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EDUCATION HAS AN IMPACT

The Power of CME in Diabetes Care

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Medscape EDUCATION

In a 2020 National Diabetes Statistic Report, the US Department of Health and Human Services Centers for Disease Control and Prevention estimated that 26.9 million people in the United States (or 8.2% of the population) had diagnosed diabetes in 2018.[1] Despite the prevalence of diabetes in the population, only a small number of physicians are pursuing a fellowship in diabetes/endocrinology. According to data from the National Resident Matching Program (NRMP), only 305 physicians matched into an endocrinology, diabetes, and metabolism fellowship in 2020.[2] The Endocrine Society, in a 2014 report, estimated that there would be a needs gap of 1,344 adult endocrinologists by 2025.[3] To help meet this need, primary care providers, nurse practitioners, and physician assistants are helping to fill the gaps and manage patients with diabetes. Keeping the entire care team educated, therefore, is of critical importance.

Continuing medical education (CME) serves a key role in supporting healthcare providers (HCPs) to stay current with the latest scientific understandings of diabetes by providing evidence-based education that is scientifically rigorous, independent, accurate, and clinically relevant. Digital continuing medical education is a demonstrably effective option[4] for preparing physicians to integrate therapeutic discoveries into clinical practice—offering high-value education rooted in science and presented in formats that align with physicians' learning preferences.

Medscape Education has provided online education opportunities for more than 25 years and has the unprecedented ability to reach the entire care team of Diabetologists/Endocrinologists, PCPs, nurses/NPs, and pharmacists. Online learning options allow for personalized learning driven by the identification of learner gaps in knowledge and skill through pre-activity assessments. Some of the topics the diabetes care team are learning about include biosimilar insulins, cardiovascular risk and event reduction in patients with type 2 diabetes (T2D), team-based approaches for T2D, new treatment strategies for managing T2D, disseminating patient education pearls for improving adherence and self-monitoring, and advances in monitoring.

Medscape Education offers a variety of engaging, innovative ways for clinicians to learn, including a case-based, virtual patient simulation (MedSims). With MedSims, learners can interact with a virtual patient, ask questions, make a diagnosis, and prescribe a treatment, all while receiving expert-authored guidance on their actions.

With many in-person conferences cancelled in 2020, Medscape has worked to provide alternative virtual solutions that allow all clinicians to retain access to late-breaking data, news, and guidelines they would have received at the conferences.

"Diabetes-related online continuing education provides an invaluable resource for healthcare providers and the diabetes care team with timely updates in clinical care and solutions to overcome common obstacles to achievement of good glycemic control. This is particularly relevant in cardiovascular (CV) risk reduction, continuous glucose monitoring (CGM), and expanded therapeutic indications due to frequent releases of new data, guidelines, and/or new products. Moreover, we are facing such challenging times due to the current COVID-19 pandemic that we have to start rethinking our current educational and communication models to be more centered on online education modalities," said Davida F. Kruger, MSN, APN-BC, BC-ADM, Certified Nurse Practitioner, Henry Ford Health System, Division of Endocrinology, Diabetes, and Bone Disorders.

And while physicians are learning, so are their patients. A survey of diabetes patients conducted on WedMD.com, which, along with Medscape Education, is part of the WebMD Health Network, found that 64% of patients living with T2D were active on the site doing research before their doctor visit. Additionally, 80% researched their treatment following their appointment, and 88% sought information on their diagnosis following their appointment. In fact, 74% of patients with T2D did their research in order to discuss with their physician what treatment to try.

Having both patients and physicians aligned on the clinical and lifestyle approach to living with diabetes can be powerful. It allows for informed discussions, better adherence, and likely better patient outcomes.

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[1] Centers for Disease Control and Prevention, National Diabetes Statistic Report, 2020. Atlanta, GA: Centers for Disease Control and Prevention, U.S. Dept of Health and Human Services; 2020.
[2] National Resident Matching Program, Results and Data: Specialties Matching Service 2020 Appointment Year. National Resident Matching Program, Washington, DC. 2020.
[3] Endocrine Clinical Workforce: Supply and Demand Projections. The Endocrine Society, Washington, DC. June 2014
[4] Medscape internal data, 2019.

Table of Contents

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What is Shaping Diabetes Care

Advances and Discoveries

Diabetes is estimated to affect approximately half a billion people globally[1] and is an escalating threat to personal health and national economies[2]. The majority of these patients have type 2 diabetes (T2D). Prevalence of type 1 diabetes (T1D) is also increasing at the rate of 3–5% annually[3,4], and 30 million patients are estimated worldwide with over 1.3 million with over 1.3 million patients in the United States[5]. T1D, representing approximately 10% of diabetes cases, and T2D, representing approximately 90% of diabetes cases, constitute the majority of the disease and are generally viewed as two different, yet biologically related disorders. T1D is an autoimmune disease with a prominent genetic component, and T2D is an age-and lifestyle related disease associated with obesity and inactivity[6,7].

The total number of insulin-requiring patients is estimated at over 200 million.

The total number of insulin-requiring patients is estimated at over 200 million[8]. Insulin may be delivered with either multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII). Daily dose adjustment of insulin is the mainstay of long-term management of diabetes. Patients need to consider the amount of food intake, duration of exercise, and dose and time of recent insulin administration when they make daily dose adjustments[9]. It is important to keep blood glucose in the acceptable normal range without increasing hypoglycemia to avoid long-term complications[10]. Despite advances in diabetes management in recent years, most patients with diabetes still do not receive target HbA1cs of <6.5 or 7%[11]. Fear of hypoglycemia may play a role in high HbA1c results. Patients who are on insulin therapy are at risk for hypoglycemia and hypoglycemia-related serious acute complications, such as a seizure, fall, and even death[12,13]. With proper implementation of diabetes technologies, hypoglycemia rates can be reduced[14,15].

Hb1Ac has been used in the last three decades for diabetes monitoring. It is a great tool for long-term diabetes complication risk assessment. However, it can be falsely high or low because of many medical conditions, such as anemia, chronic kidney disease, and hemoglobinopathies[16]. It does not give information about glucose variability and hypoglycemic episodes, which can be life-threatening. With the help of new technologies, going beyond HbA1c, time in range, such as the percentage of 70-180mg/dl on CGM, is a new tool to monitor glucose levels on a regular basis and has been suggested to be used in clinical trials as an outcome metric[17,18].

REGULATION OF GLUCOSE METABOLISM

Peripheral Control of Glucose Metabolism

For almost a century, research on glucose homeostatic processes has predominantly focused on the role of peripheral control mechanisms, most notable the role of pancreatic islets as the key organ for regulating glycemic control[19]. The prevailing dogma is that a meal-induced rise in blood glucose stimulates beta cells in the endocrine pancreas to secrete insulin. Insulin lowers this postprandial glucose surge by acting on the energy-storing organs, such as skeletal muscle and adipose tissue, to facilitate uptake of glucose production and to suppress glucose output via inhibition of hepatic gluconeogenesis. Conversely, in fasted and hypoglycemic states, the pancreatic alpha cells secrete glucagon, which stimulates hepatic glucose production and opposes the actions of insulin[20]. Under non-disease physiological conditions, these processes efficiently maintain blood glucose levels within a relatively narrow and stable range[21].

Half a century ago, it was discovered that oral ingestion of glucose elicits an enhanced insulin response relative to that of an intravenous glucose infusion.

