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Emerging frontiers in type 1 diabetes: exploring novel therapies and their potential to transform care

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Thesis

**EMERGING FRONTIERS IN TYPE 1 DIABETES: EXPLORING NOVEL
THERAPIES AND THEIR POTENTIAL TO TRANSFORM CARE**

by

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B.S., Baylor University, 2020

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DEDICATION

I would like to dedicate this work to my amazing parents who continue to support me and cheer me on through everything.

ACKNOWLEDGMENTS

I would like to thank those who have guided me in writing this thesis. Primarily, I would like to thank my advisor, Dr. Herscovitz, who has continuously guided me in the right direction and answered any questions I had. Secondly, I would like to thank Dr. Foley who has provided me with endless support and encouragement as well as inspiring me to enjoy the pursuit of knowledge. I would also like to thank the Boston University Alumni Medical Library for assisting me with obtaining access to resources that were vital to the completion of this thesis. Lastly, I would like to acknowledge the Master of Medical Sciences program at Boston University for encouraging me to grow into a student I only dreamed I could be.

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ABSTRACT

Incidence of type 1 diabetes mellitus (T1DM) is rapidly increasing and there are no cures for this disease. There is a significant cost burden placed on patients and healthcare systems due to type 1 diabetes mellitus. Most patients diagnosed are not meeting their glycemic targets with insulin administration alone. There is a call for therapies and treatments that replenish β cell mass in turn halting or even reversing disease progression.

Current treatments for T1DM include insulin monotherapy, adjunctive therapies to insulin, such as biguanide, GLP-1 RA, SGLT2 inhibitor, and amylin analog drugs, and transplantation. The adjunctive therapies have been shown to be beneficial for an overweight and obese patient population by reducing BMI, HbA1C, and insulin resistance. However, some of these adjuvant therapies, such as SGLT2 inhibitors and amylin analogs, have been shown to increase the risk of adverse events such as diabetic ketoacidosis, nausea, and vomiting. Whole-organ and islet transplantation both require donor tissue and lifelong immunosuppressive drug administration. There is a significant shortage of donor tissue and lifelong immunosuppression can lead to increased risk of

infection. Even with the benefits of transplantation, such as achieving insulin independence, most patients revert back to insulin monotherapy after five years.

Emerging research has led to new avenues of treatment such as stem cell-derived islet transplantation, fully closed-loop insulin delivery systems, pancreatic organoid models, and immunotherapies like teplizumab. Fully closed-loop insulin delivery systems, also known as artificial pancreas systems, have reduced the burden of carbohydrate counting and bolus administration, as well as increase the time spent in the optimal blood glucose range, improving overall glycemic control, however, these systems are not yet widely available. Pancreatic organoid models have been shown to be useful in modeling T1DM pathophysiology as well as testing the efficacy of drugs such as liraglutide, a GLP-1 RA. Therapies such as stem-cell derived islet transplantation and teplizumab treatment have shown promise in reversing or delaying the onset of T1DM. Teplizumab has also shown that it can increase C-peptide to clinically significant levels (>0.2 pmol/mL) in patients with new-onset T1DM. Although these treatments are not without their side effects, they should be more widely available as standard treatments and prevention for T1DM.

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LIST OF ABBREVIATIONS

AMPK.....	AMP-activated Protein Kinase
BMI.....	Body Mass Index
CDC	Centers for Disease Control and Prevention
CGM	Continuous Glucose Monitoring
CSII.....	Continuous Subcutaneous Insulin Infusion
CTLA4	Cytotoxic T-lymphocyte Associated Protein 4
DAISY	The Diabetes Autoimmunity Study in the Young
DCCT.....	The Diabetes Control and Complications Trial
EDIC	Epidemiology of Diabetes Interventions and Complications Study
FDA.....	Food and Drug Administration
GAD.....	Glutamate Decarboxylase
GLP-1.....	Glucagon-like Peptide 1
GLP-1 RA.....	Glucagon-like Peptide 1 Receptor Agonist
GSIS.....	Glucose-Stimulated Insulin Secretion
HbA1C.....	Glycated Hemoglobin
HLA	Human Leukocyte Antigen
IA2	Islet Tyrosine Phosphatase 2
IL2RA	IL-2 Receptor Subunit Alpha
INS	Insulin
IPT.....	Insulin Pump Therapy
MDI.....	Multiple Daily Injections

MHC	Major Histocompatibility Complex
PTPN22.....	Protein Tyrosine Phosphatase
QOL	Quality of Life
SAP	Sensor Augmented Pump
SGLT2.....	Sodium-Glucose Cotransporter 2
T1DM.....	Type 1 Diabetes Mellitus
T2DM.....	Type 2 Diabetes Mellitus
TDD	Total Daily Dose
TIR	Time in Range
ZnT8.....	Zinc Transporter 8

INTRODUCTION

Epidemiology

Type 1 diabetes mellitus (T1DM) represents a major global health concern with around 2 million patients in the United States and about 8.42 million people worldwide diagnosed with T1DM as of 2021 (CDC, 2024; Gregory et al., 2022). There does not appear to be a difference in prevalence on the basis of gender (Warshauer et al., 2020). Incidence is higher in adolescence and early adulthood, however, T1DM prevalence is greater in adults than in children (DiMeglio et al., 2018; Gregory et al., 2022; Holt et al., 2021). The prevalence of T1DM is projected to increase to between 13.5 and 17.4 million people worldwide by 2040, with the heaviest burden being placed on low-income and lower-middle income countries as a consequence of larger increases in prevalence, 141% and 131% in Sub-Saharan Africa and Middle East and North Africa regions, respectively, and limited access to T1DM care (Figure 1) (Gregory et al., 2022).

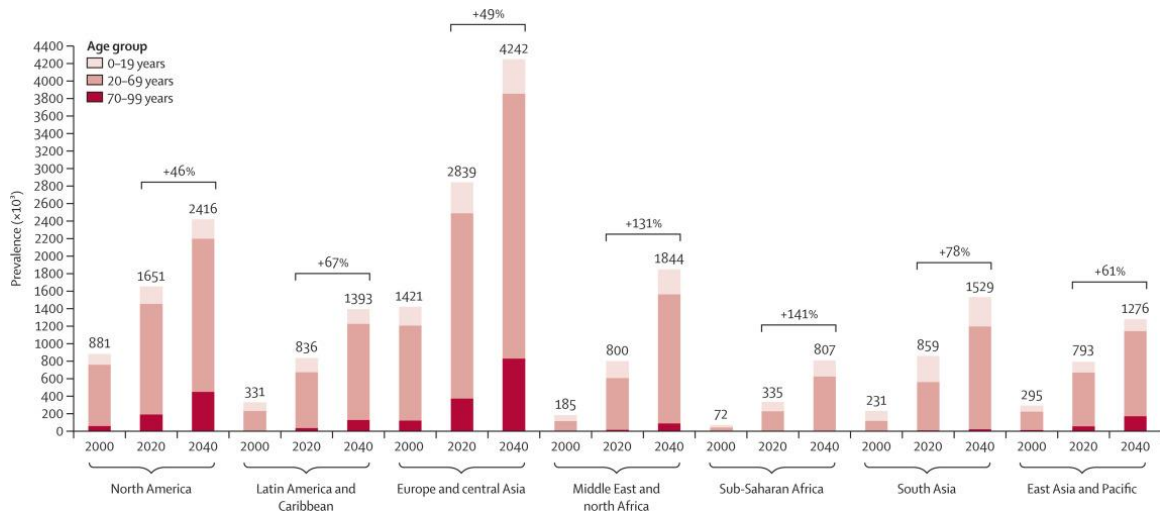


Figure 1. Projected prevalence in 2040. Prevalence of T1DM is projected to continue to increase. This chart shows past, present, and projected future prevalence by region and categorized further by age group (Gregory et al., 2022).

Cost of T1DM

T1DM incurs substantial costs to the individual and to healthcare systems (Gregory et al., 2022; Parker et al., 2023). The aggregate cost of all T1DM and T2DM care in the United States in 2022 amounted to \$412.9 billion, a 35% increase from 2012, with \$306.6 billion associated with direct medical costs and \$106.3 billion associated with indirect costs (Parker et al., 2023). Costs for individuals with T1DM are significantly higher than individuals with T2DM (Tao et al., 2010). In 2010, medical costs for T1DM alone added up to \$14.4 billion (Tao et al., 2010). This substantial difference in cost may be attributable to the rising costs of insulin and diabetes technology. From 2012 to 2016, the cost of insulin increased from \$3,285 to \$6,255, while the cost of associated technology increased from \$1,747 to \$4,581 (Crossen et al., 2020).

The United States is not the only country affected by the high medical costs associated with T1DM. In Europe, diabetes is one of the major determinants of overall healthcare costs (Sharma et al., 2022; Stedman et al., 2020). In 2020, a study in England compared costs between nondiabetic patients, patients with T2DM, and patients with T1DM in 5,468 general practitioner offices. They found the costs per patient were £560, £1,686, and £3,280 respectively, with T1DM patients incurring almost 6 times higher costs than nondiabetic patients (Stedman et al., 2020). In Ireland, the cost of T1DM was €129 million, with an estimated per patient cost of €3,994 in direct costs and €2,326 in indirect costs (Sharma et al., 2022).

Access and Affordability

Variations in access and affordability of care can greatly affect disease outcomes, including early mortality. A study of worldwide prevalence compared estimated life expectancy for a 10-year-old child diagnosed with T1DM and a nondiabetic 10-year-old child in each country found that the global average of difference of life expectancy between nondiabetic and diabetic children was 24 years. This gap rose to 36 years in lower-middle income countries and 45 in low-income countries (Gregory et al., 2022).

Overview of T1DM

T1DM is an autoimmune disease resulting in destruction of β cells in the islets of Langerhans of the pancreas, leading to pancreatic β cell dysfunction, giving rise to a

deficiency of endogenous insulin secretion (Gregory et al., 2022; Holt et al., 2021; Lucier & Mathias, 2025; Warshauer et al., 2020). Common symptoms at onset of disease include the classic triad of excessive urination (polyuria), excessive thirst (polydipsia), and unintentional weight loss, along with excessive hunger (polyphagia) and fatigue (Holt et al., 2021; Insel et al., 2015; Lucier & Mathias, 2025). One third of children present with diabetic ketoacidosis if symptoms are not treated in a timely manner due to a buildup of ketone bodies, the product of excessive β -oxidation of fatty acids (DiMeglio et al., 2018; Holt et al., 2021). Symptoms of diabetic ketoacidosis include hyperglycemia, ketone bodies present in urine, and metabolic acidosis, with severe cases including additional symptoms such as fruity-smelling breath and coma (Holt et al., 2021; Lucier & Mathias, 2025).

