to lipid overload. Recent studies found convergent gain-of-function somatic mutations in *FOXO1* that appear to be clonally selected in liver biopsies of patients with MASLD/MASH.[128] Conceptually similar work identified mutations in other metabolic pathways in mouse models.[129] These data suggest the attractive hypothesis that chronic lipid overload may lead to genetic alterations to protect from further injury. Equally intriguing, this finding also represents a plausible mechanism to explain the epidemiologic associations between MASLD and incident T2D.

Relationship with CVD. Hepatic lipid excess increases likelihood of liver-related mortality, but similar to associations in individuals with T2D, the leading cause of death in patients with MASLD/MASH is CVD.[130] Given prevalent comorbidities that directly accelerate CVD, disentangling potential mechanisms will require further mechanistic studies in preclinical animal models and humans.

Social drivers of health: Environments, populations, and molecular mechanisms

Diabetes is a global pandemic, impacting 500 million lives worldwide that disproportionately burdens low and middle-income populations and countries.[2] Social drivers (determinants) of health (SDoH) are the conditions in which people are born, grow, live, work, and age.[131–133] SDoH are shaped by power, money, and resources and are responsible for greater than 60%–70% of health and deleteriously impact T2D.[131–133] The SDoH can be considered within the socioecological model, where social factors, community, and interpersonal relationships influence health behaviors.[6] The SDoH include economic stability (employment, income, expenses, debt, etc.), neighborhood and physical environment (housing, transportation, safety, parks, pollution, geography, etc.), education (literacy, language, etc.), food (food security, nutrition security, access to healthy options, etc.), community and social context (social integration, support systems, community engagement, discrimination, stress, etc.), and the healthcare system (insurance, provider access and availability, linguistic and cultural competency, quality of care, etc.).[131,132] SDoH have both population-level components (e.g., the food system) and individual-level components (e.g., food insecurity), with the individual-level components being referred to as non-medical health-related social needs.[132] The development and control of T2D is uniquely sensitive to SDoH due to the multifaceted effect of SDoH on dysglycemia, from lifestyle behaviors (poor nutritional intake, physical inactivity, sleep insufficiency, stress, etc.) to molecular mechanisms governed by inflammation, hypothalamic-pituitary-adrenal (HPA) axis activation, sympathetic nervous system activation, gut microbial dysbiosis, epigenetic modification, and mitochondrial dysfunction. The impact of SDoH on inequity in T2D outcomes among people and populations has been recently reviewed.[131,132] Here, we review mechanisms linking SDoH and T2D development and progression, using food insecurity and air pollution as two exemplars, and discuss future directions to advance the field.

Food and nutrition insecurity

Food security is defined as "access by all people at all times to enough food for an active, healthy life," while nutrition security was recently defined as "a condition of having equitable and stable availability, access, affordability, and utilization of foods and beverages that promote well-being and prevent and treat disease."[134,135] Thus, nutrition security encompasses food security, dietary quality, and SDoH. Community and individual-level food insecurity are associated with diabetes incidence, prevalence, and poorer control leading to worse long-term outcomes.[134] Food insecurity drives its deleterious impact on diabetes through: (1) diet and nutrition; and (2) stress. Food insecurity is associated with lower fruit and vegetable intake, along with increased processed foods, refined carbohydrates, saturated fats, added sugars, and unhealthy snacks, leading to worse overall diet quality.[134] The overconsumption of these ultra-processed and calorically dense foods and underconsumption of whole grains, fish, nuts, and legumes, essential components of the Mediterranean and American Heart Association's Life's Essential 8 diet are linked to inflammation in the short term through oxidative stress and in the long term lead to adipose tissue expansion, with resultant adipokine-mediated inflammation.[136,137] Food insecurity has been associated with increased inflammation (elevated C-reactive protein [CRP] and white blood cell count),[138] allostatic load (neuroendocrine and inflammatory components including serum DHEA-S and urinary cortisol [HPA axis] and urinary epinephrine and norepinephrine [SNS]), and dietary inflammatory index.[139] Inflammation mediates the association of food insecurity with IR in diabetes[140] and supplemental nutrition assistance moderates the association of food insecurity with inflammation.[141] Food insecurity has also been linked with reductions in gut microbial diversity in a limited set of studies, which could contribute to perturbed inflammatory responses.[142,143] Food insecurity stress impacts compensatory behaviors (time and effort to secure food) and inflammation (toxic stress activates inflammatory pathways).[134,144] The multidimensional complexity of food and nutrition security makes it difficult to establish animal models to interrogate mechanisms, but investigators have recently used unpredictability in the timing and amount of food to recapitulate food insecurity.[145,146] This protocol led to changes in food intake with a heightened attraction to palatable food, weight gain, and impaired coping mechanisms and memory.[145,146] Future studies are warranted to determine the best model to interrogate the pathophysiological pathways of food insecurity to determine precise molecular mechanisms.

Air pollution

Air pollution is a leading environmental health risk.[147] Air pollution is an exemplar SDoH, with people living in lower socioeconomic status environments being more adversely impacted by

air pollution.[147] Three leading air pollutants are ozone (O_3) in smog, nitrogen dioxide (NO_2), an atmospheric gas formed by the oxidation of nitric oxide, and particulate matter (PM), solid, small particles within aerosolized liquid droplets formed during the combustion of fuels.[147] PM is defined by size: coarse (PM10), fine (PM2.5), and ultrafine particles with aerodynamic diameters of 2.5–10 μm, <2.5 μm, and <0.1 μm, respectively.[147] PM is associated with IR, dysglycemia, hyperlipidemia, incident T2D, prevalent T2D, progression to T2D complications, and mortality across the world with Mendelian randomization studies suggesting a causal relationship.[148–155] These associations are strongest among individuals with underlying comorbidities and lower socioeconomic status.[156,157]

Evolving evidence from observational studies, human and non-human acute exposure, and non-human chronic exposure studies suggests that pollution mechanistically impacts IR, glycemia, and T2D through pathophysiological activation of multiple pathways, including primary initiating pathways and secondary effector pathways. Primary initiating pathways include (1) oxidative stress (reactive oxygen and nitrogen species) via redox cycling, depleting cellular thiols, or activating lymphocytes in pulmonary and non-pulmonary vascular beds as mediator of cellular stress signaling, inflammation (e.g., nuclear factor kappa B and NLRP3 inflammasome), and direct impacts on pancreatic beta cells[158–163]; (2) biological intermediates such as damage-associated molecular patterns (DAMPs) generated from tissue damage that recruit neutrophils and activate other immune cells to drive systemic effects[158] (3) direct translocation of pollution components into extrapulmonary organs including the liver and kidney[164]; and (4) alteration of epigenetics through DNA methylation and histone modification.[165] Secondary effector pathways include (1) systemic inflammation with innate and adaptive immune activation[162,166–170]; (2) neurohormonal stress pathway dysregulation with increased sympathetic tone and HPA axis activation[171–176]; (3) hepatic steatosis with impaired glucose metabolism due to mitochondrial dysfunction, ER stress, and impaired lipid catabolism[168,177–179]; and (4) potentially alterations in the gut microbiome, including diversity, relative abundance, gut permeability, and increased inflammation.[180]

DOHaD and SDoH

Consistent with the developmental programming of health and disease (DOHaD) paradigm, SDoH, including food insecurity and air pollution, impacts future development of diabetes in offspring from the periconceptional period through infancy.[181] Some of the best evidence for poor maternal nutrition impacting offspring comes from famines. Adults born across many periods of famine have greater glucose intolerance and risk of T2D as adults.[181] Maternal exposure to air pollution during preconception and gestation has been shown to significantly impair beta cell function and size in adult male offspring of C57Bl/6J mice.[182] These effects are thought to be driven by epigenetic changes including DNA methylation/demethylation, histone modifications, microRNAs, and long non-coding RNAs.[181]

In summary, as exemplars, nutrition security and PM, although contextually different, share common pathophysiological impacts on T2D, including oxidative stress, inflammation, and HPA axis activation (Figure 4). SDoH impact T2D development and progression through direct and indirect pathophysiological effects from environmental, biological, and social factors.[133,183] Further understanding of varying SDoH pathophysiology in exposome-based approaches is critical for developing novel interventions and policies to address SDoH and advance equity in T2D prevention and management.[132,144] Cross-disciplinary team science with diverse human participants and novel animal models capitalizing on expertise across the translational research continuum are key to determining precise mechanistic insights.[184,185]

MECHANISMS OF DIABETES COMPLICATIONS

The persistent metabolic abnormalities associated with diabetes are responsible for tissue dysfunction that lead to the associated morbidity and excess mortality. Diabetic retinopathy is a leading cause of vision loss. Neuropathy and impaired wound healing directly contribute to painful syndromes or limb loss, and autonomic neuropathy may increase CVD mortality and impair gut and genitourinary function. Epidemiologically, diabetes and IR are linked to increased prevalence of certain cancers or to reduced survival or response to therapy. This section will focus on two major drivers of diabetes-related morbidity and mortality, namely CVD and chronic kidney disease (CKD).