Half a century ago, it was discovered that oral ingestion of glucose elicits an enhanced insulin response relative to that of an intravenous glucose infusion[22,23]. This observation, subsequently termed "the incretin effect," introduced the gut as a metabolically relevant endocrine organ and led to the identification and glucoregulatory impact of many gut-derived peptides[24]. Thus, in the 1970 and 1980s, the most prominent incretin hormones glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) were identified and their ability to augment glucose metabolism delineated[25,26]. Both GIP and GLP-1 are secreted from the gut in response to ingested nutrients and exhibit insulinotropic actions at pancreatic beta cells, contributing to postprandial glucose homeostasis[27].

In addition to insulin, glucagon, and the incretin hormones, other humoral factors including epinephrine (adrenaline), and glucocorticoids, and growth hormone can impact glucose homeostasis[28]. More recently, the field has enlarged with the realization of the glucoregulatory role of an array of more recently discovered factors including fibroblast growth factors (FGFs)[29], cytokines[30], and peptides secreted from muscle[31], fat[32], and bone[33].

Central Control of Glucose Metabolism

A growing body of evidence has established that the brain directly affects glucose homeostasis through both insulin-dependent and insulin-independent mechanisms[34,35]. The mechanisms underlying the ability of centrally acting hormones to lower blood glucose in diabetic animal models are still under investigation but hypothesized to implicate lowering of hepatic glucose production while increasing glucose uptake in skeletal muscle and brown adipose tissue[36,37]. Thus, glucose homeostasis is likely controlled by complex and coordinated interactions between brain-, gut-, and islet-related biological systems. Importantly, as indicated above, our understanding of how factors secreted from other peripheral tissues feed into the major glucoregulatory systems is now starting to be revealed.

PATHOGENESIS AND PATHOPHYSIOLOGY OF DIABETES

Type 1 Diabetes

T1D is an autoimmune in which the insulin-producing beta cells of the pancreas are selectively destroyed by autoreactive T cells

T1D is an autoimmune in which the insulin-producing beta cells of the pancreas are selectively destroyed by autoreactive T cells[38]. The autoreactive T cells have been shown to recognize islet autoantigens including insulin, glutamic acid decarboxylase (GAD), and zinc transporter 8 (Znt8)[39]. Eventually the depleted pancreatic beta-cell function cannot sustain sufficient insulin to maintain euglycemia, and the patients ultimately require insulin replacement therapy. The etiology and pathophysiology of the autoimmunity preceding the diagnosis of T1D are influenced by a combination of genetic and environmental factors[40]. Despite a growing understanding of T1D pathogenesis, the driving immune triggers orchestrating the attack of the beta cells remain enigmatic. Autoantibodies can be detected before the clinical onset of T1D. However, the gap between early biochemical alterations and the clinical manifestation complicates the elucidation of causative environmental triggers[41]. Until now, environmental triggers proposed to be involved in the disease pathogenesis include viruses, bacteria, and nutrients[42]. Unraveling how these stimuli might interact with specific molecular targets to initiate the autoimmune cascade is crucial for intervening as early as possible in order to preserve functional beta-cell mass.

Type 2 Diabetes

T2D is a progressive disorder with a pathogenesis that involves a reciprocal interplay of persistent increases in insulin demand and its subsequent production.

Historically, T2D was considered an age-related disease linked to a sedentary lifestyle and hypercaloric diet. It is now acknowledged that genetic factors also play a prominent role for the onset and progression of the disease[43]. T2D is a progressive disorder with a pathogenesis that involves a reciprocal interplay of persistent increases in insulin demand and its subsequent production. Insulin resistance is the most well-defined pathological gateway to T2D[44] and frequently coincides with excess adipose tissue mass and ectopic lipid deposition in tissues involved in glucose disposal[45]. Insulin resistance results from a reduced response of cells in adipose tissue and skeletal muscle to stimulate insulin-mediated glucose uptake as well as a blunted response of cells in the liver to shut down hepatic glucose production. Under normal circumstances, pancreatic beta cells balance the loss of insulin sensitivity by increasing insulin production and release. This compensation by pancreatic beta cells often prevents hyperglycemia despite the prevailing insulin-resistance state. However, it is only upon failure of beta cells to fully compensate for the increased insulin demand that hyperglycemia and T2D ensue[46]. This loss of beta-cell plasticity is not solely a consequence of cellular loss but also reflects reduced functionality and an impaired response to insulin secretagogues[47]. In parallel, without insulin to act as a brake on glucagon secretion from pancreatic alpha cells, elevated glucagon levels and hepatic insulin resistance lead to uncontrolled hepatic glucose production. These reciprocal events intensify the metabolic rearrangements and an ever-escalating glucotoxicity that eventually exhausts beta-cell function to amplify the disease cascade[48]. Additionally, the altered islet biology may impact the glucoregulatory capacity of the brain, which may be further deranged in obese patients in which central leptin resistance coincides with hampered insulin control[49]. Ultimately, late-stage insulin-deficient T2D patients require insulin supplementation to maintain euglycemia.

Subgroups of Type 2 Diabetes

For decades, diabetes has been classified into two forms, based on the presence (T1D) or the absence (T2D) of autoantibodies against pancreatic islet β-cell antigens and age at diagnosis. Nevertheless, diabetes is a highly heterogeneous disorder. Consequently, current classifications are not sufficient for disease stratification and outcome prediction. Indeed, this is exemplified by the identification of a third subgroup of diabetes termed “latent autoimmune diabetes in adults” that is diagnosed by the presence of glutamic acid decarboxylase antibodies[50]. Refining diabetes classifications based on

biomarkers and deep phenotyping may bring clinicians closer to personalized medicine and better assessment of the risk of complications at diagnosis.

To assess whether T2D is a uniform disease and if the response to intervention can be predicted based on biomarkers, Leif Groop and colleagues performed a "data-driven" cluster analysis with newly diagnosed diabetes from the Swedish All New Diabetics in Scania cohort[51]. The authors identified five novel subgroups of adult-onset diabetes and their association with clinical outcomes including severe autoimmune disease (SAID); severe insulin-deficient diabetes (SIDD); severe insulin-resistant diabetes (SIRD); mild obesity-related diabetes (MOD); and mild age-related diabetes (MARD). The authors propose that the combined information from the six variables (glutamate decarboxylase antibodies, age at diagnosis, body mass index (BMI), glycated hemoglobin (HbA1c), and homeostatic model assessment 2 estimates of β-cell function and insulin resistance), which are central to the development of diabetes, offers a superior metric for sub-classification of T2D versus the conventional assessment of glucose levels.

CURRENT TREATMENTS FOR DIABETES

The primary goal of antidiabetic treatment is to restore or improve glucose control.

The primary goal of antidiabetic treatment is to restore or improve glucose control. Hemoglobin A1c is a biochemical marker that reflects chronic improvements in plasma glucose levels and I frequently employed for the clinical evaluation of therapeutic efficacy[52]. As outlines above, T2D manifests in numerous states of impaired insulin function, and it is the failure of the beta cells to secrete sufficient insulin to compensate for the defect that results in hyperglycemia. Accordingly, drugs that can enhance insulin sensitivity as well as compounds that can amplify insulin secretion may serve to improve glycemic control[53]. Current antidiabetic pharmacotherapy primarily consists of insulin, biguanides, sulfonylureas, thiazolidinediones, alpha-glucosidase inhibitors, incretin enhances, GLP-1 analogs, amylin analogs, sodium-glucose co-transporter 2 inhibitors (SGLT2 inhibitors), and bile acid sequestrants. This multitude of antidiabetic therapeutics allows for a degree of personalized treatment that can be tailored to glycemic status for each patient. However, each class of drugs is associated with specific efficacy shortcomings and safety concerns that need to be accounted for when selecting a pharmacotherapy. Furthermore, diabetics (in particular T2D) frequently suffer from comorbidities such as cardiovascular disease and obesity, which may complicate treatment and limit therapeutic options.