A diagnosis of T1DM is made through certain criteria. These measures include fasting plasma glucose of at least 126 mg/dL or 7 mmol/L, random plasma glucose of at least 200 mg/dL or 11.1 mmol/L with symptoms, abnormal results (≥ 200 mg/dL) 2 hours after an oral glucose tolerance test with 75 g of glucose, or glycated hemoglobin (HbA1C) greater than or equal to 6.5% (DiMeglio et al., 2018; Lucier & Mathias, 2025). Over 40% of adults with new-onset T1DM are misdiagnosed with type 2 diabetes mellitus (T2DM) due to variability of symptoms in comparison to children and adolescents (DiMeglio et al., 2018; Holt et al., 2021; Lucier & Mathias, 2025). A key method for differentiating between a diagnosis of T1DM and T2DM is testing for islet cell autoantibodies as presence of these autoantibodies is representative of a T1DM

diagnosis (Holt et al., 2021; Lucier & Mathias, 2025) (Figure 1). C-peptide is a 31-amino acid polypeptide. It links the A and B chains of proinsulin and is secreted from the β cells alongside insulin (Venugopal et al., 2025). C-peptide levels can also be measured after 3 years to assist with making a definitive diagnosis, if C-peptide levels are low, it is indicative of low insulin secretion (Holt et al., 2021; Lucier & Mathias, 2025).

Flow chart for investigation of suspected type 1 diabetes in newly diagnosed adults, based on data from White European populations

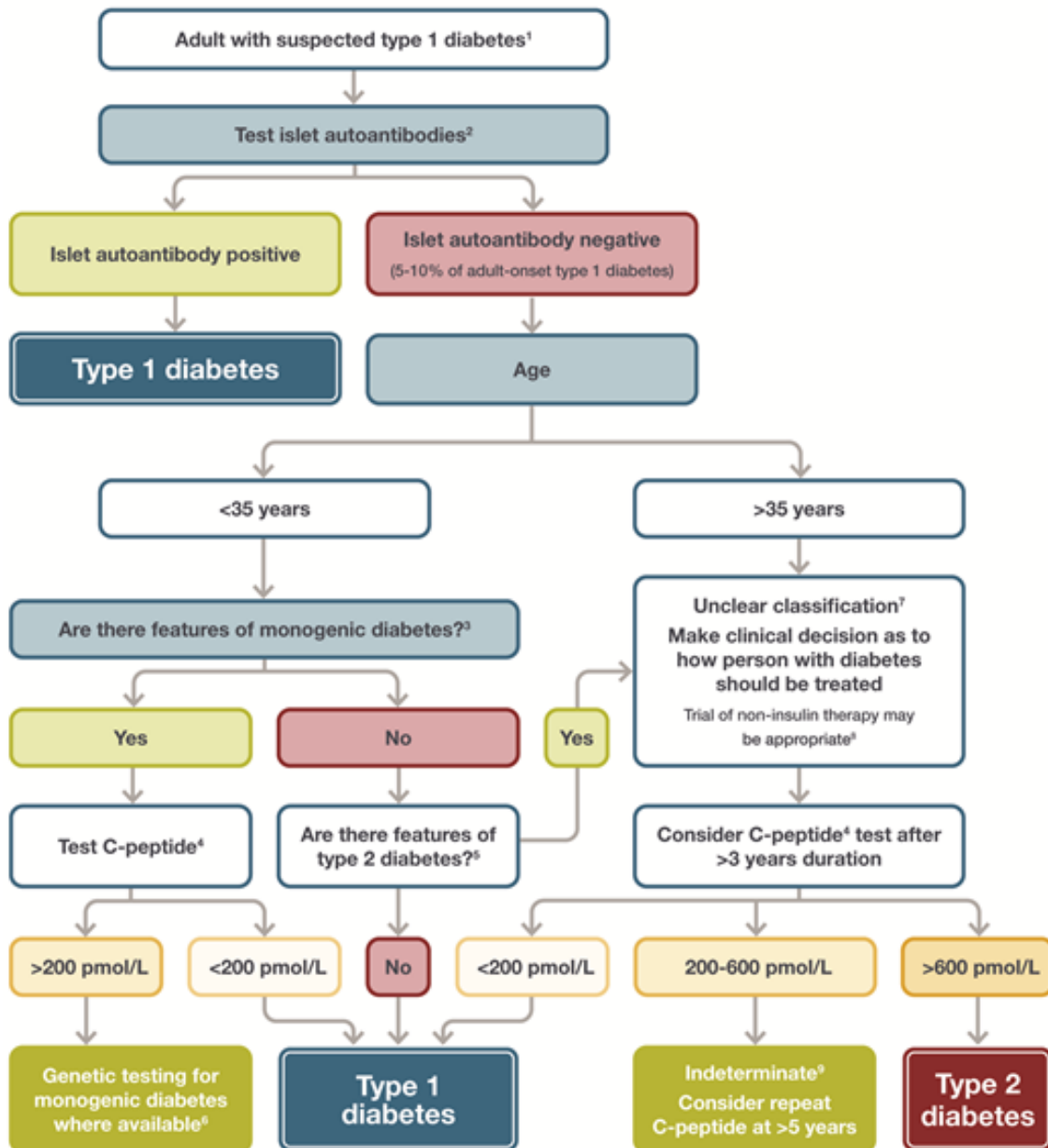


Figure 2. Differentiating between T1DM/T2DM diagnosis in adults. This flowchart outlines the clinical avenues explored in adults who are suspected of having diabetes mellitus. Key differentiating factors include age, presence of islet autoantibodies, and C-peptide (Holt et al., 2021).

T1DM was previously a death sentence before the discovery of insulin in 1921 by Frederick Banting and Charles Best (Banting et al., 1922; Holt et al., 2021; Warshauer et al., 2020). Now, exogenous insulin administration is the primary therapy for patients with T1DM (Gregory et al., 2022; Holt et al., 2021; Lucier & Mathias, 2025; Warshauer et al., 2020). This includes three separate types of insulin administration: basal insulin, prandial insulin, and corrective insulin. Basal insulin blocks the actions of glucagon, such as gluconeogenesis, ketogenesis, and glycogenolysis (Ajmal et al., 2023; Holt et al., 2021). Prandial or mealtime insulin is administered around meals and mitigates the rise in blood glucose levels that occur due to the intake of carbohydrates. Correction insulin also plays a crucial part in diabetes management by treating and preventing hyperglycemic events, when blood glucose levels are greater than the optimal glycemic range due to incorrect insulin doses or higher carbohydrate intake during meals (Holt et al., 2021).

After the discovery of insulin, patients with T1DM were able to live longer, however, due to this longer life expectancy, long-term complications of T1DM are now the primary cause of fatality in diabetic patients (Holt et al., 2021; C. C. Quianzon & Cheikh, 2012; The Diabetes Control and Complications Trial Research Group, 1993). These long-term microvascular and macrovascular complications include retinopathy, nephropathy, neuropathy, cardiovascular disease, diabetic foot infections, peripheral artery disease, stroke, and blindness (Lucier & Mathias, 2025; Szablewski, 2014). A study of 1441 patients completed in 1993, The Diabetes Control and Complications Trial, showed that intensive insulin therapy and proper glycemic control slow the rate of

development of diabetes complications such as retinopathy, neuropathy, and nephropathy. Intensive insulin therapy includes delivery of basal insulin and mealtime insulin either through multiple daily injections or an external insulin administration device. (The Diabetes Control and Complications Trial Research Group, 1993). After follow-up, intensive insulin therapy still had beneficial effects on incidence of concomitant cardiovascular disease 30 years after study end (The Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Study Research Group, 2016). These results led to an increase in utilization of continuous subcutaneous insulin infusion (CSII) therapy since the actions of this therapy more closely resembles physiologic insulin secretion. In 1990, there were less than 7,000 users and this increased to over 350,000 in 2019 (Alnaim et al., 2024; Berget et al., 2019).

Potential Side Effects of Insulin Therapy

Hypoglycemia is an unfavorable outcome of insulin therapy that is characterized by sweating, tachycardia, dizziness, and confusion, occurring when plasma glucose levels decrease to lower than 70 mg/dL or 3.9 mmol/L with more severe symptoms occurring with plasma glucose levels below 54 mg/dL or 3.0 mmol/L (Holt et al., 2021; Lucier & Mathias, 2025; Savard et al., 2016). Severe hypoglycemia is defined as the patient needing assistance from another person (Holt et al., 2021; Karges et al., 2017; Savard et al., 2016). Hypoglycemia is typically treated with oral administration of 15-20 grams of carbohydrates, such as glucose, subsequently retesting blood glucose values, and

repeating these steps until euglycemia is restored (Lucier & Mathias, 2025; Savard et al., 2016). Fear of hypoglycemia is a significant factor in suboptimal glycaemic control in patients. Patients aim to avoid hypoglycemia and by doing so, they end up in a hyperglycaemic state (Holt et al., 2021; Savard et al., 2016). An observational study completed in Canada found that 73% of their participants overtreated their hypoglycemia episodes (Savard et al., 2016). The investigators noted that the average amount of episodes per participant was 2.9 during the 48-hour observation period (Savard et al., 2016). The mean carbohydrate intake for hypoglycemia correction was around 32 grams, which is more than double the recommended intake (Savard et al., 2016).

In order to avoid adverse effects and diabetes complications, glycaemic targets should be met. Typical glycaemic targets include an HbA1C of less than 7% or 53 mmol/L, above 70% of time in the target glucose range of 70 to 180 mg/dL, less than 4% of time spent below 70 mg/dL or 3.9 mmol/L, less than 25% of time spent with blood glucose higher than 180 mg/dL or 10 mmol/L, as well as fasting glucose between 80 and 130 mg/dL or 4.4 to 7.2 mmol/L and a postprandial glucose below 180 mg/dL or 10 mmol/L (Holt et al., 2021) (Table 1). These targets should be personalized to each patient. For example, older individuals may benefit from less stringent targets because of their increased risk of hypoglycemia (Holt et al., 2021; Lucier & Mathias, 2025; McAuley et al., 2021). These glycaemic targets can be effectively reached by insulin administration, carbohydrate counting, which consists of estimating the carbohydrate intake per meal and determining how many units of insulin to administer based meal size,

and monitoring glucose levels (Holt et al., 2021; Lucier & Mathias, 2025). However, even with the new developments in T1DM care and technology, such as continuous glucose monitoring (CGM) devices, which help patients keep track of their glucose values, most patients are not meeting their glycemic targets (Garg et al., 2024; Holt et al., 2021; Lu et al., 2021).