Diabetes and CVD

CVD is the major driver of morbidity and mortality in people with T1D and T2D. Multiple epidemiological surveys across diverse populations reveal that diabetes amplifies the risk of atherosclerotic CVD (ASCVD) by 2–5-fold.[186,187] Despite significant improvement over the past 2 decades in the management of traditional CVD risks such as hypercholesterolemia and hypertension that have reduced ASCVD prevalence in the general population, the risk of ASCVD in individuals with diabetes continues to exceed that of the general population.[186,187] Moreover, the continuum of IR, glucose intolerance, dyslipidemia, and obesity that characterize the metabolic syndrome or prediabetes further amplifies ASCVD. The specific manifestations of ASCVD include coronary artery disease (CAD, manifesting as myocardial ischemia and its sequelae), stroke (ischemic and hemorrhagic), and peripheral vascular disease. The increased risk of heart failure in diabetes, although due in part to increased ASCVD, cannot be completely attributable to CAD but also represents direct effects of the abnormal metabolic milieu characteristic of diabetes and the metabolic syndrome on cardiac structure and function, commonly described as diabetic cardiomyopathy.[188] A large body of work at population levels and mechanistic studies in humans and animal models have provided insight into the complex pathophysiology of CVD in diabetes.

No one mechanism singularly accounts for the increased CVD risk in diabetes. The association between increased prevalence of multiple risks that cluster in diabetes (i.e., hypertension, dyslipidemia, obesity, hypercoagulability, increased inflammation, hyperglycemia, IR, kidney disease, physical inactivity, and others) interact in complex ways to drive CVD.[189] Thus, the clinical challenge implicit in strategies aimed at reducing the burden of CVD transcends efforts that focus on a single risk factor such as hyperglycemia.[190] Moreover, certain specific comorbidities appear to cluster with specific manifestations of CVD. For

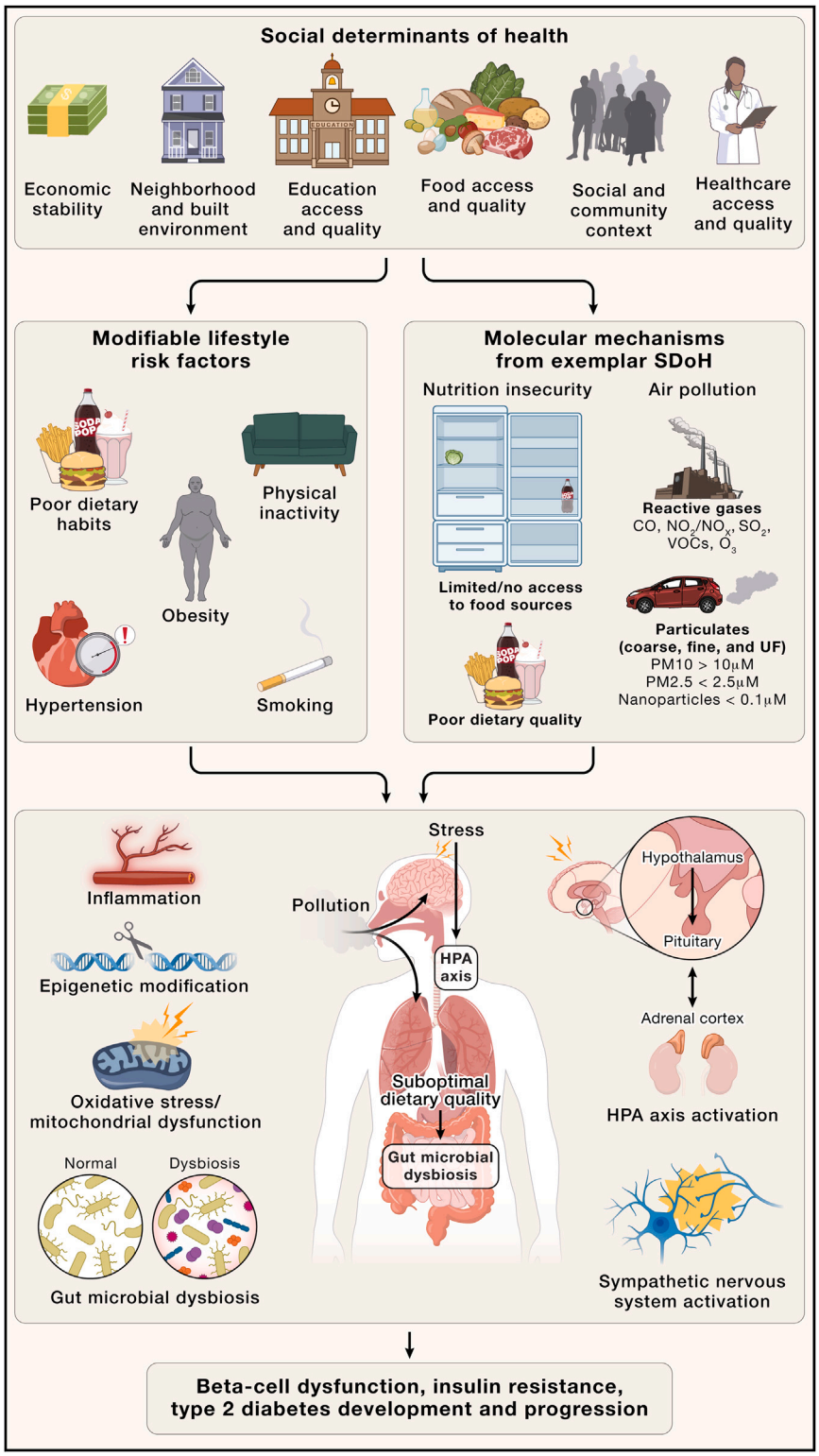
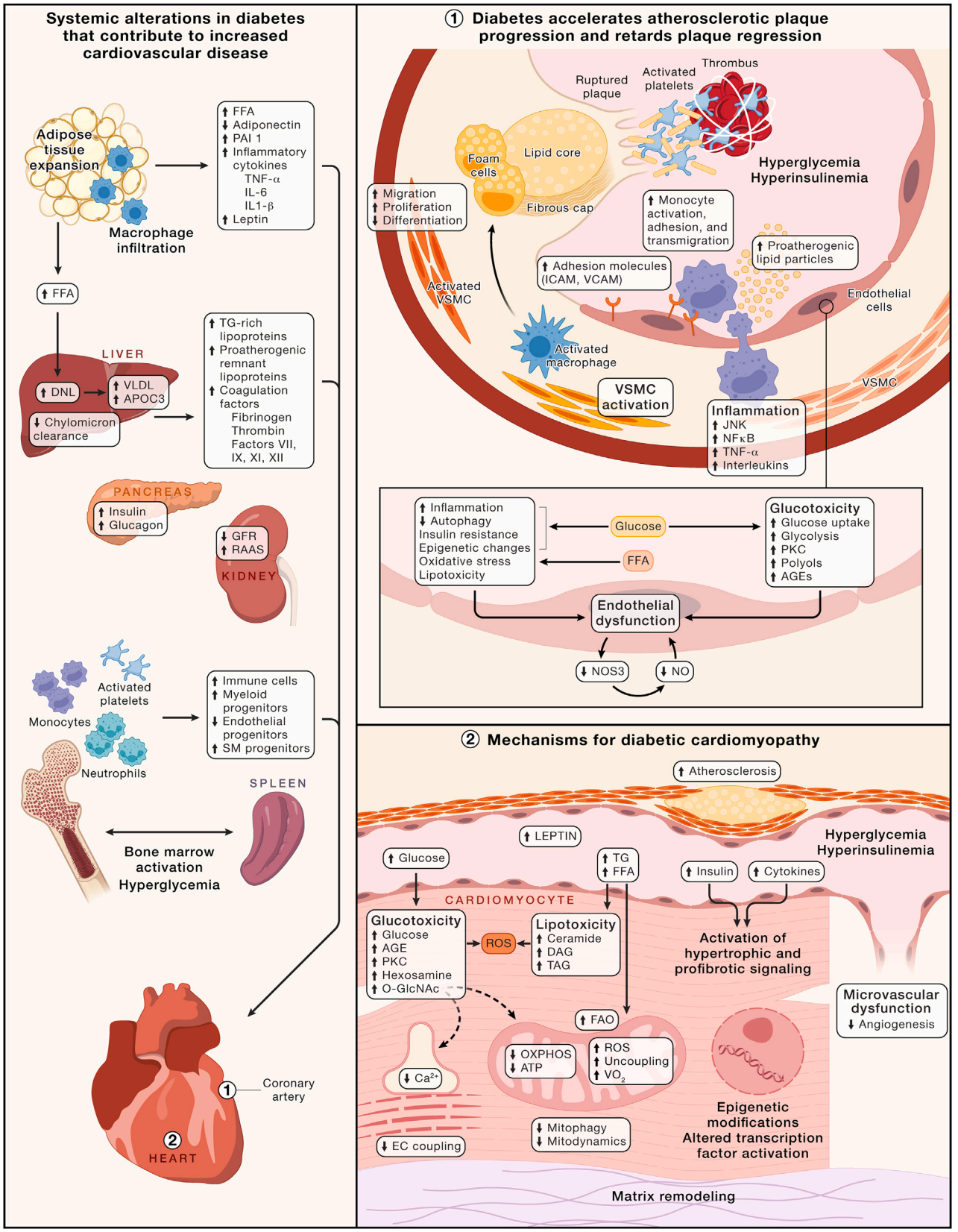