Insulin replacement therapy is indispensable for T1D patients. Also, patients suffering from T2D may eventually require exogenous insulin to maintain glycemic control[54]. Much progress has been made since the initial discovery of insulin. Insulin analogs with diverse pharmacokinetic properties are now available and employed to tailor individualized regiments in personalizing glycemic control[55]. Insulin-induced hypoglycemia is typically not a risk factor for diabetics suffering from insulin resistance, and for T1D patients, the development of insulin analogs with more "peakless" profiles has helped lower the risk of treatment-induced hypoglycemia. Insulin is frequently employed to support the therapeutic efficacy of other antidiabetic compounds including metformin, TZDs, and incretin-based therapies[57,58]. The pharmacological efficacy of these compounds may be significantly hampered if sufficient insulin is not available to support their independent molecular action.

Having the highest benefit-risk profile compared to other available medications, metformin is the most frequently used biguanide and the first-in-line oral therapy for treating T2D[59]. Metformin reduces fasting glucose levels by inhibiting hepatic glucose output and stimulating uptake and utilization of glucose in skeletal muscle[60,61].The underlying cellular mechanisms of action are being investigated but remain somewhat elusive to date[62]. Metformin is often used in combination with drugs that can complement its pharmacological profile, such as insulin secretagogues or insulin sensitizers[63]. Interestingly, diabetics treated with metformin have a relatively lower risk of developing cancers as compared to patients treated with insulin or sulfonylureas[64]. The protective effect is sustained in combination therapies involving metformin[65]. The most common adverse effects associated with metformin treatment are dose-related gastrointestinal disturbances.

Thiazolidinediones (TZDs) bind to and activate the peroxisome proliferator-activated receptor gamma (PPARγ) to enhance insulin sensitivity and reduce hyperglycemia[66,67]. TZDs exert a number of pleiotropic effects, such as reducing circulating levels of pro-inflammatory cytokines and increasing adiponectin levels, which may add to the insuin-sensitizing effects associated with their usage[68,69,70]. However, PPARγ is abundantly expressed in fat cells (also in the muscle and liver), and activation by TZDs initiates lipogenic transcriptional signaling and the most common adverse effect associated with TZDs — weight gain. Further, and increased risk of congestive heart failure has been associated with the use of TZDs. The FDA has approved adjunctive therapy with TZDs in combination with metformin, insulin, sulfonylureas, and glinides.

Sulfonylureas and glinides improve glycemia by enhancing insulin secretion[76,77]. Both compounds bind to an ATP-dependent K+ channel, albeit at different sites, expressed on the pancreatic beta-cell membrane. This leads to a membrane depolarization and calcium-mediated insulin secretion[78,79]. The major adverse risk associated with their usage is hypoglycemia. Moreover, as with TZDs, sulfonylureas and glinides stimulate adiposity and lead to weight gain[81].

Inhibitors of dipeptidyl peptide-IV (DPP-IV), the enzyme responsible for degrading GLP-1, are referred to as incretin enhancers, whereas incretin mimetics refers to the group of synthetic analogs of GLP-1. GLP-1 signals through its receptor on pancreatic beta cells to promote glucose-stimulates insulin secretion. Unlike sulfonylureas, which cause nonspecific insulin secretion, there is little hypoglycemic risk with treatment of incretin-based therapies. They only promote glucose-stimulated insulin secretion, thus offering an internal buffering capacity due to their mechanism of action. While GLP-1 analogs promote clinically relevant, albeit modest, weight loss, DPP-4 inhibitors present a weight-neutral profile[82]. GLP-1R agonists may improve cardiovascular risk factors however, dose-dependent adverse gastrointestinal events and nausea are linked to their usage[83,84].

Alpha-glucosidase is an enzyme involved in the intestinal degradation of complex carbohydrates. Specific enzyme inhibitors protect against postprandial hyperglycemia by delaying carbohydrate absorption in the proximal gut[85]. However, the interference with nutrient absorption induces gastrointestinal side effects, which have limited their usage, Further, the impact of HbA1c levels is modest, and the alpha-glucosidase inhibitors are less effective in lowering glycemia than metformin and sulfonylureas[86,87].

The **peptide amylin** is synthesized in the pancreatic beta cells and co-secreted with insulin in response to a meal[88,89]. The administration of amylin analogs is purported to inhibit glucagon secretion from the islet alpha cells leading to a decrease in post prandial glucose excursions[90]. The reduction in glucagon secretion assist in attenuating hepatic glucose production. Further, amylin analogs slow gastric emptying, elicit hypophagia, and are associated with weight loss[91]. The effect of amylin-based therapy as measured by HbA1c lowering is modest[92,93]. Amylin decreases body weight in both diabetics and nondiabetics and is currently being investigated for its anti-obesity potential[94,95].

Recently, **pharmacological inhibitors of sodium-glucose co-transporter 2 (SGLT2)** were approved for the treatment of T2D[96]. Blocking SGLT2 lowers the reabsorption of renal glucose excretion and thus reduces circulating glucose levels[97]. Chronic administration lowers HbA1c levels by 0.5-1.5% without risk of causing hypoglycemia[98]. The somewhat distinctive mechanism of action of SGLT2 inhibitors implies a therapeutic opportunity for adjunctive administration with an insulin secretagogue or sensitizing agent. Common adverse events include genital and urinary tract infections; however more serious safety concerns pertaining to increased cancer risk have been recently raised[99].

Bile acid sequestrants (BASs) were originally developed for treating dyslipidemia[100]. Importantly, BASs were shown to reduce hyperglycemia in patients with coexisting diabetes and dyslipidemia[101].

The glucose-lowering mechanism of BASs remains elusive but seems to involve increasing the circulating bile acid pool, subsequent activation of bile acid receptors such as the farnesoid X receptor (FXR) or Takeda G protein-couple receptor 5 (TGR5) and the resulting endogenous release of GLP-1 and/or FGF19[102]. The efficacy of BASs to concurrently improve HbA1x and LDL cholesterol makes them an attractive add-on the existing glucose-lowering agents. Thus far, reported adverse events associated with their usage primarily relate to mild gastrointestinal discomfort[103].

As a function of time, the majority of T2D patients receive more than one type of medication[104,105], and designing an individual medicinal strategy entails a multitude of factors for consideration. These include beta-cell functionality and insulin sensitivity but also the ease of use, financial costs, tolerability, disease comorbidities, and the history of diabetes[106,107]. Conversely, it has been shown that combining insulin therapy with sulfonylureas instead of metformin is associated with increased mortality[108], underscoring the complexity of prescribing safe and efficacious antidiabetic pharmacotherapies.