Variable	Target value
HbA _{1c}	<53 mmol/mol (<7.0%)
GMI	<53 mmol/mol (<7.0%)
Preprandial glucose	4.4–7.2 mmol/L (80–130 mg/dL)
1–2 h postprandial glucose ^a	<10.0 mmol/L (<180 mg/dL)
TIR	>70%
TBR	
Readings and time <3.9 mmol/L (<70 mg/dL; level 1 and level 2 hypoglycemia) ^b	<4%
Readings and time <3.0 mmol/L (<54 mg/dL; level 2 hypoglycemia) ^b	<1%
Time above range	
Readings and time >10.0 mmol/L (>180 mg/dL; level 1 and level 2 hyperglycemia) ^c	<25%
Readings and time >13.9 mmol/L (>250 mg/dL; level 2 hyperglycemia) ^c	<5%
Glycemic variability (%CV) ^d	≤36%

Table 1. Recommended glycemic targets. This table outlines the typical glycemic targets for patients with T1DM. Targets should be individualized based on the needs of the patient (Holt et al., 2021).

Etiology

It is unknown what causes an individual to develop T1DM. There is no one single factor that triggers the onset of T1DM, with multifaceted interactions between genetic susceptibility and environmental influences contributing to overall risk of developing symptomatic T1DM (Insel et al., 2015; Lucier & Mathias, 2025; Primavera et al., 2020; Y. Wang et al., 2023; Warshauer et al., 2020).

Between 30-50% of genetic susceptibility to T1DM is accounted for by the human leukocyte antigen (HLA) region located on chromosome 6, particularly HLA class II haplotypes HLA-DR and HLA-DQ. The class II HLA haplotypes DR4/DQ8 and DR3/DQ2 as well as individuals heterozygous for DR3/DR4 confer the highest risk, while the HLA-DQB1*0602, DRB1*1501, and DQB1*0602 haplotypes are protective against T1DM (Eisenbarth, 1986; Insel et al., 2015; Taka et al., 2023; Warshauer et al., 2020). Incidence of T1DM in individuals carrying these haplotypes is around 45 times higher than those with neutral or protective haplotypes (Taka et al., 2023). Ninety percent of children diagnosed with T1DM have the HLA DR4/DQ8 and DR3/DQ2 haplotypes (Lucier & Mathias, 2025). Effects of these high-risk HLA haplotypes are shown in relatives of individuals with T1DM. It has further been shown that relatives have a greater risk of developing T1DM than the general population with risk increasing with the number of shared HLA haplotypes (Eisenbarth, 1986; Insel et al., 2015; Lucier & Mathias, 2025). In monozygotic twins, the risk of the nondiabetic twin developing T1DM is up to 65-70%, however, the concordance rate is less than 100% pointing to additional

factors involved in the progression to symptomatic T1DM (Eisenbarth, 1986; Insel et al., 2015; Primavera et al., 2020). Development of islet autoantibodies is more prevalent in patients with these HLA haplotypes; also, the order of islet autoantibody development is linked to the HLA DQ haplotype (Insel et al., 2015). However, there are many individuals with these high-risk HLA class II haplotypes that do not go on to develop T1DM, so there must be other factors or genes involved in progression to clinical disease (Insel et al., 2015).

Genetic risk can also be conferred by non-HLA genes, including insulin (INS), cytotoxic T-lymphocyte associated protein 4 (CTLA4), IL-2 receptor subunit alpha (IL2RA), and protein tyrosine phosphatase (PTPN22) with some of these non-HLA genes being shown to influence progression of T1DM (Insel et al., 2015; Primavera et al., 2020; Szablewski, 2014). Using this information, genetic risk scores have been created to project the progression of T1DM in high-risk populations (Primavera et al., 2020; Warshauer et al., 2020).

Environmental factors are thought to trigger the onset of T1DM in individuals who are genetically susceptible (Lucier & Mathias, 2025; Warshauer et al., 2020). Environmental factors such as viruses, host microbiome, antibiotics, and diet have been hypothesized to contribute to T1DM disease onset (Blanter et al., 2019; Insel et al., 2015; Primavera et al., 2020; Y. Wang et al., 2023). The importance of viral infections in the

progression of T1DM has been endorsed by various studies (Primavera et al., 2020; Y. Wang et al., 2023).

Enteroviruses, such as Coxsackievirus B, have been relatively well-studied as a trigger for the development of T1DM. One study in 38 children linked the presence of enterovirus RNA in the blood to the development of clinical T1DM in children. Enterovirus RNA was identified more frequently in participants who progressed to clinical T1DM than in those who did not (Oikarinen et al., 2010). Presence of enterovirus RNA was most frequently found in the 6 months prior to the appearance of the first islet autoantibody and was associated with a higher risk of progression to clinical T1DM (Oikarinen et al., 2010). The increased risk seemed to be more pronounced in boys than in girls due to the fact that boys are more susceptible to the complications of enterovirus infection (Oikarinen et al., 2010). Enteroviruses are thought to trigger T1DM progression by inducing cytotoxicity in the β cells of the islets of Langerhans or by triggering β cell autoimmunity. However, the results are still inconclusive in showing a definitive linkage between T1DM and enteroviruses (Oikarinen et al., 2010; Y. Wang et al., 2023).

The COVID-19 pandemic had a profound effect on the world in 2020 (Y. Wang et al., 2023; Weiss et al., 2023). COVID-19 is caused by the SARS-CoV-2 virus that was first discovered in China in December 2019 (Y. Wang et al., 2023). A study of 1,181,096 children conducted in Bavaria, Germany observed an increase in incidence of T1DM in children during the COVID-19 pandemic (Weiss et al., 2023). These results are

consistent with increased incidences of new-onset T1DM in other countries such as England, Romania, and the United States (Y. Wang et al., 2023). This dramatic increase in incidence has led investigators to believe that SARS-CoV-2 has an impact on the development and progression of T1DM. The investigators in Bavaria, Germany found the incidence rate was 28.5 per 100,000 person-years prior to or without a COVID-19 diagnosis and subsequently rose to 55.2 per 100,000 person-years within the same quarter as a COVID-19 diagnosis ($p < 0.001$), with an overall increase in incidence 6 to 15 months following a COVID-19 diagnosis ($p = 0.004$) (Weiss et al., 2023). A study of 181,280 participants conducted by the United States Department of Veterans Affairs supports these results as they also observed that participants infected with COVID-19 were at a higher risk for developing T1DM than those who did not have COVID-19 (Y. Wang et al., 2023). Possible mechanisms by which SARS-CoV-2 could contribute to T1DM pathogenesis have been explored and include the initiation of autoimmunity, inducing β cell damage, or by expediting disease progression (Y. Wang et al., 2023; Weiss et al., 2023). We are just at the beginning of learning about the lasting impacts of COVID-19, therefore, further research is needed to determine if there is a causal effect of the SARS-CoV-2 virus on T1DM. An international registry, the CoviDiab Project, has been created to assess the linkage between COVID-19 and T1DM as well as to help inform future research (Y. Wang et al., 2023).

Another environmental consideration is the hygiene hypothesis. The hygiene hypothesis considers that the introduction of viral and microbial infections early in life

may lower the risk of autoimmune disease development and the active prevention of these infections may deplete the gut microbiome, therefore, removing colonies that would be beneficial in training the immune system (Norris et al., 2020; Xia et al., 2019). It has also been shown that countries with more stringent sanitary practices as well as the increased use of vaccines and antibiotics are correlated with a higher T1DM incidence (Norris et al., 2020; Warshauer et al., 2020; Xia et al., 2019).

Dietary intake of cow's milk products containing bovine serum albumin, such as milk and cheese, has been proposed to lead to increased risk or trigger of islet autoimmunity and development of T1DM. This is thought to be due to the increased intake of these cow's milk products over time in countries such as the United States, China, and Japan, which coincides with increased incidence of T1DM in these countries (Norris et al., 2020). The Diabetes Autoimmunity Study in the Young (DAISY) showed that this effect was only observed in participants that possessed low to moderate risk HLA haplotypes (Primavera et al., 2020). However, the connection between dietary intake and T1DM remains unclear.

Although increasing cases of new-onset T1DM within a single generation points to the contribution of environmental factors, none of these environmental factors have been shown to clearly lead to the progression of T1DM (Insel et al., 2015; Lucier & Mathias, 2025; Warshauer et al., 2020; Xia et al., 2019).

Pathogenesis and Natural History

After the discovery of insulin, the pathogenesis of T1DM was not yet deeply understood. Now, due to the work of George Eisenbarth, our current understanding of T1DM is as an autoimmune disease and a chronic process beginning with genetic susceptibility, followed by the appearance of islet autoimmunity, and finally, complete pancreatic β cell destruction and overt diabetes (Eisenbarth, 1986). An update from Eisenbarth's initial six stages was proposed by Richard Insel in 2015. Insel consolidated these six stages into three stages (Figure 3). Stage 1 is characterized by the presence of two or more islet autoantibodies; however, the patient still remains in a normoglycemic state. Stage 2 also includes the presence of two or more islet antibodies with added dysglycemia due to loss of β cell function, which is defined by a fasting glucose of $\geq 100\text{mg/dL}$ (5.6 mmol/L), impaired glucose of $\geq 140\text{mg/dL}$ (7.8 mmol/L) with 75g of oral glucose, and HbA1C of $\geq 5.7\%$ (39 mmol/mol). During stages 1 and 2, the patient is presymptomatic. Stage 3 marks the onset of clinical symptoms (Insel et al., 2015). The patient presents with the classic manifestations of T1DM, polyuria, polydipsia, unintentional weight loss, and occasionally, diabetic ketoacidosis (Insel et al., 2015). The time frame for each of these stages is variable and progression depends on a variety of factors, such as genetic susceptibility, diet, and number of islet autoantibodies (Primavera et al., 2020). This updated staging has allowed for studies on interventions aiming to prevent progression of T1DM during stages 1 and 2 (DiMeglio et al., 2018; Insel et al., 2015).