Figure 4. Mechanisms by which environmental and social determinants increase the likelihood of developing type 2 diabetes in susceptible individuals

Social determinants of health including air pollution and nutrition insecurity activate several pathways including hypothalamic-pituitary-adrenal (HPA) axis, which contributes to insulin resistance and exacerbates beta cell dysfunction. These environmental stressors have also been associated with activation of inflammatory pathways, promotion of oxidative stress, gut microbial dysbiosis, and epigenetic modifications, all of which have been implicated in accelerating metabolic disturbances that are characteristic of T2D and the metabolic syndrome.



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example, dyslipidemia, characterized by increased low-density lipoprotein (LDL) cholesterol, reduced high-density lipoprotein (HDL) (or altered HDL composition), and hypertriglyceridemia (with persistence of atherogenic remnant lipoprotein particles derived by lipolysis from very low-density lipoprotein [VLDL] and chylomicrons), is an important driver of CAD in diabetes.[191] A diabetes-specific mechanism linked in humans to decreased clearance of atherogenic triglyceride rich lipoproteins is induction of apolipoprotein C3 (APOC3).[191] The major predictors of CAD in a large European population cohort, including individuals with and without diabetes, were in descending order: diabetes duration, dyslipidemia, HbA1c, blood pressure, and renal function. Whereas acute myocardial infarction was predicted in descending order by LDL cholesterol, HbA1c, smoking, and diabetes duration, the major drivers of heart failure were obesity, HbA1c, renal function, and physical activity. Similarly, the major drivers of cerebrovascular disease were HbA1c, blood pressure, and smoking.[187] Thus, targeting single comorbidities will fall short in reversing CVD burden in diabetes, and therapies will require a personalized approach based on risk evaluation. This has prompted investigations into whether novel biomarkers such as mitochondrial metabolites may also predict major adverse cardiovascular events,[192] which could have utility in risk stratification. Additional epidemiological insights of relevance to heart failure include observations that diabetes is associated with subclinical evidence of myocardial injury manifested by troponin leak and subtle changes in cardiac structure,[193–195] which predict the lifetime risk of heart failure, CVD, and all-cause mortality. Moreover, the presence of or duration of diabetes amplifies the transition from preclinical heart failure to overt disease.[196,197] The clinical efficacy of novel diabetes therapeutics such as GLP-1RAs or SGLT2 inhibitors in reducing CVD is likely mediated by multiple and synergistic effects on diverse comorbidities, the individual effects of which are difficult to quantify.

Atherosclerosis

Atherosclerosis a major driver of ASCVD, develops in the background of endothelial cell (EC) and vascular smooth muscle cell (VSMC) dysfunction. These abnormalities are characterized by increased homing of inflammatory cells such as monocytes and macrophages to ECs that increase their expression of adhesion molecules, including intercellular and vascular cell adhesion molecule -1 (ICAM-1) and VCAM-1, respectively, in concert with VSMC proliferation.[198] Increased uptake of LDL cholesterol in vascular macrophages and VSMC contributes to endothelial dysfunction and hypercholesterolemia activates bone marrow-derived inflammatory monocytes via multiple mechanisms. Once atheromatous lesions develop, there are feedforward mechanisms that promote atherosclerotic plaque expansion, necrosis, and rupture, precipitating vascular occlusion. Diabetes, which is characterized by endothelial dysfunction including nitric oxide synthase (NOS3) dysfunction and NO deficiency,[199] amplifies all of these underlying pathophysiological variables (Figure 5). A large body of evidence implicates diabetes in activating myelopoiesis and inflammatory cell activation via direct mechanisms in the bone marrow and cross talk between adipose-derived macrophages via inflammatory cytokines release including IL-1β.[191,200] Activation of inflammatory cells in diabetes is associated with cell-autonomous changes in glucose and fatty acid metabolism.[201,202] Aggressive lipid lowering can lead to atheroma regression. Importantly, hyperglycemia and uncontrolled diabetes retard plaque regression despite lipid lowering via multiple mechanisms, including persistent myelopoiesis, monocytosis, neutrophilia, and persistence of macrophages in the M1 (pro-inflammatory state) versus the M2 state that promotes plaque regression.[203]

Diabetes is also associated with increased risk of thrombosis, due in part to endothelial dysfunction that accelerates the activation of procoagulant factors, whose generation by the liver and adipose tissue is also augmented in diabetes and insulin-resistant states (Figure 5).[204] In addition, metabolic disturbances in platelets have also been described, whereby increased glucose metabolism in platelets correlate with increased platelet activation. Notably, genetic inhibition of platelet glucose transport or metabolism protects animals from diabetes-related platelet overactivation.[205,206]

Heart failure

Diabetes increases the risk of heart failure independently of the increased risk of CAD.[207,208] A large number of studies in animal models have identified mechanisms that impair cardiomyocyte and coronary microvascular function and have been extensively reviewed.[207–209] These mechanisms include carbotoxicity (lipotoxicity and glucotoxicity), oxidative stress, impaired mitochondrial bioenergetics, mitochondrial uncoupling, impaired myocardial excitation-contraction coupling, and activation of pro-fibrotic pathways (Figure 5). Additionally, activation of hypertrophic signaling pathways results in part

Figure 5. Systemic changes and mechanisms leading to increased risk of cardiovascular disease in diabetes

Systemic changes characterized by altered release of adipokines and increased release of inflammatory cytokines by adipose tissues, bone marrow activation by hyperglycemia, and increased hepatic generation of pro-atherogenic lipoproteins and procoagulant factors perturbs the systemic metabolic milieu leading to accelerated atherosclerosis and diabetic cardiomyopathy. Diabetes accelerates atherosclerotic plaque progression and retards plaque regression as a result of endothelial dysfunction, monocyte activation, increased inflammation, and vascular smooth muscle cell proliferation. The prothrombotic milieu and platelet activation increases the likelihood of thrombotic events. In the heart, glucotoxicity and lipotoxicity induces mitochondrial bioenergetic disturbances (decreased oxidative phosphorylation and increased mitochondrial uncoupling), oxidative stress, and altered excitation-contraction (EC) coupling. Coupled with pro-hypertrophic insulin and cytokine signaling, disturbances in cellular metabolic homeostasis induces epigenetic and transcriptional regulation changes leading to altered gene expression that induce pathological ventricular remodeling, matrix remodeling, and increased fibrosis. Coupled with microvascular dysfunction and increased coronary ischemia, these changes synergistically increase the likelihood of heart failure in patients with diabetes.