FDA-Approved Antidiabetic Agents for the Treatment of T2D *Table 1*

Class	Drug (brand)	Mechanism of action*	HbA_{1c} reduction, %#	Effect on weight	Adverse Effects*	Precautions and comments
Alpha-glucosidase inhibitors	Acarbose (Precose); Miglitol (Glyset)	Delay complex carbohydrate absorption	0.5-0.8	Neutral	Flatulence, diarrhea, abdominal pain	Titrate slowly to minimize GI effects
Amylin analog	Pramlintide (Symlin)	Acts in conjunction with insulin to prolong gastric emptying, reduce postprandial glycose secretion, promote appetite suppression	0.5-1	Loss	Nausea, vomiting	Black box warning: Coadministration with insulin may induce severe hypoglycemia; injectable drug
Biguanide	Metformin (Glucophage)	Decrease hepatic glucose output; Increase peripheral glucose uptake	1-2	Neutral	Nausea, vomiting, diarrhea, flatulence	Taken with meals; Avoid use in patients with renal or hepatic impairment or with CHF, because of increased risk for lactic acidosis

Class	Drug (brand)	Mechanism of action*	HbA_{1c} reduction, %#	Effect on weight	Adverse Effects*	Precautions and comments
Bile acid sequestrant	Colesevelam (Welchol)	Binds to the intestinal bile acids, MOA for diabetes control: unknown	0.5	Neutral	Constipation, dyspepsia, nausea	
DPP-4 inhibitors	Sitagliptin (Januvia); Saxagliptin (Onglyza); Linagliptin (Tradjenta)	Slow inactivation of incretin hormones	0.5-0.8	Neutral	Not clinically significant	
Dopamine agonist	Bromocriptine (Parlodel)	MOA for diabetes control: unknown	0.5-0.7	Neutral	Nausea, vomiting, dizziness, headache, diarrhea	
Incretin mimetics	Exanetide (Byetta); Liraglutide (Victoza)	Stimulate insulin secretion, slows gastric emptying, suppresses glucagon release, induces satiety	0.5-1	Loss	Nausea, vomiting, diarrhea	Acute pancreatitis has been reported; Injectable drug
Insulin preparations: rapid-, short-, intermediate-, long-acting, premixed	Refer to Table 2	Exogenous insulin	Up to 3.5	Gain	Hypoglycemia	
Nonsulfonylurea secretagogues	Nateglinide (Starlix), Repaglinide (Prandin)	Stimulate insulin secretion from the pancreas	1-1.5	Gain	Hypoglycemia	Taken with meals to control rapid onset
First-generation sulfonylureas	Chlorpropamide (Diabinese), Tolazamide (Tolinase), Tolbutamide (Orinase)	Stimulate insulin secretion from the pancreas	1-2	Gain	Hypoglycemia	Use of these agents has declined response due to AEs and unpredictable results
Second-generation sulfonylureas	Glimepiride (Amaryl), Glipizide (Glucotrol), Glyburide (Micronase, Diabeta, Glynase)	Stimulate insulin secretion from the pancreas	1-2	Gain	Hypoglycemia	

Class	Drug (brand)	Mechanism of action*	HbA_{1c} reduction, %#	Effect on weight	Adverse Effects*	Precautions and comments
Thiazolidinediones	Pioglitazone (Actos), Rosiglitazone (Avandia)	Increase peripheral tissue insulin sensitivity	0.5-1.4	Gain	Edema	Black box warning: These agents can cause or exacerbate CHF; Contraindicated in patients with NYHA class III or IV heart failure

*Lacy CF, et al. *Drug Information Handbook*

#Nathan DM, et al. "Management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy." Diabetes Care. 2006

Abbreviations: CHF- Congestive Heart Failure; DPP- dipeptidyl peptidase; HbA_{1c}- glycated hemoglobin; NYHA- New York Heart Association

Insulin Preparations *Table 2*

Drug (brand)	Onset time*	Peak time*	Duration	Comments
Rapid-Acting				
Insulin aspart (Novolog)	10-20 min	1-3 hr	3-5 hr	Administer within 15 minutes before or immediately after meals
Insulin glulisone (Apidra)	25 min	45-48 min	4-5 hr	
Insulin lispro (Humalog)	15-30 min	0.5-2.5 hr	3-6.5 hr	
Short-acting				
Insulin regular (Novolin R, Humilin R)	30-60 min	1-5 hr	6-10 hr	Administer 30 min before meals
Intermediate-acting				
Insulin NPH (Novolin N, Humilin N)	1-2 hr	6-14 hr	16-24+ hr	Cloudy appearance
Long-Acting				
Insulin detemir (Levermir)	1.1-2 hr	3.2-9.3 hr	5.7-24 hr**	Do not mi with other insulins
Insulin glargine (Lantus)	1.1 hr	None	24 hr	
Premixed				
70% Insulin aspart protamine/30% insulin aspart (NovoLog Mix 70/30)	10-20 min	1-4 hr	24 hr	Cloudy appearance; Administer 15 minutes before meals
75% Insulin lispro protamine/25%insulin lispro protamine (Humalog Mix 75/25)	15-30 min	2 hr	22 hr	
50% Insulin lisprp protamine/50% insulin lispro protamine (Humalog Mix 50/50)	15-30 min	2 hr	22 hr	

70% Insulin NPH/30% insulin regular (Humulin 70/30, Novolin 70/30)	30 min	1.5-12 hr	24 hr	Cloudy appearance; Administer 30 minutes before meals
50% Insulin NPH/50% insulin regular (Humulin 50/50)	30-60 min	1.5-4.5 hr	7.5-24 hr	

*McEvoy GK, ed. *American Society of Health-System Pharmacists Drug Information*

***Dose-dependent*

Abbreviations: NPH- Neutral Protamine Hagedorn

NOVEL AVENUES FOR TREATING DIABETES

Research programs aiming to illuminate the molecular underpinnings of diabetic pathologies have increased exponentially in recent years. This effort is being directed increasingly toward the development of novel drugs for the treatment of diabetes and the comorbidities. In addition to the broadened scope of basic discovery research and exploratory pharmacology, investment continues to refine, supplement, and optimize the therapeutic utility of current treatment options. Although there is a broad set of quality options for patients and the prescribing physician, glycemic control in both T1D and R2D remains suboptimal. Additionally, many current medicines possess dose-limiting adverse effects and are of narrow therapeutic index. In the following sections, some of the more prominent and promising preclinical strategies for treating diabetes are reviewed.

Next-Generation Insulin Analogs

Insulin is a miraculous substance but a dangerous drug.

Insulin is a miraculous substance but a dangerous drug. It is the first-in-line treatment for T1D and advanced stages of T2D. Throughout the last decade, we have witnessed a steady progression in the production of quality of insulin in the highest chromatographic purity. Biosynthesis has also been employed to refine the pharmacokinetics of the hormone where site-specific mutations have been introduced to either accelerate or to postpone insulin action[109]. Consequently, the primary objective of cutting-edge research has advanced from pharmacokinetics to pharmacodynamics. The discovery of an insulin that is glucose sensitive is a primary target, much in the manner that an incretin only operates in hyperglycemia. Such an insulin analog or novel formulation would provide for more aggressive treatment of hyperglycemia with less risk of life-threatening hypoglycemia. Simultaneously, the perfection of pump-infused insulin is being attempted through the development of novel glucagon formulations and structural analogs, coupled with continual glucose monitoring[110,111]. It is not inconceivable that

in the not-so-distance future, a much improved approach to insulin-dependent control of glycemia could emerge. Separately, attempts to minimize body weight in concert with insulin therapy have reached an advanced development state. Obesity is a common feature of advanced insulin dependent T2D, and it serves to accelerate pancreatic failure while promoting weight gain. Combination basal insulin therapy with GLP-1 agonism has proven clinically that improved glycemic control, with less hypoglycemia and weight gain, can be achieved[112,113,114]. It represents a paradigm shift where it is likely that increased effort will be devoted to further minimize the use of insulin through the identification of additional mechanisms to restore insulin sensitivity and endogenous beta-cell function.