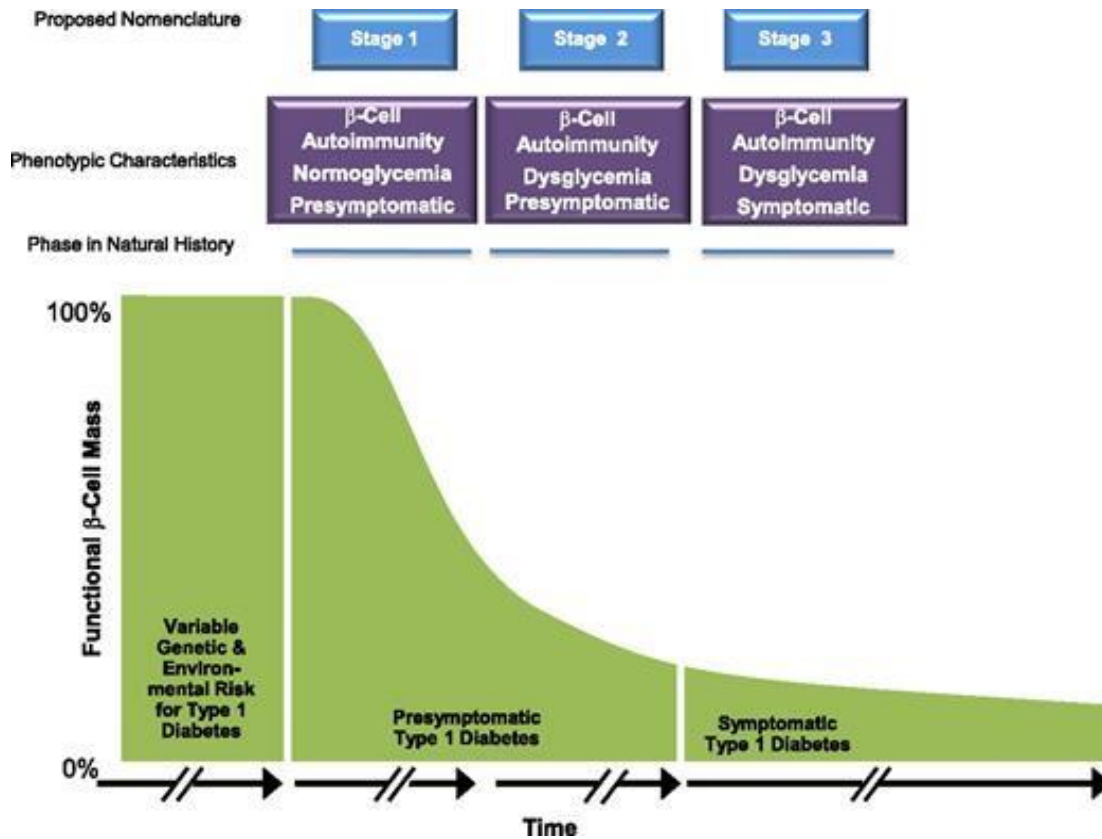


Figure 3. T1DM Staging. This figure shows the 3 stages proposed by Insel and colleagues along with the phenotypes and β cell mass associated with each stage. Functional β cell mass continues to decrease through progression of stages (Insel et al., 2015).

The interactions involved in the pathogenesis of T1DM is not completely understood. It is an elaborate interplay between the islets of Langerhans and innate and adaptive immune systems, and it is assumed to occur in the following sequence of events (Figure 4). Pancreatic β cells display self-antigens on the cell surface to antigen presenting cells via the major histocompatibility complex (MHC) 1 protein (Ajmal et al., 2023; DiMeglio et al., 2018; Szablewski, 2014). These antigen presenting cells then migrate to the pancreatic lymph nodes, where they interact with and activate autoreactive CD4⁺ T-lymphocytes. These newly activated autoreactive CD4⁺ T-lymphocytes then

mediate the activation of CD8⁺ T-lymphocytes (DiMeglio et al., 2018; Szablewski, 2014). These CD8⁺ T-lymphocytes are thought of as the main effectors of β cell destruction (DiMeglio et al., 2018; Insel et al., 2015; Szablewski, 2014). The activated CD8⁺ T-lymphocytes migrate to the pancreas and destroy any β cells displaying the autoantigen. This destruction is amplified by the release of cytokines, such as TNF- α , IL-1 β , IFN- γ , and IL-6, and reactive oxygen species by cells of the innate immune system (DiMeglio et al., 2018; Szablewski, 2014). B-lymphocytes are stimulated by activated T-lymphocytes in the lymph nodes, which then produce autoantibodies against the β cell autoantigen (DiMeglio et al., 2018). Typically, upon presentation of clinical T1DM, patients present with hyperexpression of MHC class I and immune infiltration of islets of Langerhans (Ajmal et al., 2023; Blanter et al., 2019; Szablewski, 2014).

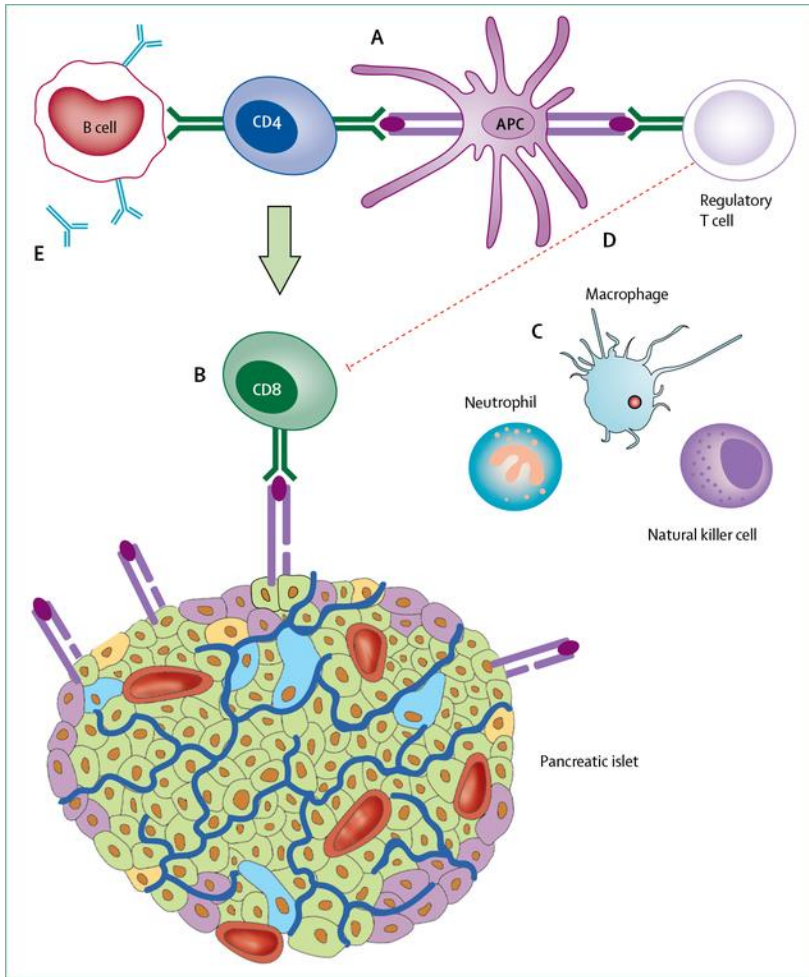


Figure 4. Immune pathogenesis of T1DM. Antigen presenting cells present autoantigen to CD4+ T-lymphocytes. Activated CD4+ T-lymphocytes activate CD8+ T-lymphocytes, which then cause damage to the islets. Cells of the innate immune system release cytokines, exacerbating islet destruction. Activated T lymphocytes stimulated B lymphocytes to produce islet autoantibodies. APC, antigen presenting cell (DiMeglio et al., 2018).

Islet autoantibodies produced by B-lymphocytes serve as biomarkers for T1DM and are important for outlining the progression of T1DM (Eisenbarth, 1986; Primavera et al., 2020). It has been shown that over 90% of new-onset T1DM patients tested positively for at least one autoantibody (DiMeglio et al., 2018; Insel et al., 2015; Warshauer et al., 2020). The autoantigens targeted are insulin (INS), glutamate decarboxylase (GAD), islet

tyrosine phosphatase 2 (IA2), and zinc transporter 8 (ZnT8) (Lucier & Mathias, 2025; Primavera et al., 2020; Szablewski, 2014; Warshauer et al., 2020). The TEDDY study showed a relationship between the number of detectable autoantibodies and the development of symptomatic disease, with the 5-year incidences being 11%, 36%, and 47% for one, two, and three detectable autoantibodies, respectively (Insel et al., 2015; Primavera et al., 2020; Szablewski, 2014; Warshauer et al., 2020). The first islet autoantibodies most frequently appear around 3 years of age and rarely appear before 6 months of age (Norris et al., 2020; Primavera et al., 2020; Szablewski, 2014). It has been demonstrated that the appearance of islet antibodies before the age of 3 and higher titers of islet autoantibodies are associated with an earlier onset of symptomatic T1DM (Insel et al., 2015; Primavera et al., 2020).

This thesis reviews the etiology, epidemiology, and natural history of T1DM as well as comparing the risks and benefits associated with the current T1DM treatments, such as insulin preparations, insulin delivery methods, and adjunctive treatments to insulin. Lastly, I will cover emerging insulin and noninsulin therapies that have shown significantly improved outcomes for patients with T1DM and improved method to study disease progression and drug efficacy and toxicity.

CURRENT STANDARD TREATMENTS AND THERAPIES

Insulin and Insulin Analogs

T1DM treatment was transformed by the discovery of insulin in 1921 by Frederick Banting and Charles Best (Banting et al., 1922). Insulin is a peptide hormone produced by the β cells of the islets of Langerhans of the pancreas. It works reciprocally with the hormone glucagon, produced by the α cells of the islets of Langerhans, to modulate glucose metabolism (Vecchio et al., 2018). The discovery of insulin followed the revelation that T1DM pathophysiology occurs within the pancreas by von Mering and Minkoswki in 1889 who observed that following pancreatectomy, dogs developed diabetes (Banting et al., 1922). Banting and Best isolated insulin by ligating the pancreatic duct, which left only the islets of Langerhans. They observed a marked reduction in blood glucose and glycosuria in diabetic dogs following injection of pancreatic extract from normal dogs (Banting et al., 1922). With continued studies, they were able to show that blood glucose could be reduced to normal levels and glycosuria could be eliminated in diabetic patients (Banting et al., 1922).

Prior to this discovery, the main treatment for T1DM, fasting and starvation diets, resulted in small improvements, but only delayed the inevitable death of the patients (C. C. Quianson & Cheikh, 2012). Over 100 years later, insulin has become an unbeatable standard for treatment for T1DM. There have been many changes and improvements in insulin preparations, delivery systems, and additions of adjunctive therapies.

In 1966, Panayotis G. Katsoyannis and his colleagues were able to fully synthesize insulin using bovine A and B chains (Figure 5) (Katsoyannis et al., 1966). This discovery represented a monumental step in T1DM treatment. Prior to this, most insulin distributed commercially was purified from the animal pancreas. (C. C. Quianzon & Cheikh, 2012). The first human insulin created by recombinant DNA technology was reported in 1978 utilizing A and B chains of insulin in *Escherichia coli* (Goeddel et al., 1979). In the late 1990s to early 2000s, human insulin analogs, lispro, aspart, and glulisine, were approved and released commercially (C. C. Quianzon & Cheikh, 2012; Vecchio et al., 2018). These analogs are a form of insulin with a modified amino acid sequence to improve its pharmacokinetics while still mimicking physiological insulin (C. C. Quianzon & Cheikh, 2012; Vecchio et al., 2018). For example, insulin lispro differs from human insulin by swapping the positions of proline and lysine (Figure 6) (Homko et al., 2003). A study conducted in 2002 compared the effects of the rapid-acting insulin analogs insulin lispro and insulin aspart on postprandial glucose levels. It was found that these insulin analogs were similarly efficacious in controlling postprandial glucose levels and have equivalent pharmacodynamic and pharmacokinetic properties (Plank et al., 2002). Another study conducted in 2003 by Homko and colleagues sought to compare the insulin levels and metabolism in participants with T1DM also using insulin lispro and insulin aspart. After the study was completed, it was observed that both analogs produced similar serum levels of free insulin at the same time points as well as comparable actions on glucose and lipid metabolism (Homko et al., 2003). These analogs are still used today

and are the standard control in many of the studies assessing efficacy and safety of insulin delivery methods (I. B. Hirsch et al., 2024; McGill et al., 2021; Pala et al., 2019).