AGE, advanced glycation end products; APOC3, apolipoprotein C3; DAG, diacyl glycerol; DNL, *de novo* lipogenesis; EC, endothelial cell; EC coupling, excitation-contraction coupling; ECAM, endothelial cell adhesion molecule; FAO, fatty acid oxidation; FFA, free fatty acids; GFR, glomerular filtration rate; ICAM, intercellular adhesion molecule; IL, interleukin; JNK, c-Jun N-terminal kinase; NF-kB, nuclear factor kappa-light-chain-enhancer of activated B cells; NO, nitric oxide; NOS3, nitric oxide synthase 3 (endothelial NOS- eNOS); OGlcNAc, O-linked-N-acetylglucosamine; OXPHOS, oxidative phosphorylation; PAI 1, plasminogen activator inhibitor 1; PKC, protein kinase C; RAAS, renin angiotensin aldosterone system; ROS, reactive oxygen species; TAG, triacylglycerol; TG, triglyceride; SM, smooth muscle; TNFα, tumor necrosis factor-alpha; VCAM, vascular cell adhesion molecule; VLDL, very low-density lipoprotein; VO_2, rate of oxygen consumption; VSMC, vascular smooth muscle cells.

from selective IR, whereby hyperinsulinemia activates hypertrophic and lipotoxic pathways. Recent studies in humans who have received heart transplantations have corroborated these findings.[210,211] By leveraging the cardiac biopsy samples obtained post-transplantation, independent groups have now confirmed that within months of cardiac transplantation, normal donor hearts that were transplanted into recipients who develop diabetes exhibit evidence of triglyceride overload and accumulation of toxic lipids such as ceramides. In addition, there is clear evidence of mitochondrial respiratory insufficiency, oxidative stress, and inflammation. Intriguingly, individuals who were treated with metformin exhibited attenuation of these changes.[210] To underscore how rapidly the heart maladapts to more subtle changes in the metabolic milieu, mitochondrial oxidative defects were also observed in transplant recipients with prediabetes relative to those who remained non-diabetic.[211] Thus, the myocardium in the context of dysregulated glucose metabolism can be likened to a canary in a coal mine. These changes develop rapidly and set the stage for long-term myocardial maladaptation to additional stressors such as ischemia or hypertrophy.[188]

Impaired angiogenesis

Diabetes is characterized by impaired angiogenic signaling that may contribute to the increased risk of peripheral vascular disease and critical limb ischemia.[212] As extensively reviewed previously, diabetes reduces the expression of multiple pro-angiogenic factors and induces perturbations in signaling pathways that promote angiogenesis, including vascular endothelial growth factor (VEGF) resistance, impaired nitric oxide signaling, reduced levels of angiogenic stem cell (SC) precursors, and pericyte loss.[212] More recent studies have focused on dysregulation of microRNAs and other non-coding RNAs, including long non-coding RNAs, whose levels are altered by the diabetic milieu and are known to regulate pro and antiangiogenic pathways.[213]

Taken together, a large body of work has identified how diabetes adversely impacts multiple cellular populations that maintain cardiovascular health and resilience (Figure 5). While hyperglycemia represents an important pathophysiological mechanism, it is just one player in the orchestra of other factors, including increased inflammation, dysregulated lipid metabolism, and impairment of regenerative pathways that conspire to impair cardiovascular resilience. Therapeutic strategies, including lifestyle, weight loss surgery, and drugs, which will have the greatest impact on reversing the persistent CVD risk in diabetes are likely to be those that simultaneously target multiple upstream metabolic mechanisms beyond glycemia or target more than one downstream pathogenic abnormality. Existing diabetes therapies and their impact on CVD reduction are discussed in the section on recent therapeutic advances in T2D.

DKD

Diabetic kidney disease (DKD) is characterized by albuminuria and a reduced estimated glomerular filtration rate (eGFR).[214] Roughly 40% of patients with diabetes will develop DKD, making DKD a leading cause of end-stage kidney disease. Despite the decline in CVD in the general population and to a certain extent in people with diabetes,[215] the prevalence of DKD has only minimally decreased. This highlights the urgent need to better understand its pathophysiology and to identify new therapies that can slow its progression.

Renal vascular dysfunction and DKD

The kidney has a unique circulation characterized by a double capillary system. The incoming renal artery (afferent) gives rise to the glomerular capillaries. The outgoing vessel from the glomerulus (efferent artery), still carrying arterial blood then becomes the peritubular capillary system.[216] One of the earliest features of DKD is glomerular hyperfiltration.[217] Systemic hyperglycemia can cause increased proximal tubule (PT) sodium reabsorption (as glucose is transported into tubular cells by a sodium-coupled transport mechanism), resulting in reduced sodium and chloride delivery to the macula densa, which is falsely sensed as reduced circulating volume. Consequently, the glomerulus responds by increasing the filtration rate (hyperfiltration) by an angiotensin-mediated constriction of the glomerular efferent artery. This mechanism is described as tubuloglomerular feedback.

DKD is a primary microvascular complication of diabetes. ECs express the insulin receptor and the insulin responsive glucose transporters. Hyperinsulinemia and hyperglycemia increases flux into the polyol pathway, increasing reactive oxygen species production and inducing the expression of adhesion molecules.[218,219] In the kidney, the glycocalyx network surrounding glomerular ECs plays a pivotal role, and the loss of this glycocalyx correlates with albuminuria.[220] Impaired angiogenesis is another crucial aspect of diabetic complications. Within the glomerulus, podocytes serve as an important source of VEGFA, which is essential for the health of glomerular ECs.[221] Animal studies indicate that the initial stage of DKD is characterized by increased glomerular VEGF levels, but in the later stages, VEGF levels are lower, contributing to the loss of glomerular and peritubular capillaries.[222] Both VEGF and insulin regulate cellular Akt levels and downstream endothelial nitic oxide synthase. Nitric oxide, an important regulator of vascular smooth muscle tone, also modulates the contractility of mesangial cells in the glomerulus.[214,223]

Glomerular and tubule epithelial cells in DKD

Podocytes are crucial for the formation of the filtration barrier in the glomerulus. Podocyte metabolism is altered early in the course of diabetes, and metabolic shifts, particularly increased oxidative stress, exacerbate podocyte dysfunction.[224] In addition, changes in podocyte cytoarchitecture and thickening of the glomerular basement membrane occur early. Reorganization of the cellular actin and myosin by RhoA/Rac1 pathways is an important cause of foot process effacement, which correlates strongly with the level of albuminuria.[225] Additionally, podocyte enlargement develops, mostly on the basis of altered mTOR and growth factor signaling.[226] Later on, loss of glomerular podocytes due to death or detachment represent an irreversible step in disease progression and development of glomerulosclerosis.[224]

While DKD has been primarily viewed as a classic glomerular disease, changes in PT cells are increasingly recognized as primary disease-driving mechanisms. Genes identified by eGFR GWASs show a strong enrichment for PT-specific expression.[227] PT cells are highly metabolically active and are responsible for

absorbing nearly 100 liters of water and a kilogram of salt daily. This metabolic burden is increased in patients with hyperglycemia and hyperfiltration. Glucose reabsorption in the PT is mostly sodium coupled via the sodium-glucose cotransporters (SGLT1 and SGLT2). Initially, PT cell size and number increase and correlate with hyperfiltration. This increased metabolic demand causes relative hypoxia and ATP depletion in PT cells, leading to activation of hypoxia and AMPK pathways. In later stages, defects in fatty acid oxidation secondary to repression of key transcription factors such as estrogen-related receptor alpha (ESRRA) and peroxisome-proliferator receptor alpha (PPARA) develop, leading to energy depletion and loss of cell identity of PT cells, resulting in declining GFR. When cellular and mitochondrial damage is not repaired, damaged mitochondria release mitochondrial RNA and DNA molecules that activate inflammatory pathways.[228,229] Mitochondrial nucleotides are recognized by cytosolic pattern recognition pathways such as cyclic GMP-AMP synthase (cGAS), stimulator of interferon genes (STING), retinoic acid-inducible gene 1 (RIG-I), and the Toll-like receptor (TLR) system, leading to the activation of transcription factors like nuclear factor κB (NF-κB) and interferon regulatory transcription factor (IRF) that induce cytokine gene expression. These injured or profibrotic tubule cells attract macrophages, lymphocytes, and fibroblasts promoting tissue fibrosis leading to irreversible progressive kidney damage.