Pancreatic Transplantation

Recent progress in the development and success rate of both pancreatic and islet transplantation procedures have made these invasive therapies increasingly appealing.

Although pancreatic transplantation is not a new procedure[115], recent progress in the development and success rate of both pancreatic and islet transplantation procedures have made these invasive therapies increasingly appealing. The surgeries can be curative and are often employed in T1D patients who are undergoing a renal transplantation or in patients with poorly controlled glycemia or with recurrent hypoglycemia[116,117]. Improvements in transplantation surgery and immunosuppressive therapy are reflected in a >95% 1-year survival rate and graft survival of close to 85%[118]. Importantly, a successful transplant is more efficient in lowering HbA1c levels and maintaining glycemic control that insulin therapy[119]. An alternative to pancreatic transplantation is the less invasive islet transplants. Despite the obvious appeal of a less invasive procedure, a pancreatic transplant typically has better long-term glycemic outcomes than islet transplants[120]. Sourcing sufficient human islets remains a constant challenge and stem cell technology possesses huge potential to address this need[121]. There still remain sizable issues to scaling the technology for commercial application while addressing a host of safety concerns pertaining to the potential for uncontrolled proliferation and insulin release that might evolve to be non-glucose regulated.

Leptin

Leptin is an adipocyte-derived hormone that serves to inform the brain of peripheral fuel availability[122]. Circulating leptin induces catabolic actions and weight loss by activating specific leptin receptors in the hypothalamus and the hindbrain[123]. In addition, hypothalamic leptin receptor

Leptin therapy corrects hyperglycemia in humans with coexisting lipodystrophy and T1D.

activation prominently regulates glucose metabolism and can correct diabetes in animal models of both T1D and T2D[124]. Infusion of leptin into the lateral cerebral ventricle in rats with uncontrolled insulin-deficient diabetes reduces hyperglycemia and improves glucose tolerance, purportedly by inhibiting hepatic glucose production and stimulating glucose uptake[125]. Furthermore, leptin therapy corrects hyperglycemia in humans with coexisting lipodystrophy and T1D[126]. Leptin is currently being studied in clinical trials for its ability to improve glycemic control and reduce the requirements for insulin replacement therapy in T1D.

Despite the capacity of leptin to enhance insulin sensitivity and reduce hyperglycemia in animal models of T2D, clinical trials investigating the efficacy of leptin to correct clinical parameters in obese T2D subjects have been discouraging[127,128]. Whether the failure of leptin to ameliorate glycemic control in T2D coincides with leptin resistance and excess body weight needs further investigation. Notably, an increasing number of preclinical studies have demonstrated that several agents (FGF21, amylin, exedin-2, and a GLP-1/glucagon co-agonist) can restore leptin sensitivity in diet-induced leptin-resistant models to harvest additional weight lowering and glycemic benefits of leptin therapy[129,130,131]. These studies have spurred new enthusiasm for leptin as an agent in novel combinatorial pharmacotherapies for the treatment of metabolic disorders. However, exogenous leptin administration has been associated with adverse effects including increased blood pressure and immunogenicity[132]. These limitations must be resolved before leptin can progress further in the pipeline.

FGF21

Experimental studies have demonstrated that the administration of recombinant FGF21 improves insulin sensitivity in multiple species.

FGF21 is a hormone with profound effects on glucose and lipid metabolism and is currently being investigated as a potential therapy for the treatment of T2D[133,134]. It is expressed in multiple tissues including liver, pancreas, adipose, and muscle tissue. Glucagon appears to regulate hepatic FGF21 production[135] as well as PPAR-alpha agonists[136]. Fasting[137] and dietary macronutrient composition[138] influence circulating levels in a circadian manner[139]. Experimental studies have demonstrated that the administration of recombinant FGF21 improves insulin sensitivity in multiple species ranging from rodents to monkeys to man. The insulin-sensitizing efficacy of FGF21 is associated with an inhibition of hepatic glucose output, increased circulating adiponectin, and a reduction in body fat[140]. The molecular

mechanisms responsible for the metabolic effects of FGF21 are still being investigated, and studies using FGF receptor-mutated mice imply that the majority of the effects are linked to FGF receptor 1 activation in adipose tissue. Recently, a novel FGF21 analog was tested in obese subjects with T2D[141], and it was observed to improve an array of metabolic parameters. Discouragingly, no significant improvements in hyperglycemia were observed through the course of 28 days of daily treatment. This may reflect differences in pharmacological properties between native FGF21 and the analog clinically tested or be consequential to the short treatment duration and the small sample size tested in the study. Future clinical trials are needed to confirm these observations and, if validated, to deter- mine the molecular basis.

Despite the wealth of preclinical literature supporting a novel role for FGF21 in treatment of metabolic disease, rodent studies have reported that FGF21 negatively regulates bone metabolism and that such therapy may impose skeletal fragility[142]. On the other hand, a positive relationship between circulating FGF21 levels and bone mineral density has been reported for healthy human subjects[143]. It is a conundrum that requires additional study, and it is warranted that a balanced analysis of the benefits to metabolism is carefully assessed in the context of bone mineral metabolism.

Bariatric Surgery

Bariatric surgery provides unquestionably superior body weight and glycemic outcomes when compared to drug therapy in obese patients with poorly controlled T2D.

Bariatric surgery provides unquestionably superior body weight and glycemic outcomes when compared to drug therapy in obese patients with poorly controlled T2D[144]. Reports indicate that 60–80% of the patients receiving a Roux-en-Y gastric bypass show a profound reversal of their diabetes[145]. The molecular basis of the glycemic improvement constitutes a subject of intense interest as an appreciable degree of it occurs before there is a meaningful difference in body weight. Clinical studies have highlighted changes in multiple gut-secreted peptides such as GLP-1 and ghrelin as a mechanistic explanation for the glycemic benefit of such surgeries[146]. Studies using genetic animal models have indicated that neither factor alone is crucial for the metabolic benefits[147]. Recent, preclinical reports imply that coordinated alteration in multiple systems including bile homeostasis, microbiota, and gut-brain communication functions in concert with humoral alterations to mediate the metabolic effects of surgery[148]. Identification of these mechanisms could lead to the development of a pharmacological strategy that may reproduce the glycemic control of surgery and render such invasive surgical procedures obsolete.

Multi-hormone Combination Therapies

It has become increasingly evident that adjusted enteroendocrine responses contribute to the massive and rapid metabolic improvements achieved by bariatric surgeries.

It has become increasingly evident that adjusted enteroendocrine responses contribute to the massive and rapid metabolic improvements achieved by bariatric surgeries. Additionally, recent clinical and preclinical advances highlight that parallel targeting of more than one biological mechanism yields superior metabolic efficacy and fewer adverse events compared to traditional monotherapies[149]. Simultaneous targeting of multiple metabolic pathways can be achieved by coadministration of two distinct hormones[150] or through the application of unimolecular polyagonists. These multifunctional hormones combine to embellish certain hormone action profiles but, more importantly, serve to recruit distinct pharmacology that leads to enhanced efficacy and safety[151].