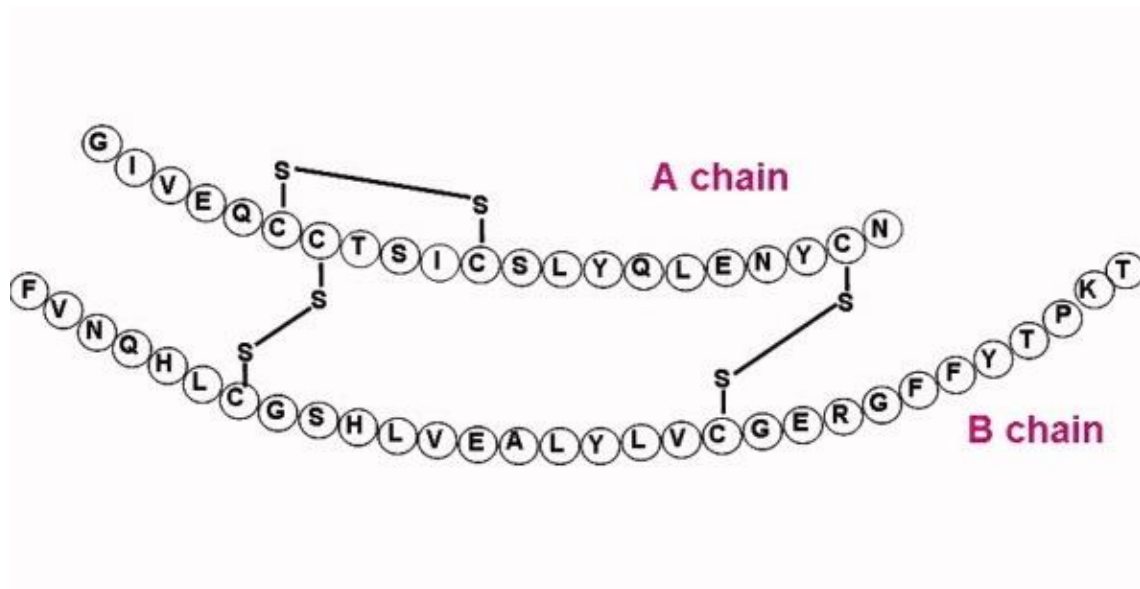


Figure 5. Structure of Human Insulin. Human insulin consists of A and B chains connected by disulfide bonds (Mayer et al., 2007).

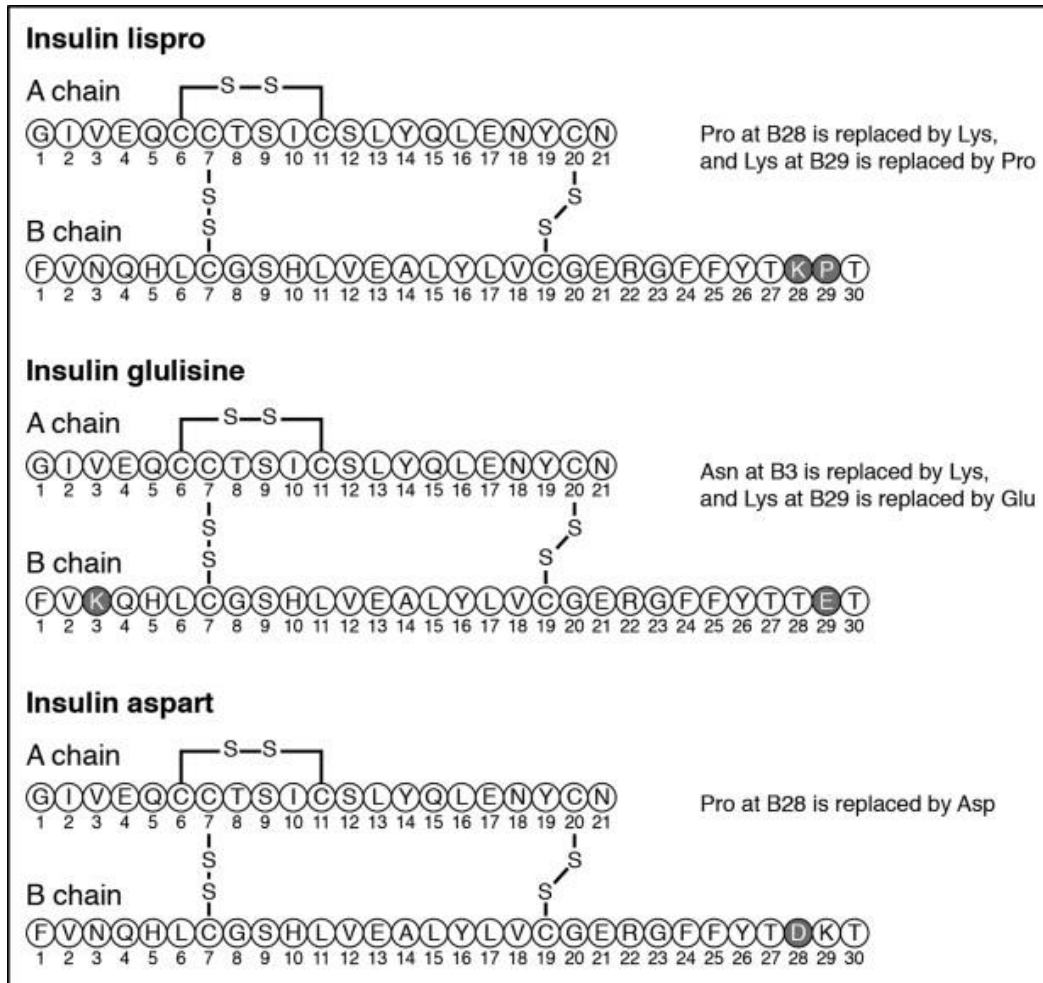


Figure 6. Structure of Insulin Analogs. Insulin lispro and insulin glargine differ from human insulin by replacing two amino acids on the B chain of insulin. In insulin lispro, lysine replaces proline at the 28th place on the B chain and proline replaces lysine in the 29th place on the B chain. In insulin glargine, asparagine is replaced by lysine in the 3rd position and lysine is replaced by glutamic acid in the 29th position. Insulin aspart differs from human insulin by only one amino acid. Aspartic acid replaces proline at the 28th position of the B chain (Tibaldi, 2014).

Insulin Delivery

Injectable

Insulin delivery systems have come a long way since the initial discovery of insulin. The first method of delivery was injectable insulin several times a day. The

earliest syringes were large and difficult to use leading to poor dose accuracy (Kesavadev et al., 2020). This remained the only method of insulin delivery until insulin pumps were developed. The first insulin pump prototype was created in 1963 by Arnold Kadish. The first iteration was a large, cumbersome backpack-like device. Now, they have evolved to come in many different sizes and with varying capabilities (Kesavadev et al., 2020).

Delivered by Pump

Currently, there are two main groups of insulin users. Those who continue using multiple daily injections (MDI) for their daily diabetes management and those who have transitioned to continuous subcutaneous insulin infusion (CSII) also known as insulin pump therapies (IPT). CSII consists of a small device that continuously administers insulin into the subcutaneous tissue, closely mimicking physiological insulin action, through either a tube or a patch placed directly on the skin (Berget et al., 2019). In the scientific community there seems to be a consensus that patients utilizing CSII have better glycemic control than those who remain on MDI (Berget et al., 2019; Howard et al., 2024; Karges et al., 2017; Pala et al., 2019). It has been shown that patients who use CSII for their insulin delivery have reduced HbA1C levels compared with patients using MDI ($p < 0.001$) (Karges et al., 2017). There was also an observed decrease in total daily dose (TDD) of insulin ($p < 0.001$) along with lower rates of severe hypoglycemia ($p < 0.001$) and diabetic ketoacidosis ($p = 0.04$) with CSII (Karges et al., 2017). Similar results were also reported for patients in Saudi Arabia. In this study there was a statistically significant decrease in HbA1C ($p \leq 0.05$) in the CSII group in comparison to

the MDI group, however, this difference was not declared clinically significant, meaning that while there was a significant difference in HbA1C between groups ($p \leq 0.05$), this difference is not large enough to be relevant in a patient's choice of care (Alnaim et al., 2024). However, there have also been studies that deny the advantages of CSII over MDI. One study observed a similarity in the HbA1C of the participants and higher insulin usage ($p = 0.01$), while there was notable increased cost of CSII compared to MDI without a significant treatment advantage and only a modest increase in quality of life (Blair et al., 2018). Another study from Australia factored carbohydrate-counting education and a bolus calculator into their comparison of CSII and MDI. Focusing on time in range (TIR), they discovered that there was not a significant difference in 24-hour TIR and postprandial glycemia between CSII and MDI treatments (Lu et al., 2021). These results mimic the insignificant difference in HbA1C between groups following diabetes education found in the REPOSE trial which also tested the efficacy of structured education (The REPOSE Study Group, 2017).

While these studies provide important insight into the benefits and drawbacks of CSII and MDI therapies, there is no agreement on which is the more effective treatment. Studies comparing these two methods of insulin delivery have varied on important definitions like hypoglycemia, however, most of the studies reliably defined severe hypoglycemia (Pala et al., 2019). There have been continued advancements in the technology of both CSII and MDI which adds to the difficulty in superimposing the results of previous studies onto current technologies and methods. Additionally, many of

the studies comparing CSII and MDI comprise a patient population that has already experienced inadequate glycemic outcomes while on MDI therapy (Pala et al., 2019). Therefore, the control arms of those studies were destined for suboptimal outcomes in comparison to CSII leading to a perceived greater advantage in the CSII therapy (Pala et al., 2019).