Genetics, epigenetics, and metabolomics

Important contributions of genetics to DKD were suggested by the familial aggregation of the disease. Large genetic consortia including genetics of nephropathy, international effort (GENIE) identified genetic variations in the *COL4A3* gene, which was found to be protective against DKD.[230] Although comprehensive eGFR GWAS investigations have identified numerous loci associated with eGFR, subsequent analyses have shown minimal differences in the genetic architecture of eGFR in diabetic and non-diabetic cohorts.[227]

The intriguing "metabolic memory" phenomenon, where historical glycemic control casts shadows on subsequent kidney disease susceptibility, has brought the role of epigenetics in DKD to the forefront.[231] Several underlying mechanisms have been posited, with DNA methylation featuring prominently. Results from the Diabetes Control and Complication Trial (DCCT) have emphasized the role of methylation variations in this enigmatic metabolic memory effect. Methylation differences in blood cells, particularly within the thioredoxin interacting protein (TXNIP) locus, are correlated with DKD trajectory.[232] Moreover, the methylation landscape in human kidney specimens reveals significant differences in healthy and DKD kidneys, supporting the potential role of epigenetics in DKD progression.[233,234] Histone modifications, another facet of epigenetics, involve processes like acetylation and methylation, which govern chromatin accessibility and the transcriptional readiness of DNA. Patterns of histone modifications, notably H3K9 and H3K4, were strongly associated with DKD in the DCCT cohort.[235] It is noteworthy that multiple epigenome-modifying enzymes ranging from histone deacetylases (HDACs) to Sirtuins, are now implicated in the development DKD, fibrosis, inflammation, and cellular injury. Recent single-cell studies of DKD and control human kidneys detected cell-specific epigenetic changes that impact chromatin accessibility in DKD.[236] These shifts suggest a potential preprogramming of kidney cells, modulating their responsiveness to external influences, thereby potentially dictating the course of DKD.[236]

Various lipid species have been identified as biomarkers or causal factors in DKD. Circulating acylcarnitines, which are intermediates in lipid metabolism linked to IR, inversely correlate with eGFR.[237] Analysis of blood samples from CKD patients revealed an abundance of specific fatty acids, with β-oxidation efficiency markers decreasing as CKD progressed. Phospholipid species also undergo dynamic changes, with associations drawn between phosphatidylcholine and eGFR decline. Intriguingly, individuals with DKD exhibited increased urinary lysophosphatidylcholine levels as kidney function declined. The role of different metabolites in DKD development remains poorly understood. Most importantly, it is difficult to distinguish between changes that cause DKD and those observed as a consequence of the disease. The contribution of novel therapeutics to DKD prevention will be discussed in the section on recent therapeutic advances in T2D.

ADVANCES IN DIAGNOSIS AND TREATMENT OF DIABETES AND ITS COMPLICATIONS

This section will review recent advances in the prevention and treatment of T1D, discuss the promise and limitations of precision medicine and personalized medicine approaches for managing T2D, and summarize current outcomes data and prospects for novel therapeutics for T2DM with important effects beyond achievement of glycemic control.

Advances in prevention and therapies for T1D

For decades, clinical trial interventions were performed at the onset of stage 3 T1D, when overt hyperglycemia is already present. While these efforts identified a handful of immunomodulatory therapies capable of preserving C-peptide in early disease, none of these therapies led to insulin independence or progressed to a regulatory approval.[30,238] An important lesson gleaned from these efforts was that interventions initiated after stage 3 T1D onset were likely too late in disease evolution to significantly modify outcomes. Thus, the new disease staging system filled an important void by providing a conceptual and regulatory framework for interventions aimed at earlier disease time points.

In 2019, Herold and colleagues reported results from a groundbreaking study performed as part of the NIH-funded T1D TrialNet network. This study tested the impact of a single 14-day course of the Fc receptor-nonbinding anti-CD3 monoclonal antibody, teplizumab, on progression from stage 2 to stage 3 T1D. When the first results were reported, teplizumab resulted in a median delay of stage 3 T1D onset of 24 months.[239] An updated analysis in 2021 showed continued extension of this median delay to approximately 32.5 months.[240] Based on these results, the US Food and Drug Administration (FDA) approved teplizumab (Tzield) as the first disease-modifying therapy in T1D. While this approval represents a paradigm-shifting event in the history of T1D, it has created an urgency to rapidly establish strategies to identify at-risk autoantibody positive

individuals. In the absence of unified guidelines, a number of approaches are being tested, including cross-sectional autoantibody screening either alone or in combination with the assessment of polygenic risk scores.[241,242] Although additional studies are needed to understand the efficacy, acceptability, and risks of these strategies within the general population, the approval of teplizumab codifies the concept that T1D begins with the development of multiple autoantibodies and provides the groundwork for additional drugs to progress to registration trials.

For those individuals who have already progressed to stage 3 T1D, options for disease management have improved dramatically since the discovery of insulin. Advancements in diabetes management include the development of insulins with optimized pharmacokinetics, algorithm-driven subcutaneous insulin pumps, continuous glucose monitoring, and improved tools for self-management.[30,243] While advancement in diabetes technology have improved quality of life and metabolic outcomes for individuals with T1D, living with T1D remains burdensome.[26,27,244] Thus, restoration of endogenous beta cell function via cell replacement therapy represents the next potentially paradigm-shifting event for those affected by T1D.

In this regard, beta cell replacement via pancreas or islet transplantation from cadaveric donors has shown promise. The development of the Edmonton Protocol in 2000 demonstrated that infusion of donor islets into the portal vein can restore glucose homeostasis and result in transient insulin independence for individuals with T1D.[245] Subsequent studies established that beta cell replacement is feasible and beneficial, especially for those who suffer from life threatening hypoglycemia,[246] and in 2023, the FDA approved donor islets in a preparation named donislecel (Lantidra) for adults who are unable to achieve hemoglobin A1c targets due to severe hypoglycemia.[247] This approval represents the first cell-based therapy for the treatment of T1D; however, there are important limitations of islet transplantation, including limited donor supply, the need for lifelong immunosuppression, and waning efficacy of the graft over time.

In vivo differentiation of SCs into beta cells has the potential to avoid several issues associated with islet transplantation by allowing for the generation of an unlimited supply of standardized and well-characterized insulin-producing beta cells from human pluripotent SCs.[248] In a trial begun in 2014 (NCT02239354) and refined in 2017 (NCT03163511), ViaCyte (now acquired by Vertex Pharmaceuticals) tested the efficacy of encapsulated SC-derived endoderm cells (PEC-01) in individuals with T1D. Initial results showed that trial participants gained glucose-responsive C-peptide production within 6–9 months post-transplantation. Evaluation of grafted cells showed that the SC-derived endoderm cells differentiated into a variety of endocrine cells; however, there was marked heterogeneity between patients.[249,250] Several groups have now developed protocols to allow for *in vitro* differentiation of SCs into functional insulin-producing cells rather than progenitors.[251–253] Transplantation of these SC-islets into diabetic mice[251–253] and non-human primates[254,255] improved glycemic control, suggesting that this method of beta cell replacement could have efficacy in humans. In an ongoing clinical trial begun in 2021 (NCT04786262), Vertex Pharmaceuticals treated individuals with T1D using their SC-islet product, VX-880. Although the results of this trial have not yet undergone peer review, exciting initial reports show that transplantation of SC-islets leads to islet cell engraftment, glucose-responsive insulin secretion, improved glycemic control, and reduced or eliminated the need for exogenous insulin.[256] The VX-880 trial was voluntarily paused early in 2024 pending scrutiny of 2 unexplained deaths necessitating independent review of safety issues (https://investors.vrtx.com/news-releases/news-release-details/vertex-provides-pipeline-and-business-updates-advance-upcoming). In addition, a clinical trial testing the efficacy of VX-246, the encapsulated version of VX-880 cells, has been initiated (NCT05791201).

The last several decades have seen tremendous advances in the ability to diagnose, manage, treat, and even prevent T1D. In the next 50 years of diabetes research, we expect to see increased utilization and advancement in immunomodulatory and cell-based therapies for the treatment and prevention of T1D. Table 1 summarizes a framework for advancing therapeutic development in relation to the stage of T1D.

Precision tools for diabetes subclassifications and implications for diverse populations

In the last 20 years, there has been a transition in the epidemiology of diabetes.[3] While T2D incidence continues to rise globally, the presentation is now occurring at earlier ages, and the burden of the disease rests in low- and middle-income countries (LMIC) with an estimated 4 out of 5 people living with T2D from these regions.[3] The study of T2D across ancestry groups has revealed considerable disease heterogeneity. For example, ketosis-prone T2D in African-Caribbean people,[257] the relatively lean Asian T2D phenotype[258] and higher risk for T2D in south Asian individuals relative to people of white ancestry.[259] Coupled with this recognition has been the analysis of carefully curated longitudinal population studies in people with T2D from European and other ancestries, which have revealed significant disease heterogeneity at presentation that can be linked to outcomes such as DKD or the need for insulin treatment.[260] This heterogeneity has catalyzed precision medicine approaches in diabetes[261] to leverage better outcomes according to subphenotype with the aim of tailoring diagnostics or therapeutics to subgroups of populations sharing similar characteristics.