In 2009, the discovery of co-agonist peptides possessing action at the glucagon and the GLP-1 receptors was reported to spectacularly lower body weight and improve glucose metabolism in animal models of obesity and glucose intolerance[152]. A follow-up study revealed that GLP-1/ glucagon co-agonism reverses leptin resistance in diet-induced obesity (DIO) animals[153]. This observation is provocative and sets the stage for future clinical studies with a central question being at what percent body weight reduction does leptin action return in human subjects. Of note, a recent human study exploring the efficacy of parallel glucagon and GLP-1 receptor agonism showed promising metabolic improvements[154].

While the development of GIP agonists for diabetes has been clouded by the prospect of promoting weight gain, a novel dual incretin co-agonist (GLP-1/GIP) was recently reported to improve glycemic control and enhance insulin secretion in rodents and nonhuman primates[155]. Furthermore, the enhanced insulinotropic effect of the co-agonist was found in clinical study to substantially reduce HbA1c levels in a dose-dependent improvement (1.1% from baseline) at the highest dose within just 6 weeks. Importantly, the treatment with the co-agonist was not associated with altered gut motility or vomiting, implying that the co-agonist can be dosed to improve efficacy while maintaining a robust safety profile. Follow- up clinical studies are ongoing to probe the efficacy and safety of these unimolecular co-agonists.

The concept of employing multi-agonists or the coadministration of several compounds with complementary mechanisms of action can be expanded to include a multitude of novel treatment protocols. The approach may thus significantly advance the possibility for individualized treatments to finally close the performance gap between drug therapy and surgical procedures.

Anti-obesity Pharmacotherapies

Several anti-obesity pharmacotherapies may have potential in the prevention and management of T2D.

It is well established that excess body fat mediates multiple metabolic disturbances that contribute to insulin resistance and pancreatic secretory defects[156], rendering obesity a prominent role in escalating the diabetes epidemic. Accordingly, several anti-obesity pharmacotherapies may have potential in the prevention and management of T2D. Equally, antidiabetic medications display modest anti-obesity activity as well (e.g., GLP-1R agonists, amylin analogs, and SGLT2 inhibitors)[157]. Of note, the FDA recently approved the antidiabetic incretin mimetic liraglutide for the treatment of obesity. In contrast to the doses used for treating T2D (1.2 mg or 1.8 mg), the dose for treating obesity is 3.0 mg.

The anti-obesity agent orlistat inhibits gastrointestinal lipases and serves to lower the availability of fatty acids for absorption[158]. Orlistat has been shown to improve glycemic control in obese T2D subjects[159] and to exhibit additive glycemic properties when co-administered with metformin[160]. Similarly, combination therapy of the sympathomimetic amine phentermine and the anticonvulsant agent topiramate results in ~10% weight loss in obese subjects (when provided in conjunction with lifestyle modification)[161]. Notably, the combination of phentermine and topiramate (parallel metformin treatment) administered to T2D patients enhances weight loss and improves glycemic control relative to placebo (SEQUEL trial)[162]. Lorcaserin is a selective serotonin 2C agonist that lowers body weight in overweight and obese adults[163]. Coadministration of lorcaserin with metformin and/or a sulfonylurea can improve HbA1c and fasting glucose levels in obese subjects with T2D[164]. Recently, co-treatment with the antidepressant bupropion and the opioid receptor antagonist naltrexone was approved by the FDA for the treatment of obesity, and this combination therapy may also exhibit meaningful glycemic improvements in obese subjects with T2D[165]. Thus, marketed anti-obesity therapies may serve as valuable adjuncts in polypharmaceutical treatment options for overweight diabetics.

Evidence supporting the prospect that melanocortin 4 receptor (MC4R) agonism may constitute an effective therapy or co-therapy for diabetes and obesity is accumulating. MC4R is acknowledged to play a seminal role in energy metabolism and MC4R agonism decreases feeding and increases energy expenditure[166]. Notably, MC4R stimulation also enhances insulin sensitivity and improves glucose tolerance in rodents and nonhuman primates[167]. Currently, MC4R agonists are being evaluated in clinical trials for the treatment of obesity. Future studies investigating the antidiabetic virtues of MC4R agonism, either as monotherapy or in combination with other agents, seem warranted.

EMERGING THERAPIES FOR TYPE 2 DIABETES

Drugs in the Pipeline for Type 2 Diabetes *Table 3*

Drug category	Mechanism of action
Sodium-glucose contransporter-2 inhibitors	Inhibit reabsorption of glucose at the proximal tubule of the kidney, thereby decreasing systemic hyperglycemia
11beta-hydroxysteroid dehydrogenase type 1 inhibitors	Inhibit an enzyme responsible for activating cortisone to cortisol, which minimized anti-glycemic effects of cortisol
Glycogen phosphorylase inhibitors	Inhibit enzymes responsible for hepatic gluconeogenesis
Glucokinase activators	Activate key enzyme to increase hepatic glucose metabolism
G protein-coupled receptor 119 agonists	Mechanisms unknown; Activation induces insulin release and increases secretion of glucagon-like peptide 1 and gastric inhibitory peptide
Protein tyrosine phosphatase	Increase leptin and insulin release
Glucagon-receptor antagonists	Block glucagon from binding to hepatic receptors, thereby decreasing gluconeogenesis

TECHNOLOGICAL ADVANCES

HbA1c has been used in the last three decades for diabetes monitoring. It is a great tool for long-term diabetes complication risk assessment. However, it can be falsely high or low because of many medical conditions, such as anemia, chronic kidney disease, and hemoglobinopathies[168]. It does not give information about glucose variability and hypoglycemic episodes, which can be life-threatening[169]. With the help of new technologies, going beyond HbA1c, time in range is a new tool to monitor glucose levels on a regular basis and has been suggested to be used in clinical trials as an outcome metric[170,171].

Providers make better treatment decisions and remote follow-ups with enormous data generated by technologies.

Diabetes technologies play a vital role for patients and caregivers. Patients have less engagement with their diabetes and more time for other daily activities, Providers make better treatment decisions and remote follow-ups with enormous data generated by technologies. Diabetes

technologies will continue to improve rapidly. Creation of the new Class II medical device pathway for continuous glucose monitors is an important cornerstone in the development of future CGM and closed-loop insulin delivery systems. In coming years, wider use of diabetes technologies will be the standard of care in diabetes management. These advancements will decrease the burden of diabetes and improve diabetes outcomes.

Glucose Monitoring

A sampling of capillary blood with finger sticks has been the gold standard for glucose monitoring for many decades. CGM technology has improved significantly in recent years. Although there are significant advances in CGM technology, many patients with diabetes continue to rely on self-monitoring of blood glucose (SMBG) because of cost and accessibility[172,173].