An equally as important factor in deciding which treatment is right for a patient is their quality of life (QOL). Patients on MDI have expressed wanting more flexibility in their treatment. Further, MDI could be distressing for patients with a phobia of needles (Berget et al., 2019). However, there are patients who have transitioned to CSII have reverted to MDI. Around 29% of these patients attributed this to wear-related issues such as physical discomfort at device site and feelings of self-consciousness due to having to constantly wear a device, and around 7% of patients cited trouble keeping the devices adhered to their body (Berget et al., 2019; Dekker et al., 2023). There have been advancements in devices that strive to advance the QOL and glycemic outcomes of T1DM patients. One such device is the Omnipod DASH. It is a tubeless insulin pump designed to overcome the physical and psychosocial barriers associated with tubed insulin pumps. Kong and colleagues assessed the level of treatment satisfaction in participants utilizing the Omnipod DASH system in comparison to their usual insulin administrations via insulin pump therapy (IPT) and multiple daily injections (MDI) across 4 diabetes centers in Australia. They observed a notable increase in treatment satisfaction ($p < 0.001$) with the subjects using the Omnipod DASH over the first 12

weeks of treatment that was sustained after the 12-week extension of the trial (Kong et al., 2024). They also noted an improvement in HbA1C of -0.3% in the Omnipod DASH group in comparison to the control group ($p = 0.037$) (Kong et al., 2024). Another study in Canada measured real-world outcomes of use of the Omnipod system. There was an observed decrease in HbA1C in those who used the Omnipod system compared to those who remained on MDI, however, this change only occurred in participants who had a baseline HbA1C of 9% (75 mmol/mol) or higher ($p < 0.001$), showing that this specific patient population may benefit from using this device (Brown et al., 2021).

The invention of CGM devices led to the development of Sensor Augmented Pump (SAP) therapy which utilizes an insulin pump and a CGM device that communicate with one another to display glucose data on the pump itself (Bergenstal et al., 2011; Berget et al., 2019). The STAR3 study showed that SAP therapy resulted in a decrease in HbA1C in comparison to MDI that was sustained after 18 months (Bergenstal et al., 2011; Berget et al., 2019). Development in low glucose suspension and predictive low glucose suspension technology, where insulin delivery is paused in order to prevent a hypoglycemic event, is leading to a new era in insulin therapy (Berget et al., 2019).

Inhaled Insulin

Inhaled insulin is an alternative to subcutaneous insulin that had a rocky entrance into the scientific community. It was created as a needle-free alternative for patients as well as a more rapidly absorbed alternative to insulin analogs (Grant et al., 2022; I. B.

Hirsch et al., 2024; Vecchio et al., 2018). The first of its kind, Exubera, was approved by the Food and Drug Administration (FDA) for the treatment of T1DM in 2006, however, due to suboptimal sales and a lack of acceptance, attributable to the bulkiness of the inhaler, continued tests of pulmonary function, and adverse events, such as coughing, it was removed from the shelves in 2007 (Bailey & Barnett, 2007; C. C. Quianzon & Cheikh, 2012; Vecchio et al., 2018). Despite this, inhaled insulin remains a viable alternative. A new inhalable insulin, Technosphere insulin (Afrezza) was FDA approved in 2014 for use in T1DM patients (Warshauer et al., 2020). Several studies compared the efficacy of Technosphere insulin to rapid-acting insulin analogs. One such study of 29 participants showed that when compared with insulin lispro, Technosphere insulin has a more rapid onset and briefer duration of action, with peak insulin concentration occurring 14-18 minutes and 73-95 minutes after administration for Technosphere insulin and insulin lispro, respectively (Grant et al., 2022). Another study (n = 122) showed that postprandial glucose variations after administration of a standardized meal were decreased ($p = 0.01$) with Technosphere insulin in comparison with a rapid-acting insulin analog. A reduction in peak glucose ($p = 0.01$) and time to peak glucose ($p = 0.006$) were also noted (I. B. Hirsch et al., 2024). Other studies showed it was not any less effective than the rapid-acting insulin analogs, insulin lispro and insulin aspart, in regard to glycemic control and HbA1C (Bode et al., 2015; McGill et al., 2021). However, there were incidences of adverse events during these studies, such as cough that developed in 31.6% of patients using Technosphere insulin compared to only 2.3% in the control that led to 5.7% of participants withdrawing from the study (Bode et al., 2015). Adverse

effects such as notable reductions in forced expiratory volume in 1 second and the onset of coughing with the use of the test drug subsided after discontinuation of use in all participants, which shows that the use of the drug was directly responsible for these effects (Bode et al., 2015; McGill et al., 2021). While this insulin delivery alternative shows promise in regard to its rapid uptake and decreased postprandial hyperglycemia, these adverse effects should be taken into consideration before prescribing to patients.

Noninsulin Therapies as Adjuvant to Insulin

With all of the advances in insulin preparations and insulin delivery technology, most patients with T1DM are still not achieving optimal glycemic outcomes (Garg et al., 2024). While a majority of the scientific focus remains on insulin-based therapies, there is now a shift towards investigating noninsulin therapies as adjuvant therapies to insulin. The drug classes being studied include biguanides, glucagon-like peptide 1 receptor agonists (GLP-1 RA), amylin analogs, and sodium-glucose cotransporter 2 (SGLT2) inhibitors.

Biguanides

Metformin seems to be the most commonly studied and prescribed noninsulin medication and is a part of the biguanide drug class. In 1995, it received approval from the FDA for treatment of T2DM and it remains the only FDA approved drug in the biguanide class as well as serving as the primary treatment for T2DM (C. C. L. Quianzon & Cheikh, 2012). Metformin has not been FDA approved for use in T1DM, however, it is

the most prescribed noninsulin drug for glycemic management in T1DM patients over 25 years of age (Gourgari et al., 2017; Warshauer et al., 2020). The use of metformin in T2DM has been shown to decrease blood glucose by lowering glucose output from the liver and encouraging more glucose uptake peripherally (Libman et al., 2015). In a systematic review of 9 studies, metformin has also demonstrated a reduction of HbA1C and fasting plasma glucose levels (Vella et al., 2010).

There have been increasing amounts of overweight and obese individuals among those diagnosed with T1DM, partially due to the side effects of insulin, leading to insulin resistance, similar to T2DM (Holt et al., 2021; Van der Schueren et al., 2021). This phenomenon has also been referred to as double diabetes (Bielka et al., 2024). It has been hypothesized that metformin could be an effective adjunctive therapy to insulin administration in this population to decrease insulin resistance. In a systematic review of 9 studies by Vella and colleagues, a notable decrease in the required dose of insulin was observed in studies testing the efficacy of adjunctive metformin (Vella et al., 2010). One of the studies measured insulin sensitivity over a 3-month period of metformin and insulin administration in 16 overweight and obese participants aged 18-40. The authors of the study observed an increase in insulin sensitivity ($p = 0.043$) and a corresponding lowering of insulin requirements ($p = 0.047$) and increased QOL ($p < 0.002$) (Moon et al., 2007). However, this study lacked a control group, so the observed benefits of metformin in this study population may be due to increased diligence in their diabetes care or a result of the maintained diet and exercise requested by the trial (Moon et al., 2007). A

study assessing the safety and efficacy of metformin as an adjunctive therapy in adolescents also observed a decrease in total required dose of insulin with some participants having a greater than 25% decrease in their insulin requirement (Libman et al., 2015). Investigators observed a decrease in HbA1C at the 13-week follow-up, however, this effect was not sustained by study completion (Libman et al., 2015).

It has been hypothesized that metformin could also slow the progression of cardiovascular disease in patients with T1DM. The REMOVAL study aimed to assess the progression of cardiovascular disease in 493 participants over 40 years of age for a period of 3 years. The primary objective of this study was to measure the average mean far-wall common carotid artery intima-media thickness, which served as a representative measure for progression of atherosclerosis (Petrie et al., 2017). At study completion, there was no reduction in atherosclerosis progression, indicating that metformin is not effective at protecting against cardiovascular disease ($p = 0.1664$). However, there was an observed decrease in progression of averaged maximal far-wall common carotid artery intima-media thickness, a tertiary outcome, which indicates a slowing of the atherosclerosis progression ($p = 0.0093$) (Petrie et al., 2017). Additionally, the results of the REMOVAL study did not support a reduction in required insulin dose, contradicting earlier studies (Petrie et al., 2017). Overall, the results regarding the effect of metformin on cardiovascular disease progression are inconclusive, warranting further investigation.

Despite the observed benefits of metformin as an adjunct therapy, many adverse gastrointestinal events were recorded (Libman et al., 2015; Petrie et al., 2017). Adverse effects should be disclosed to patients considering adding metformin to their T1DM treatment. These findings show that the use of metformin as an adjunct therapy in T1DM warrants further studies.

GLP-1 Receptor Agonists

GLP-1 RAs or glucagon analogs is a group of drugs used to treat of T2DM. There are many drugs in this class including semaglutide, liraglutide, dulaglutide, exenatide, and others. The first drug in this class was FDA approved for use in T2DM in 2005 (C. C. L. Quianzon & Cheikh, 2012). These drugs are based on the endogenous glucagon-like peptide-1 (GLP-1), a gut peptide hormone secreted by L cells in the small intestine, that is released after a meal in response to nutrients, such as carbohydrates (Warshauer et al., 2020). They mainly act in T2DM via the incretin effect in order to increase insulin secretion, however, this mechanism is almost absent in patients with T1DM due to the loss of β cell function (Pasqua et al., 2025). These drugs also have effects in decreasing glucagon secretion, suppressing appetite, and delaying gastric emptying (Park et al., 2024; C. C. L. Quianzon & Cheikh, 2012; Yesildag et al., 2022). Additionally, unlike endogenous GLP-1, these GLP-1 analogs are less susceptible to breakdown by dipeptidyl peptidase-4, enabling these drugs to have a longer half-life (C. C. L. Quianzon & Cheikh, 2012). These drugs are well characterized and have been shown to be beneficial in patients with T2DM with changes such as increased weight loss, mitigating weight gain

from insulin administration, as well as improvements in HbA1C, glycemic control, and insulin responsiveness (Park et al., 2024; Zenz et al., 2022). Similar to the biguanide class of drugs, GLP-1 RA mediated weight loss can improve insulin sensitivity (Pasqua et al., 2025).

Effects of GLP-1 RAs have been increasingly investigated in patients with T1DM. The ADJUNCT ONE (n = 1398) and ADJUNCT TWO (n = 835) phase III trials measured the safety and performance of the GLP-1 RA liraglutide compared to placebo. Both trials found enhanced management of glucose levels as well as decreased weight and insulin dose requirements ($p < 0.05$), while increasing the risk of hypoglycemia (Dejgaard et al., 2021). Contrarily, another study (n = 14) showed that liraglutide did not encourage hypoglycemia in C-peptide positive T1DM patients using a hyperinsulinemic stepwise hypoglycemic clamp (Zenz et al., 2022). This study also noted better outcomes in weight loss, body mass index (BMI), and HbA1C ($p < 0.001$) (Zenz et al., 2022). A more recent completed study (n = 24) assessed the effect on TIR of another GLP-1 RA, semaglutide, as an adjunct to automated insulin therapy. The investigators noted a significant increase in TIR of 4.8 percentage points ($p = 0.006$) in the semaglutide arm of the study in comparison to placebo without an extending the duration of time spent below the optimal blood glucose range (Pasqua et al., 2025). They also observed decreases in HbA1C, weight, and daily insulin dose ($p < 0.001$) in participants taking semaglutide, which were more pronounced in participants with a higher BMI at baseline (Pasqua et al.,

2025). This trial did not record any diabetic ketoacidosis or severe hypoglycemic events (Pasqua et al., 2025).