The focus on precision medicine approaches in T2D is anchored in the success of monogenic diabetes as an exemplar, which has proven that identification of the specific molecular mechanisms underpinning diabetes can lead to precise diabetes treatment. For example, mutations in the glucokinase gene require no medical treatment as affected individuals demonstrate no significant increase in lifetime risk of microvascular or macrovascular complications despite lifelong fasting hyperglycemia,[262] whereas mutations in the transcription factor gene *HNF1A* can be managed with low-dose sulfonylurea therapy,[263] to achieve superior glycemic control compared with standard care.[264] However, it is not just target-based therapeutics that makes monogenic diabetes a successful front-runner in the diabetes precision medicine space. The implementation of clinical pathways to enable genetic diagnosis in people with suspected monogenic diabetes has demonstrated that patient stratification through use of biomarker and clinical data and provision of

Table 1. Summary of challenges and opportunities in preventing and treating type 1 diabetes

Pre-stage 1	Stage 1	Stage 2	Stage 3
Major challenges	Major challenges	Major challenges	Major challenges
Identifying individuals at risk of developing T1D through general population screening	developing safe and effective disease-modifying therapies for T1D prevention/delay	developing safe and effective disease-modifying therapies for T1D prevention/delay	optimizing glycemic control
Data-driven approaches to rescreening and follow-up	N/A	N/A	minimizing hypoglycemia
Understanding the acceptability of screening in unaffected populations	N/A	N/A	prevention of complications
	N/A	N/A	improving life expectancy
Opportunities	Opportunities	Opportunities	Opportunities
Optimizing genetic risk assessment across diverse populations	precision approaches for disease-modification	precision approaches for disease-modification	improvements in insulins, insulin delivery, and glucose monitoring
Develop optimized and cost-effective protocols for longitudinal monitoring of antibody status	biomarker development to guide therapeutic selection, timing of interventions or redosing	biomarker development to guide therapeutic selection, timing of interventions or redosing	non-insulin therapies to reduce risk of complications
	therapies that address immune activation and β cell health	therapies that address immune activation and β cell health	β cell replacement with islet transplantation or stem-cell-derived β cells
	N/A	N/A	durable remission or disease prevention with disease-modifying therapies

Early detection of individuals at high risk for developing T1D may enable earlier use of disease-modifying therapies. Once T1D develops, insulin treatment is required. Advances in modified insulin analogs, integrated insulin delivery, and glucose monitoring technologies have improved glycemic management. Beta cell replacement therapy with stem-cell-derived islets may offer the hope of lasting cure.

DNA-based diagnostics can be integrated into clinical care across different health systems. This advance illustrates how ''omics'' or complex datasets that may be necessary for precision medicine could be integrated into real-world clinics rather than merely being a fanciful future prospect.

Precision medicine has been defined as an approach that tailors diagnostics or therapeutics to subgroups of populations sharing similar characteristics, thereby improving accuracy in medical decisions and health recommendations.[261] While precision medicine and personalized medicine are often used interchangeably, the latter extends the definition by incorporating a subjective approach that customizes treatment to align with an individual's preferences, circumstances, and capabilities.[265] Precision tools are the instruments with which the more nuanced approach (based on objective data) can be taken. For diabetes subclassification, these tools can be considered in terms of complexity.[266] At a rudimentary level, simple clinical features or other objective data have been used in isolation to identify subpopulations with similar characteristics. For example, younger age at onset of T2D is associated with a shortened life expectancy[267] and a rapid progression to cardiovascular complications. Earlier age at diagnosis is often observed in East Asian and South Asian populations and has been associated with worse beta cell function at diagnosis, which appears in part to be linked to genotype.[268] However, identifying subpopulations sharing similar characteristics does not itself fulfill the central tenet of precision medicine; tailored treatment is also needed to make the subclassification meaningful.[261] Such an approach has been exemplified in the first randomized study (with crossover) of precision treatment for T2D.[269] The study demonstrated that using dichotomous BMI or eGFR cut-offs as stratification tools predicted greater reduction in HbA1c in people with T2D. Participants with obesity (BMI > 30 kg/m^2) exhibited improved glycemic outcomes when treated with pioglitazone compared with sitagliptin.[269] Additionally, those with lower eGFR (60–90 ml/min/1.73 m^2) demonstrated a greater reduction in HbA1c levels in response to sitagliptin versus canagliflozin. A similar study conducted in New Zealand showed that the presence of obesity and/or hypertriglyceridemia predicted a greater reduction in HbA1c with pioglitazone than vildagliptin.[270]

A separate approach to diabetes subclassifications has stemmed from the integration of several clinical and biomarker variables and/or genetic data using machine learning or complex mathematical algorithms.[266] A clustering approach to classification was pioneered in a study that used HbA1c, BMI, age-at-diagnosis, GAD-65 antibody positivity, HOMA-2IR, and HOMA-B to identify five distinct subgroups of diabetes. These groups were differently associated with a variety of outcomes.[260] For example, people in the cluster with severe IR (characterized by higher BMI and highest HOMA2-IR) were far more likely to progress to CKD despite similar treatment and HbA1c relative to the mild-obesity and mild-age related clusters. The clustering approach has certainly taken hold, with over 22 studies replicating those initial subclassifications in diverse study populations that also associate with similar clusters.[266] Of course, the clusters identified simply reflect the input variables, and other studies have shown different clusters by incorporation of additional variables.[271] The clusters identified may not be

transethnic, however, and may perform variably across different ancestries. For example, a study in India identified two novel clusters that likely reflect differences in pathophysiology in Indian Asians with T2D that are characterized by insulin deficiency and IR manifesting without obesity, relative to the white European Scandinavian population in the original study.[272]

Another approach to subclassification that is anchored in genetic etiology has been clustering of genetic variants and associated traits, which most recently has used Bayesian non-negative matrix factorization to identify 10 distinct genetic clusters that associate with a variety of clinical outcomes.[273] The field is advancing rapidly with multiple machine learning algorithms that also predict treatment failure through the subgroups identified. For example, in a recent study using non-linear transformation of nine clinical variables, certain subgroups associated more with treatment failure over time, with replication in external datasets.[274] While much research is focused on stratifying T2D, the field would benefit from standardization in approaches, with some consensus over what constitutes a useful clinical outcome, and the optimal study designs to prove efficacy of the precision medicine approach over standard care.

Although the field of precision diabetes is advancing rapidly, major gaps in the evidence-base remain.[261,265] Initially, for broad adoption to occur, a fundamental requirement must be met, which is to demonstrate that the benefits of the precision medicine approach are clinically superior to standard care and are cost-effective and implementable. This evidence will need to come from randomized trials. It is important to ensure that appropriate outcomes are used for evaluation of utility. A systematic review of the literature to examine all studies that attempt to subclassify T2D revealed considerable heterogeneity in study exposures and outcomes and with mostly poor Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) quality.[266] More robust studies are starting to emerge, most recently a randomized study assessing the response to a GLP-1RA versus an SGLT-2 inhibitor in people assigned to two different T2D clusters.[275] Future studies should scrutinize the precision medicine approach against standard care and consider clinically relevant outcomes, feasible implementation of usable technology, and evaluating appropriate use of therapeutic agents.[261,265]

Precision medicine and health equity

It remains to be seen if any successful precision medicine approaches for T2D can be implemented at scale and in all resource settings. Even monogenic diabetes testing, the poster child, is not available universally. The issue of resource is one that is frequently cited by opponents of precision medicine, which is often perceived to be costly[276] and leads many to believe bigger gains are to be made by delivering current "less precise" models of care with equality and reach. Indeed, if there are potential cost-savings from precisely classifying diabetes at diagnosis or choosing treatments more effectively, these are currently challenging to quantify because they are likely to be downstream in the clinical pathway and/or life course of the person living with diabetes.

The cost argument is compounded by statistics showing the burden of T2D now lies in LMIC regions.[3] Is it reasonable to expect precision medicine for diabetes in regions where essential medication pipelines are not secure, let alone the provision of sophisticated diagnostics? Certainly, if wedded to the notion of precision medicine involving complex "omic diagnostics" and data analytics with end-to-end implementation, then it seems unlikely that such approaches would work in LMIC regions.[276] It is evident that more simple approaches to subclassification, for example, BMI cut-offs (and other routinely available measures) or decision support tools to help stratify risk and/or select treatments, may be more feasible to implement in such regions. However, there is huge potential to innovate in delivery of precision approaches in LMIC populations, and if precision medicine is an approach that yields lower error, then arguably there is much to gain in these regions where infrastructure to diagnose and treat communicable diseases already exists and use of point-of-care diagnostics has had success.[276]

Even in high-income countries, there is significant health inequality and variation in diabetes care, often affecting people from socioeconomically deprived backgrounds, those from minority ethnic groups, and other minoritized groups, e.g., the homeless or those with mental illness. If implementation of precision medicine is not planned and considered carefully, it has the potential to widen inequalities and provide access to only those who can afford it in countries where there is not universal healthcare. It behooves all involved to consider these risks.