Self-monitoring of blood glucose and digital health

T1D Exchange data showed that increased SMBG monitoring directly correlates with HbA1c reduction in patients with T1D[174]. However, SMBG only gives a snapshot of blood glucose levels and does not give any input regarding the direction of change in glucose and glucose variability. Many patients may still experience severe hypoglycemia despite frequent SMBG checks. For patients who cannot afford or do not want to use CGM, diabetes apps can be an alternative option. There are many apps for diabetes. Many of them focus on nutrition, healthy-living, exercise, and diabetes education. Some of them have the ability to keep a log of food, exercise habits, and insulin doses with even direct connection with glucometers[175,176,177]. Insulin calculator and diabetes-coaching apps have the potential for better outcomes even though all available studies were based on short-term safety. Accu-Chek Connect (Roche, Basel, Switzerland) is the first FDA-approved bolus insulin calculator app, other FDA-approved apps are Dario (Dario Health, Israel), InPen (Companion Medical, San Diego, California, USA) Insulia (Voluntis, Cambridge, Massachusettes, USA), iSage Rx (Amalgam, Wilmington, Delaware, USA) and My Dose Coach (Sanofi, Paris, France)[178]. One Touch Reveal (LifeScan, Milpitas, California, USA) is another diabetes app that connects to One Touch Verio Flex (LifeScan) meter directly and syncs the data seamlessly and has the ability to store and share with healthcare providers. A recent systematic review concluded that mobile apps may improve short-term diabetes-related outcomes, especially HbA1c; however, we do not have enough long-term data to conclude their efficacy in long-term complications[179].

Continuous glucose monitoring and data management systems

The first real-time display CGM, GlucoWatch (Cygnus, Redwood City, California, USA) was approved in 1999 by FDA to be used in T1D for 12 hours[180,181]. Since then, many CGM systems were developed such as Enlite 1, 2, 3 and Guardian (Medtronic, Northridge, California, USA), Dexcom STS (Short-term sensor), Dexcom 3, 7, 7 plus, Gen 4, 5 (Dexcom, San Diego, California, USA), Navigator (Abbott, Alameda, California, USA). Recently Dexcom Gen 6 (Dexcom) and Guardian Connect (Medtronic), were introduced [24]. Current evidence from Continuous Glucose Monitoring versus Conventional Therapy for Glycemic Control in Adults With Type 1 Diabetes Treated With Multiple Daily Insulin Injections (GOLD) and Effect of Continuous Glucose Monitorng on Glycemic Control in Adults With Type 1 Diabetes Using Insulin Injections (DIAMOND) studies showed the improvement of blood glucose control with the use of CGM in patients with T1D using MDI[182,183]. A follow-up study from DIAMOND subgroup participants who are on CGM with MDI when transitioned to CGM with CSII showed improvement of time in range and less time in hyperglycemia on CGM. However, more time was spent in hypoglycemia and there was no change in HbA1c[184].

The use of CGM has significantly increased in western countries especially in patients with T1D.

The use of CGM has significantly increased in western countries especially in patients with T1D[185]. Despite the increase in CGM use, patients still do not achieve HbA1c targets[186]. Since 2010, CGM use in T1D Exchange registry increased from 7 to 28%[187]. FDA created a new category of Class II integrated CGM (iCGM) devices for 510(k) approval. This new system has higher standards for 510(k) approval and aims to bypass prolonged pre- market approval (PMA) submission. Only CGM fits in this category currently is Dexcom Gen 6 (Dexcom). Dexcom Gen 6 CGM does not require any calibration (factory calibrated, approved for nonadjunctive use), eliminated acetaminophen interference. A Randomized Trial Comparing Continuous Glucose Monitoring With and Without Routine Blood Glucose Monitoring in Adults With Well Controlled Type 1 Diabetes (The REPLACE-BG) study, which was designed to determine CGM use without SMBG confirmation is as well tolerated as CGM use with SMBG in well-controlled T1D[188]. Time in range (70–180mg/dl) on CGM was similar in both groups and no severe hypoglycemia was observed in CGM use without SMBG confirmation group. This study and the approval of iCGM (Dexcom G6) opened a new era of 'nonadjunctive' use of CGM for treatment decisions. Nonadjunctive CGM systems may eliminate calibration errors, decrease healthcare costs in long run, and increase the quality of life[189]. Verily (Alphabet, Mountain View, California, USA) and Dexcom (Dexcom) are developing miniaturized patch wearable CGM.

Medtronic Guardian Connect CGM (Medtronic), was also recently approved that requires two calibrations per day. It uses Guardian 3 sensor, which is the sensor used in Minimed 670G hybrid closed loop. It has the option of predictive alerts for high and low glucose to smartphones and watches[190]. It has Sugar. IQ technology developed by IBM Watson (IBM, Armonk, New York, USA) to help patients. Artificial intelligence technology guides the patients for daily diabetes care and helps them understand the relationship with high and low blood sugars with exercise, food, and recent insulin dose. Artificial intelligence is a new model in diabetes care, uses complex management strategies and likely in the future clinical guidelines will be shaped by these analytics rather than known statistical calculation[191]. DreaMed Advisor Pro (DreaMed Diabetes, Israel) is another cloud-based program that uses artificial intelligence to make insulin dose recommendations and it was recently approved by the FDA[192].

Many software programs are also available to download pumps, meters, and CGM data. Commonly used ones are Medtronic Carelink (Medtronic), Dexcom Clarity (Dexcom), Abbott CoPilot (Abbott, Alameda, California, USA), LifeScan One- Touch (LifeScan, Milpitas, California, USA). These platforms connect patients to healthcare providers and enable faster insulin dosing adjustments. How- ever, no uniformity among these platforms limits their direct comparison and effectiveness. There are platforms to standardize the reporting of CGM data, such as ambulatory glucose profile, Glooko-Diasend (Glooko, Mountain View, California, USA) and Tidepool (Tidepool, Palo Alto, California, USA) but not all software programs are compatible with them[193].

Telemedicine, a healthcare delivery system via video conference can be utilized to reach patients who require close monitoring or live far from the diabetes care providers. Telemedicine may increase patient compliance, decrease missed school- or work-days, and in long-term may decrease health- care-related costs[194].

Flash glucose monitoring

The term, flash glucose monitoring (FGM) is referred for CGM systems that can only be used on demand[195]. Patients use a reader device to scan the sensor to see the glucose level. The only FGM is available in the United States is Freestyle Libre (Abbott, Alameda, California, USA). Last year, a 10-day FGM was approved with a 12-h warm-up period. A 14-day FGM was recently introduced in the US with a 1-h warm-up period. Both versions do not require any calibration, both have a similar low mean absolute relative difference (MARD)[196]. Comparing the other available CGM systems, its main advantage is the cost[197]. The disadvantage is that there are no alarms/notifications for either low or high glucose values (the version with alarm feature recently approved in European

Union but not in the United States at the time of this manuscript preparation). The recently approved 14-day version has also the capability of pairing with a smartphone (at the time of this manuscript preparation only can be paired with an iPhone 7 and above) and eliminates the necessity of reader device since a smartphone can be used as a reader.

Implantable continuous glucose monitoring

The first implantable CGM was developed by Dexcom (Dexcom). It was evaluated in 15 patients in a pilot study with promising results but eventually, it was discontinued because of its size and local sub- cutaneous reactions[198]. Its size and local sub- cutaneous reactions [45]. Currently, Eversense (Senseonics, Germantown, Maryland, USA) is the only FDA approved for 90 days implantable CGM in the United States (In European Union it is 180 days). It has a small sensor that is inserted underneath the skin in an outpatient setting. An external rechargeable and removable transmitter are applied to the sensor daily to capture the data and transmit to smartphones[199]. It requires two calibrations per day and has optional alarms for high and low glucose. In Accuracy and Longevity of an Implantable Continuous Glucose Sensor Study (PRECISE) trial in Europe, the median sensor lifetime was 149 days and MARD was 11.1%[200]. In A Prospective Multicenter Evaluation of the Accuracy of a Novel Implanted Continuous Glucose Sensor (PRECISE II) trial in the United States, sensor lifetime probability for 90 days was 91% and MARD was 8.8%[201]. Eclipse (Glysens, San Diego, California, USA) is another implantable CGM under development. It is expected to be fully integrated without any external component and has a lifespan up to 2 years[202].