Another study sought to observe the real-world effects of the same drug, semaglutide, in a population of 100 T1DM patients 18-80 years of age who are overweight and obese. They measured differences in HbA1C, BMI, weight, insulin dose, and TIR. Participants administered semaglutide during the study period showed a significant decrease in weight and BMI, losing an average of 15.9 pounds from a baseline of 213 ± 37 lbs (96.9 ± 16.8 kg), compared to the control group, which had an overall weight gain from their baseline weight of 208 ± 42 lbs (94.5 ± 19.1 kg) (Garg et al., 2024). They also experienced greater decrease in their HbA1C values compared to control at 3 months ($p = 0.0054$) and 6 months ($p = 0.0219$) after initiation of semaglutide. However, this effect was not sustained at the 9-month ($p = 0.2064$) and 12-month ($p = 0.1820$) measurements (Garg et al., 2024). There was no variation in insulin requirements between the two groups nor any reports of serious adverse events such as severe hypoglycemia or diabetic ketoacidosis (Garg et al., 2024). A meta-analysis evaluating an overweight and obese T1DM population observed more considerable effects with the GLP-1 RA liraglutide over other GLP-1 RAs exenatide and albiglutide after reviewing 24 studies (Park et al., 2024). It was observed that liraglutide had the most improvements in weight, HbA1C, and TDD of insulin, especially with an increase in dose of liraglutide, however, this increase in dose was also found to increase risk of nausea and ketosis (Park et al., 2024).

Liraglutide has also been shown to preserve and protect β cell function from immune attack in in-vitro islet organoid models. In these models, it was shown that β cell function, insulin content, and glucose-stimulated insulin secretion (GSIS) were all decreased (Yesildag et al., 2022). Using these models, the investigators were able to demonstrate that cells treated with liraglutide exhibited maintenance of GSIS and intracellular insulin content as well as decreased immune cell infiltration and cytokine secretion compared to cells treated with a vehicle control (Figure 7) (Yesildag et al., 2022).

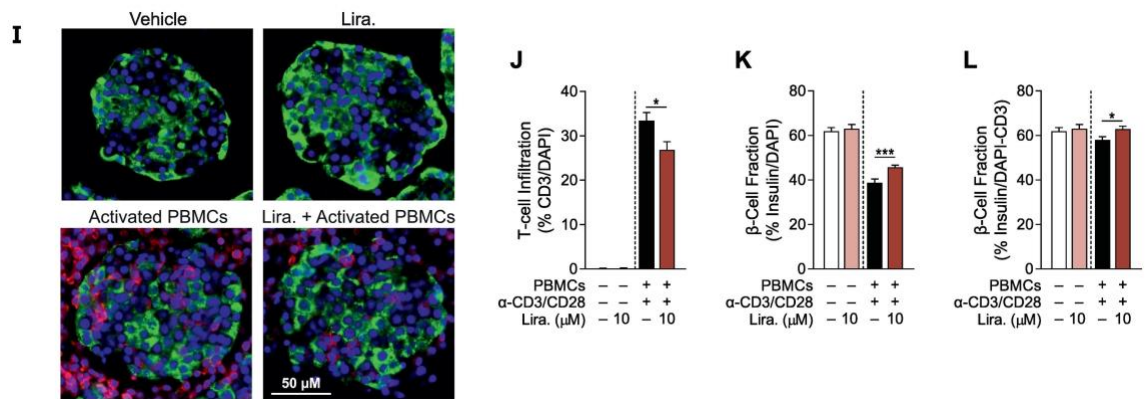


Figure 7. Liraglutide effects in organoid model. I). Islet organoids were fixed with paraffin and incubated with DAPI, anti-insulin, and anti-CD3 antibodies giving the blue, green, and red colors, respectively. J). T cells infiltrating the islet shown as a fraction of the total cell count. K). β -cell fraction shown as the percentage of insulin-positive cells. L). β -cell fraction shown as the percentage of insulin- and CD3-positive cells. Liraglutide is shown in to reduce immune infiltration in pancreatic islets (I & J). This led to a higher fraction of insulin-positive β cells (K & L) in organoids treated with liraglutide. * p <0.05, ** p <0.01, *** p <0.001 (Yesildag et al., 2022).

There are many ongoing clinical trials including one that is currently recruiting subjects that aims to study the GLP-1 RA, dulaglutide, as a therapeutic for microvascular outcomes related to T1DM. This study is estimated to be completed in 2027 (Love, 2024)(NCT05478707). Data regarding the safety and efficacy of the GLP-1 RA drugs is inconclusive, which shows a need for more studies, especially those directly comparing the differences between the various GLP-1 RAs. However, it seems they have all been effective in reducing overall body weight in patients, which could be beneficial for obese and overweight patients (Garg et al., 2024; Park et al., 2024).

SGLT2 inhibitors

The SGLT2 is found in the proximal tubules of the kidney and is the primary mechanism for reabsorbing glucose that has been filtered by the kidney (Warshauer et al., 2020). Drugs inhibiting its action that lead to increased renal excretion of glucose have received FDA approval for treating T2DM (Warshauer et al., 2020). The FDA approved SGLT2 inhibitors include empagliflozin, sotagliflozin, and dapagliflozin, as well as recently approved bexagliflozin (Hoy, 2023; Warshauer et al., 2020). A different class of SGLT2 inhibitors, dapagliflozin and sotagliflozin, are approved in the European Union for treating T1DM in those with a BMI greater than 27 kg/m² (Holt et al., 2021; Warshauer et al., 2020).

Studies have shown that use of SGLT2 inhibitors elicits improvements in glycemic outcomes, however, there is also an elevated risk of diabetic ketoacidosis. One

study compared the long-term outcomes of safety and efficacy after 5 years of utilization of GLP-1 RAs or SGLT2 inhibitors as adjunctive treatments for T1DM (Anson et al., 2023). The investigators noted that patients using SGLT2 inhibitors had higher rates of diabetic ketoacidosis than those using GLP-1 RAs, however, the cause of this increase is unclear (Figure 8) (Anson et al., 2023). Another study analyzing the Japanese subgroup of the DEPICT-2 study observed a higher occurrence of diabetic ketoacidosis in participants administered dapagliflozin (Araki et al., 2021).

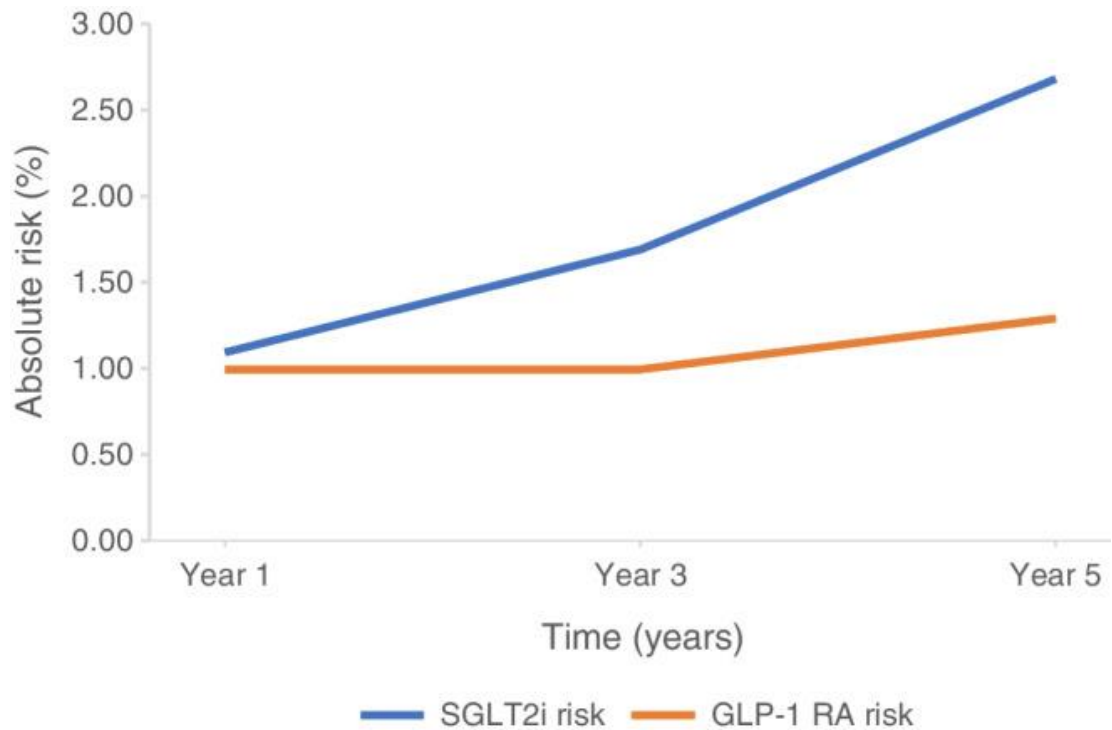


Figure 8. Risk of diabetic ketoacidosis. The risk of diabetic ketoacidosis with the use of SGLT2 inhibitors is significantly higher ($p = 0.0309$) than with GLP-1 RAs. This difference in risk increases over time. SGLT2i: SGLT2 inhibitor (Anson et al., 2023).

The increase in risk of diabetic ketoacidosis is likely preventing SGLT2s from being FDA approved for the treatment of T1DM (Boeder et al., 2024; Holt et al., 2021;

Warshauer et al., 2020). Studies have been conducted exploring methods to lower the likelihood of diabetic ketoacidosis linked to SGLT2 inhibitors. One study noted that the use of lower doses of empagliflozin did not raise ketone levels and participants did not experience episodes of diabetic ketoacidosis during the study (Pasqua et al., 2022). A clinical trial aimed to examine the use of a glucagon receptor antagonist, volagidemab, alongside the SGLT2 inhibitor, dapagliflozin. The investigators observed improvements in TIR, total daily insulin dose, and patient satisfaction in comparison to dapagliflozin treatment alone or control (Boeder et al., 2024). Notably, they observed that the effect of volagidemab may increase the advantages of dapagliflozin while simultaneously reducing the risk of diabetic ketoacidosis linked to SGLT2 inhibitor use (Boeder et al., 2024). These studies show promising results for the use of a combination therapy of SGLT2 inhibitors and glucagon receptor antagonists or lower doses of SGLT2 inhibitors, but more studies are needed to determine long-term safety and efficacy.