Impact of population diversity

Most precision medicine studies to date, be they relating to diagnosis, treatment, or complications, have occurred in predominantly white European populations, and this represents a significant limitation of the field.[261] Greater ethnic diversity in all aspects of T2D research is needed to ensure tailored solutions are derived in representative populations to leverage or address the significant disease heterogeneity reflecting differences in underlying pathogenesis. An approach that takes a precision medicine solution derived in one ancestry and maps it to another is unlikely to yield success, even if the imprecision of such an approach is deemed acceptable. Moreover, this approach is challenged by studies revealing that T2D clusters are different in some ethnic groups.[272]

Lack of diversity in GWAS is also problematic, and where GWAS have been performed in diverse ancestries, it is often for a specific disease with data on associated traits lacking.[277] Often the same limited non-European cohorts are utilized recurrently in consortia leading to potential biases and over-sampling. While some genetic risk scores (GRSs) such as the T1D GRSs, have shown portability across ancestry groups,[278] there are many GRSs that have not shown good portability across ancestries. The lack of diverse genomic data has led to alternative approaches that fine-tune existing scores for a particular population by modifying effect sizes[279] or by creating trans-ancestry scores.[9] While these approaches make the best of what is available, both alternatives risk overlooking potential novel variants and rare disease variants in understudied populations. Even in drug trials for T2D, there is considerable under-enrollment of minority populations or if they are enrolled, the numbers are not large enough to study.[280] In a survey of over 400 randomized controlled trials (RCTs) of drugs for T2D, diversity improved over the 10 years studied but remained well below the expected proportional representation of multiple minority ethnic groups.

Not only ancestry but also age, gender, and other protected characteristics should be considered in proposed precision medicine studies. If the potential of precision medicine is to be fully realized, it is also important that precision medicine solutions are derived in specific populations without *a priori* hypotheses and with consideration for implementation in all resource settings.

Recent therapeutic advances in T2D

Here, we provide an overview of the major advances in therapeutics for T2D, emphasizing the actions of new medicines to reduce glucose while preventing weight gain and improving cardiorenal outcomes. Three classes of glucose-lowering medicines were introduced for the treatment T2D in the last 20 years, starting with GLP-1RAs, followed by dipeptidylpeptidase (DPP)-4 inhibitors, and SGLT-2 inhibitors. These new medicines enabled control of glucose without weight gain and with a very low risk of hypoglycemia. DPP-4 inhibitors have few AEs, are generally administered as once-daily tablets, can easily be combined with metformin, and are well suited for treatment of individuals not requiring simultaneous reduction of cardiovascular risk. In contrast, SGLT-2 inhibitors, also administered as a once-daily tablet, reduce rates of hospitalization for heart failure and CKD in people with or without T2D. As a result, SGLT2 inhibitors are indicated for reduction of CVD and CKD in people with T2D. Importantly, although the glucose-lowering efficacy of SGLT2 inhibitors is diminished in people with a reduced eGFR < 60 mL/min/1.73 m^2, these agents still exert nephroprotective effects in people with or without T2D, even when administered to individuals with an eGFR as low as 20–25 mL/min/1.73 m^2.[281] The dual sodium-glucose cotransporter-1 and -2 inhibitor sotagliflozin does not consistently reduce rates of renal outcomes in people with pre-existing renal impairment and T1D or T2D, although this result might have related to study design. However, sotagliflozin rapidly reduced rates of re-hospitalization for heart failure and cardiovascular death in subjects with T2D with a history of recent worsening heart failure.[282] The SGLT2 inhibitor class of medicine is now established for cardiorenal protection in people with and without T2D, with less extensive innovation expected in these classes beyond several ongoing trials exploring possible new indications. SGLT2 inhibitors and sotagliflozin have been extensively studied in people with T1D, and ongoing trials are exploring the extent to which the benefits may be safely captured while mitigating the risks by using new technologies to identify and forestall the risk of ketoacidosis.

GLP-1 was originally identified as an insulin-stimulating hormone, with subsequent actions encompassing reduction of glucagon secretion and gastric emptying, supporting its development for the treatment of T2D.[48] Subsequent preclinical studies in 1996 identified that icv administration of GLP-1 inhibited food intake, leading to weight loss. Exenatide, a naturally occurring GLP-1RA isolated from the venom of the lizard Heloderma suspectum, was the first GLP-1RA approved for the treatment of T2D in 2005. Exenatide was first developed as a twice-daily injectable medicine, followed a few years later by the introduction of lixisenatide, a once-daily short-acting GLP-1RA, and liraglutide, an acylated long-acting human GLP-1RA suitable for once-daily administration.[48] The AEs associated with GLP-1RAs are predominantly gastrointestinal (GI), principally nausea, vomiting, diarrhea, constipation, and gallstones or gallbladder inflammation.[48] These AEs are most notable at the time of drug initiation and dose up-titration. Persistent GI AEs compromising food and water intake may lead to dehydration and, rarely, acute kidney injury, highlighting the importance of maintaining adequate hydration. Gallbladder events including cholecystitis and cholelithiasis have been reported with GLP-1RAs. The incidence of the GI AEs wanes over time in the majority of subjects; however, in some individuals, the AEs persist, necessitating treatment discontinuation.

Exenatide, once weekly, was formulated by incorporating synthetic exenatide into microspheres and injected subcutaneously once a week, enabling sustained delivery of exenatide for the treatment of T2D.[283] It was approved as the world's first once-weekly medicine for people with T2D in 2012. Dulaglutide, a once-weekly GLP-1RA, containing a DPP-4-resistant GLP-1 peptide covalently attached to a human IgG4-Fc heavy chain via a small peptide linker, was approved for the treatment of T2D in 2014. Semaglutide first developed as a small acylated peptide GLP-1RA suitable for once-weekly administration was approved for T2D in 2017. An oral once-daily version of semaglutide, co-formulated with an absorption enhancer sodium N-(8-[2-hydroxybenzoyl]amino) caprylate, enabling transcellular absorption of semaglutide across the gastric mucosa[284] was approved in 2019. The efficacy of oral versus injectable semaglutide is proportional to the plasma levels achieved, with somewhat greater bioavailability evident in women and individuals with a lower BMI.[284]

Each iteration of novel GLP-1RAs has achieved greater efficacy both for the reduction of HbA1c and, secondarily, for weight loss. Observations of weight loss in people treated with GLP-1RAs spurred the development of liraglutide, 3 mg once daily, for the treatment of obesity, an indication approved in 2014. Subsequent studies demonstrated even greater weight loss with semaglutide 2.4 mg once weekly, which was approved in the USA in 2021 for people with a BMI over 30, or over 27, with one or more weight-related risk factors for CVD. The use of GLP-1RAs for the treatment of T2D in people with risk factors for or with established CVD was bolstered by results from a series of cardiovascular outcome trials, first reported in 2016. Collectively, these studies demonstrated that sustained GLP-1R activation reduces the rates of non-fatal myocardial infarction, stroke, and cardiovascular death, with an overall reduction of ~12% in all-cause mortality.[285] Importantly, the cardioprotective benefit of GLP-1RAs is achieved in the presence or absence of concomitant SGLT-2 inhibitor therapy,[286] and the combination appears to confer an additive cardioprotective benefit, consistent with their distinct mechanisms of action.

The SELECT trial extended the cardiovascular safety of once-weekly semaglutide (2.4 mg) to people with overweight or obesity and a history of CVD. A 20% reduction in the primary composite endpoint of non-fatal MI, non-fatal stroke, and cardiovascular death was observed in subjects randomized to semaglutide.[287] A cardiovascular benefit became evident within the first several months, raising the possibility that some of the cardiovascular benefit achieved with semaglutide in the SELECT trial is independent of weight loss. In the STEP heart failure with preserved ejection fraction (HFpEF) trial, once-weekly semaglutide (2.4 mg) in patients with obesity and HFpEF improved

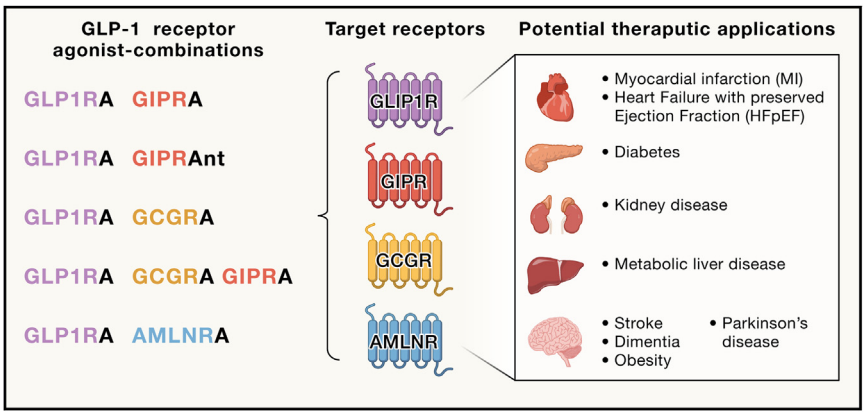

Figure 6. Evolution of GLP-1-based therapeutics for the treatment of cardiometabolic and neurodegenerative disorders