Insulin pumps and sensor-augmented insulin pumps

Threshold suspend and suspend before low insulin pump systems reduced hypoglycemia without increasing HbA1c[203]. The systems were Minimed 530 G and 630 G in the United States and in Europe 640 G (Medtronic). It is also used in Minimed 670 G in manual mode. Recently approved Tandem t: slim X2 pump with Basal-IQ integrated with a Dexcom iCGM and a predictive low-glucose suspend algorithm (PLGS) showed in Predictive Low-Glucose Suspend Reduces Hypoglycemia in Adults, Adolescents, and Children With Type 1 Diabetes in an At-Home Randomized Crossover Study (PROLOG) trial decreased hypoglycemia with- out any rebound hyperglycemia [51]. Omnipod (Insulet, Billerica, Massachusetts, USA) recently launched DASH system that has Bluetooth technology, a new user-friendly controller, direct connectivity to Contour Next One (Ascensia, Parsippany, New Jersey, USA) glucometer, and Calorie King app (Calorie King, La Mesa, California, USA). It is not integrated with a CGM; however, Dexcom CGM data can be monitored side by side on a smartphone.

Hybrid closed loop systems

The first hybrid closed-loop system (also called artificial pancreas), was FDA-approved in September of 2016 in the United States (Minimed 670G, Medtronic). This system uses a target glucose level of 120 mg/dl, requires calibrations, adjust insulin based on CGM data and total daily dose. Adjustments of insulin carb ratio and active insulin time are recommended for better outcomes at the beginning of the therapy[204]. Patients input of carbohydrate intake (hybrid part of the Closed-Loop) is necessary to receive the bolus insulin dose before/around meals. This system was shown to reduce HbA1c and hypo- glycemia in pivotal trials[205]. A recent study that tested the safety and performance of Omnipod (Insulet) personalized model predictive control algorithm showed that system was well tolerated in response to overestimated, missed, and extended meal boluses in adults with T1D[206]. Use of do-it-yourself artificial pancreas systems, such as Open APS and Loop that use an old hacked insulin pump with a CGM has been also increasing. There are no clinical trials assessing the efficacy and safety of these products, however, only survey-based small studies showed improvement of the quality of life[207].

Future of insulin pumps and hybrid-closed loop

New generation hybrid-closed loop systems aim to improve blood glucose control with minimizing hypoglycemia and decreasing postprandial excursions. An accurate CGM, more rapid-acting insulin, and a more robust algorithm are the essentials of a closed-loop insulin delivery system, where patient input of carbohydrate may not be needed. The accuracy of CGMs has greatly improved in recent years. Unfortunately, despite all advances in insulin analogs in the recent years, currently available rapid insulin analogs are not fast enough to react for rapid post-meal rise in blood glucose. Algorithms that are in development for future hybrid closed-loop systems should consider meal and exercise adjustments to better mimic pancreas physiology. A true artificial pancreas system may have glucagon and insulin delivery to mimic normal physiology[208]. However, no stable glucagon is approved to be used in artificial pancreas systems. Zealand pharmaceutical (Denmark) is working on a stable glucagon that can be used in the pumps. Another hormone that is co-secreted from the beta cell is amylin. Some investigators are pursuing the use of pramlintide (an amylin analog) to be used in the artificial pancreas systems to reduce post-meal glucose excursions[209]. Clinical use of pramlintide is limited because of gastrointestinal side effects[210].

Algorithms that are in development for future hybrid closed-loop systems should consider meal and exercise adjustments to better mimic pancreas physiology.

Future of multiple daily injections

Smart insulin pens with decision support systems will automatically log insulin data to a smartphone app. The app also has a bolus insulin calculator and a basal insulin titration feature, that will make insulin dose recommendations based on CGM data, food intake, insulin dose history, and exercise. The first generation of this system is FDA-approved InPen (Companion Medical). InPen can be used with rapid insulin analogs (Humalog and Novolog only), can be paired with Dexcom CGM and some glucometers via smartphone health app using Bluetooth technology[211]. It also has a bolus calculator and real-time insulin on board tracking[212]. Timesulin (Patients Pending, London, UK), Clipsulin (Diabnext, Cambridge, Massachusetts, USA), Gocap (Common Sensing, Cambridge, Massachusetts, USA) are other alternatives that use small 'add-ons' to currently available insulin pens for insulin dose tracking and sharing of data without insulin dose calculators.

CONCLUSION

Diabetes is a disease that was identified thousands of years ago. How ironic it is that we are currently experiencing a global epidemic of disease. The increased prevalence is associated with enhanced urbanization and increased body weight. Fortunately, through the second half of the last century, a number of effective anti-diabetes drugs emerged, and recombinant DNA technology emerged to provide human insulin in virtually unlimited quantity. In concert with advances in glucose monitoring and the full appreciation of hyperglycemic danger, these drugs have been used to provide much improved glycemic control and patient outcomes. Nonetheless, there is much that still needs to be addressed. Insulin remains a drug of exceedingly narrow therapeutic index and the prospect of life-threatening hypo- glycemia remains the largest impediment to normalizing plasma glucose. The epidemic of obesity represents a huge challenge, as currently registered anti-obesity drugs are only fractionally effective in normalizing body weight. Bariatric surgeries have emerged to address the most advanced forms of obesity, and they are very effective in providing sizable decreases in weight and eliminating diabetes in a sizable percent of patients. However, what is needed is a less invasive approach to manage obesity and preferably one that can be used in adolescents and young adults where T2D has now made its appearance.

There is reason for optimization. Our knowledge of the molecular basis of T2D and obesity has never been greater. The emergence of multiple new antidiabetic medicines demonstrates what can be accomplished when translational research is focused on a specific disease. The first-generation anti-obesity drugs have established a foundation from which more effective therapies, and combinations with these first-generation drugs, can be developed to provide more meaningful reductions in body

The simultaneous advances in biotechnology, material sciences, synthetic chemistry, and information technology are integrating to provide novel approaches to insulin-dependent diabetes that were impossible as recent as a decade ago.

weight with the ultimate goal eliminating the current performance difference relative to gut surgery. Separately, insulin therapy is destined to improve with the renewed emphasis to discover a more glucose-sensitive approach to therapy. The simultaneous advances in biotechnology, material sciences, synthetic chemistry, and information technology are integrating to provide novel approaches to insulin-dependent diabetes that were impossible as recent as a decade ago. While it is impossible to predict the future with certainty, especially against such lofty goals as outlined in this chapter, the discovery of next-generation medicines with greater transformative impact are certainly plausible. While it is not uncommon for technology to fail in delivering near-term solutions to large medical challenges, when it is viewed over a longer period, it is likely to exceed expectations. If we can maintain the level of interest in addressing diabetes and obesity across academic, biotechnology, and large pharmaceutical companies, then we remain optimistic for the future.

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THERAPEUTIC DIGESTS

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