GLP-1RAs targeting the GLP-1 receptor (GLP1R) alone or in combination with one or more additional metabolic peptides are being studied beyond classical indications such as T2D or obesity. The figure summarizes existing combination molecules that are being tested in a variety of syndromes including heart failure, diabetes, obesity, CKD, MAFLD, and neurodegenerative syndromes. GIPRA, GIP receptor agonist; GIPRAnt, GIP receptor antagonist; GCGRA, glucagon receptor agonist; AMLNRA, amylin receptor agonist; GLP-1R, GLP-1 receptor; GIPR, GIP receptor; GCGR, glucagon receptor; AMLNR, amylin receptor; HFpEF, heart failure with preserved ejection fraction.

heart failure symptoms and walk test time in concert with weight loss and reduction in CRP.[288,289]

DKD is strongly associated with and might even explain a substantial proportion of diabetes-associated mortality. Significant efforts have been focused on glycemic control to prevent diabetic complications. However, tight glycemic control alone is insufficient to prevent DKD. GLP-1RAs reduced renal composite endpoints in cardiovascular safety trials, driven by a reduction in albumin excretion.[285] Several recent outcome trials with prespecified renal endpoints have also revealed important benefits[290] of novel glucose-lowering agents. These agents correct multiple defects observed in DKD. Renin angiotensin and aldosterone system (RAAS) inhibitors reduce glomerular hyperfiltration[291] by directly targeting the efferent glomerular artery. SGLT2i by targeting glucose and sodium uptake of kidney PTs reduce the metabolic demand on these cells.[292,293] In addition to improving tubule health, SGLT2i also reduce glomerular hyperfiltration and stress. Non-steroidal mineralocorticoid receptor agonists not only reduce the salt reabsorption in principal cells but also reduce inflammation and fibrosis. Finerenone reduced rates of composite renal outcomes by 20% in people with T2D in the FIDELIO study.[294] Most recently GLP-1RAs have shown efficacy in renal protection. GLP-1Rs are expressed at low levels in renal VSMCs and pericytes in the kidney, although it remains to be established if benefits are due to primary or secondary effects. FLOW a randomized, double-blind, parallel-group, multinational, phase 3b trial of participants with T2D was stopped early due to the effectiveness of semaglutide to reduce progression of CKD exemplified by a 24% reduction in a composite of major kidney disease events relative to placebo.[295] Thus, the therapeutic pillars for DKD therapy are expanding beyond the classic inhibitors of the RAAS to include blockers of the SGLT2 transporter, non-steroidal mineralocorticoid receptor blockers, and GLP-1RAs.

Efforts to improve upon the efficacy of GLP-1-based therapies have favored the development of GLP-1-based multi-agonists, either as unimolecular entities or as combination therapy using a single delivery system (Figure 6). Tirzepatide is a GIP receptor-GLP-1R co-agonist developed as a single acylated peptide suitable for once-weekly administration that was approved for the therapy of T2D in May of 2022 and for people with obesity in November of 2023. Tirzepatide produces double-digit weight loss and substantial A1c reduction, to a greater extent than that achieved with semaglutide in a head-to-head randomized trial of people with T2D.[296] The cardiovascular safety of tirzepatide in T2D is being directly compared with dulaglutide in 13,299 people enrolled in the SURPASS-CVOT trial.[297] Eligibility criteria include subjects with T2D and established ASCVD (a history of CAD, stroke, or peripheral vascular disease). The composite primary outcome is 3-point major adverse cardiovasclar events (MACE). Randomization was also stratified by the use of SGLT-2 inhibitors at trial entry. Recently, tirzepatide was reported to significantly reduce obstructive sleep apnea in obese patients, the majority of whom had prediabetes, in concert with weight loss.[298]

Multiple GLP-1-based combination therapies are in late-stage clinical development, with the promise of developing greater efficacy (better glucose control, greater weight loss) while preserving the cardiovascular benefits evident to date for the class (Figure 6). These include the long-acting amylin analog cagrilintide in combination with once-weekly semaglutide,[299] glucagon receptor-GLP-1R co-agonists exemplified by survodutide,[300] a GIP receptor antagonist-GLP-1R agonist antibody, maritide,[301] and the triple glucagon-GIP-GLP-1R multi-agonist, retatrutide.[302] Moreover small-molecule orally available GLP-1R agonists, such as danuglipron,[303] orforglipron[299,304] and the small-molecule GLP-1RA ECC5004 and GSBR-1290, also exhibit promise in the clinic, potentially enabling greater efficacy with a once-daily tablet relative to the efficacy achieved with once-daily oral semaglutide. Higher doses of oral semaglutide, up to 50 mg once daily, with a new absorption enhancer formulation, are also being explored. This dose and formulation achieve greater weight loss in people living with T2D[305] and/or obesity[306] and more effective A1c reduction, relative to the currently approved 14mg once-daily tablet. The extent to which these innovative new GLP-1 medicines will meaningfully improve therapeutic outcomes, with an acceptable safety profile, will require additional scrutiny in larger and longer clinical trials. Mechanistically, whether GLP-1 medicines produce glucoregulatory and anti-inflammatory benefits in humans in part through CNS circuits remains to be determined.[49] GLP-1RAs are also being studied in phase 3 trials in people with peripheral artery disease, metabolic liver disease, and neurodegenerative disorders, potentially broadening their therapeutic utility beyond T2D and obesity.[48]

Moreover, investigator-initiated studies are underway in diverse conditions such as addiction-related behaviors, genetic forms of obesity, polycystic ovary disease, and T1D (Figure 6). Hence, the next decade will yield innovation in the form of new, more convenient, and powerful GLP-1 medicines, supported by an expanding array of clinical indications buttressed by forthcoming clinical trial data.

CONCLUDING REMARKS

As the diabetes pandemic has evolved, our understanding of pathophysiology and approaches to treatment and prevention has exponentially increased. Current knowledge sets the stage for increased specificity in identifying markers that increase the susceptibility for beta cell dysfunction, particularly in obesogenic environments. Our understanding of the role of the brain in body weight regulation and novel secreted factors from adipose tissue may enable refinement of approaches for treating or preventing obesity. Increased understanding of the contribution of hepatic dysfunction to IR and increasing understanding of metabolic dysfunction-associated liver disease represents an important area for additional research to avert what could become a growing epidemic of liver failure. Cardiovascular and renal disease remain the major driver of mortality and morbidity in diabetes. It is clear that the underlying pathophysiology is complex and involves multifactorial interactions between organ systems and changes in the systemic milieu. The diabetes pandemic is driven by environmental and social factors that exacerbate these mechanisms, and comprehensive approaches to managing this pandemic must involve considerations of these factors. Advances in therapy now raise the hope of preventing or curing T1D and treating T2D in ways that not only improve metabolic homeostasis but also concretely reduce the risk and progression of cardiorenal disease. Finally, as we understand and develop tools for discerning the underlying heterogeneity leading to diabetes and its complications, the stage will be set for targeting therapies and prevention strategies to optimize their impact, in ways that will be broadly applicable across diverse populations and availability of health care resources.

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DECLARATION OF INTERESTS

E.D.A. has served as a consultant within the past 12 months to Amgen and Pfizer, Inc. C.E.-M. has served on advisory boards for Isla Technologies, Avotres, DiogenyX, and Neurodon. She is a member of the INNODIA external advisory board, has received in-kind research support from Bristol Myers Squibb and Nimbus Pharmaceuticals, and investigator-initiated grants from Lilly Pharmaceuticals and Astellas Pharmaceuticals. A.L.G.'s spouse is employed by Genentech and holds stock options in Roche. J.J.J. is a board member for Buckeye Health Plan. S.M. has received speaker Honoraria from Lilly and Sanofi, UK. K.S. has served as consultant within the past 12 months to Otsuka, Pfizer, Jnana, Maze, Chinook/Novartis, and her laboratory received funding from Astra Zeneca, Boehringer Ingelheim, Genentech, Gilead, Novartis, Novo Nordisk, Regeneron, ONO Pharma, KKC, and Calico. J.S. has served as an invited speaker to Altos and Sanford Burnham Prebys in the last 12 months. D.J.D. has served as a consultant or speaker within the past 12 months to Altimmune, Amgen, AstraZeneca, Boehringer Ingelheim, Kallyope, Merck Research Laboratories, Novo Nordisk Inc., Pfizer Inc., and Zealand Pharma. Neither D.J.D. nor his family members hold issued stock directly or indirectly in any of these companies. D.J.D. holds non-exercised options in Kallyope.

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

All authors attest that they have not used AI technology in the writing of the manuscript.

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