Amylin Analogs

The amylin analog, pramlintide, is the only drug that is FDA approved for use for adjunctive treatment of T1DM, however, it is not widely used due to the increasing dose requirements and adverse side effects such as nausea and vomiting (Anson et al., 2023; Holt et al., 2021; C. C. L. Quianzon & Cheikh, 2012; Warshauer et al., 2020).

Pramlintide is not approved by the European Union for the treatment of T1DM (Anson et al., 2023; Holt et al., 2021). Modest decreases in HbA1C, lower daily doses of insulin, and delays in gastric emptying have been observed with the use of pramlintide as an

adjunctive treatment to insulin administration (Garg et al., 2024; Holt et al., 2021; C. C. L. Quianzon & Cheikh, 2012; Warshauer et al., 2020). Co-formulations of pramlintide and insulin have had positive results, such as reduction in postprandial blood glucose levels, and have been relatively well tolerated (Andersen et al., 2021, 2023; Holt et al., 2021).

EMERGING THERAPIES

Artificial Pancreas: A Closed-Loop Insulin Delivery

Recent advances in insulin delivery technologies include the artificial pancreas which is otherwise known as a closed-loop system. Components of these systems include an insulin pump, CGM device, and a program that automatically adjusts insulin delivery based on data received from the CGM device (Berget et al., 2019). Some of these systems included adjuvant therapy (Pasqua et al., 2025). These systems aim to increase TIR and reduce time spent in hyperglycemia and hypoglycemia, thereby improving overall glycemic control (Berget et al., 2019). The first generation of these devices is known as a hybrid closed loop system, the first of which was the Minimed 670G that gained FDA approval in 2016 (Berget et al., 2019). These hybrid closed loop systems regulate basal insulin delivery; however, meal announcements and carbohydrate counting are still a requirement for the patient (Lakshman et al., 2024). Missing meal bolus administration and incorrect calculations in carbohydrate counting play a significant role in poor glycemic control in patients (Boughton et al., 2023; Russell et al., 2022). Unfortunately, these fully closed loop systems are not yet widely available. Many patients have developed their own do-it-yourself fully closed loop systems to bridge the gap in available technology (Berget et al., 2019; Holt et al., 2021). Due to this, many emerging insulin pump technologies have been investigated in an effort to close the loop (Berget et al., 2019; Russell et al., 2022).

In an attempt to alleviate the burden of carbohydrate counting, such as worry of incorrect carbohydrate or meal size estimation, one study (n = 34) assessed the efficacy of simplified meal announcements in comparison with traditional carbohydrate counting in adolescents aged 12-18 years using a hybrid closed loop system, the Minimed 780G. The simplified meal announcements consisted of 3 personalized, preset carbohydrate values for participants to choose from (Petrovski et al., 2023). The results showed that the traditional carbohydrate counting group had a higher TIR with a difference of 6.8% between groups (p = 0.043), which indicated that it was more effective for improving glycemic outcomes than simplified meal announcements (Petrovski et al., 2023). Importantly, a large percentage of the simplified meal announcement group did meet internationally recognized targets for glycemic control, however, the percentage of participants was not as pronounced as in the precise carbohydrate counting control group, still leaving patients with the burden of carbohydrate counting for the best available intensive glycemic control (Petrovski et al., 2023).

The advent of fully closed loop systems removes the patient's need for carbohydrate counting and bolus administration (Lakshman et al., 2024). One study aimed to further understand the influence of a closed loop system on glycemic outcomes by comparing it to CSII with a CGM. In this study, participants were crossed over from one therapy to another and acting as their own control. The investigators observed that the percentage of TIR was 13.2 percentage points (p < 0.001) higher for patients when utilizing the closed loop system compared to CSII with CGM (Boughton et al., 2023).

There was also a substantial decline in HbA1C ($p = 0.002$) (Boughton et al., 2023).

Despite this, during the control period, participants were permitted to use their normal insulin preparations, rapid or ultra-rapid acting, and during the closed loop system period, all participants were using ultra-rapid insulin lispro (Boughton et al., 2023). This could explain some of the perceived benefit of the closed loop system, especially since only 1 of 26 participants used the ultra-rapid insulin lispro as their primary insulin preparation (Boughton et al., 2023).

Another study analyzed the difference between the closed loop system and an SAP system specifically in patients over 60 years old with T1DM through a randomized crossover trial. Elderly patients with T1DM face further obstacles compared to younger patients, such as decreased manual dexterity and mental decline (McAuley et al., 2021). The investigators primarily aimed at identifying the differences in TIR between these arms of the trial. There was an increase in TIR seen with the closed loop therapy arm of the trial, with a mean TIR of 72.5%, that was equivalent to an additional 90 minutes daily in the optimal glycemic range (McAuley et al., 2021). The time spent in the hypoglycemic range and glucose variability were also decreased in the closed loop group, with the effects being more pronounced overnight (McAuley et al., 2021).

Artificial Pancreas

The iLet Bionic Pancreas is the first FDA approved artificial pancreas device (FDA, 2023). The only information the device requires is the patient's body weight

(Russell et al., 2022). It also allows them to announce meals via indicators of meal size such as, “usual for me”, “more”, or “less”, rather than overwhelming carbohydrate counting (Russell et al., 2022). A clinical trial completed in the United States by the Bionic Pancreas Research Group aimed to observe changes in mean HbA1C over 13 weeks between participants utilizing the iLet Bionic Pancreas and those utilizing any insulin delivery paired with a CGM device (Russell et al., 2022). Overall, there was a decrease in mean HbA1C from 7.9% to 7.3% in participants randomized to the iLet Bionic Pancreas device group while there was no change in mean HbA1C was seen in the control group (Russell et al., 2022). The investigators also reported an increase in TIR in the iLet Bionic Pancreas group that was equivalent to an additional 2.6 hours in range per day (Russell et al., 2022). In this study, 30% of participants in the control group were using hybrid closed-loop systems as their diabetes treatment (Russell et al., 2022). This study provides data showing that fully closed-loop systems have made effective improvements upon the hybrid closed-loop systems that are widely available, leading to improved glycemic control in patients.

The CLEAR study sought to compare differences in QOL between a fully closed loop insulin delivery system and insulin pump therapy in conjunction with a CGM device through interviews and validated questionnaires. Participants reported a reduction in treatment burden and anxiety around mealtime, as well as improved sleep and feelings of freedom (Lakshman et al., 2024). Some patients even reported feeling like they were living as non-diabetic. Participants did note feelings of apprehension after initiation of the

new device describing trouble with relinquishing control of their diabetes treatment to the device, however, these concerns subsided within a few weeks with patients reporting that the system was effectively learning their body (Lakshman et al., 2024). Another study assessed the QOL of children and adolescents utilizing the iLet Bionic Pancreas for their disease management and perspectives of their parents. In focus groups, participants expressed an overall positive experience with the device (Howard et al., 2024). Like the CLEAR study, the investigators observed decreased disease burden and increased feelings of freedom and flexibility as well as some participants reporting challenges in releasing control of their diabetes management (Howard et al., 2024). Specifically, participants and their parents noted improvements in their relationships including a decrease in conversations centering around T1DM (Howard et al., 2024). Most parents expressed increased feelings of ease when their children were at school or away from them (Howard et al., 2024). However, there were some negative experiences related to increased glucose variability as well as concerns with the small size of the insulin cartridges (Howard et al., 2024).

The advent of fully closed-loop insulin delivery systems has shown substantial enhancements in QOL and glycemic outcomes, nevertheless, there are still improvements and adjustments to be made. Additional investigation is needed to further develop these systems in preparation for worldwide commercial use.

Stem Cell-Derived Islet Transplantation

Currently, the only methods for replacing β cells in patients with T1DM are whole-organ pancreas transplantation and pancreatic islet transplantation (Holt et al., 2021; Warshauer et al., 2020). However, there are significant issues associated with these therapies, including a shortage of donor tissue and lifelong immunosuppressive regimens, preventing rejection or destruction of transplanted tissue (DiMeglio et al., 2018; Holt et al., 2021; Warshauer et al., 2020).

Whole-pancreas transplants have been a standard since the 1960s (DiMeglio et al., 2018; Hoglebe et al., 2023). They are recommended to be completed in conjunction with a kidney transplantation in T1DM patients with end-stage renal disease, with a transplanted tissue survival rate of 83% 5 years after transplantation (DiMeglio et al., 2018; Holt et al., 2021; Warshauer et al., 2020). The combination of pancreas and kidney transplantation has been shown to be more effective than pancreas transplantation alone or pancreas transplantation following kidney transplantation (Holt et al., 2021).

In the 2000s, the Edmonton protocol was developed, which exhibited that pancreatic islet infusion through the portal vein improved insulin secretion and glycemic control (Ajmal et al., 2024; DiMeglio et al., 2018; Hoglebe et al., 2023). Islet transplantation is a low risk, minimally invasive transplantation option and is recommended for patients with recurrent episodes of severe hypoglycemia and uncontrolled glycemic variability as well as patients who are deemed ineligible for

whole-pancreas transplantation, such as elderly patients and patients with coronary heart disease (DiMeglio et al., 2018; Holt et al., 2021). The first allogenic islet-cell therapy, Lantidra (Donisecel) was approved in June of 2023 by the FDA (Ajmal et al., 2024). In 50% of patients, insulin independence is maintained for 5 years after transplantation, however, exogenous insulin administration is ultimately reinstated (Hogrebe et al., 2023; Holt et al., 2021; Keymeulen et al., 2024). Patients who do not achieve insulin independence post-transplantation report reduction of severe hypoglycemic events as well as improvements in glycemic variability (Holt et al., 2021). Conventionally, islet transplantation is done through donor islet infusion into the hepatic portal vein, however, this can lead to loss of graft tissue through instant blood-mediated inflammatory response (Ghoneim et al., 2024; Hogrebe et al., 2023; S. Wang et al., 2024).

Pluripotent Stem Cells

Pluripotent stem cells serve as a potential remedy for the scarcity of donor tissue (Ghoneim et al., 2024; Hogrebe et al., 2023; Holt et al., 2021; S. Wang et al., 2024). They are an unlimited cell source due to their capability to self-replicate and differentiate into different cell types (Ghoneim et al., 2024; S. Wang et al., 2024). Various differentiation protocols have been developed to create pancreatic progenitor cells or fully differentiated pancreatic β cells from allogenic stem cells and patient-derived stem cells (Ghoneim et al., 2024; Holt et al., 2021).

A clinical trial completed in China was the first in-human clinical trial that demonstrated the possibility of transplanting autologous stem cell-derived islets in a patient with T1DM (S. Wang et al., 2024). Prior to trial initiation, in 2017, the patient underwent whole-pancreas transplantation to reduce glycemic variability that could not be controlled with intensive insulin therapy. The transplanted pancreas was subsequently removed in 2018 due to severe thrombotic complications. In prior years, the patient also received two liver transplantations and maintained immunosuppression therapy during the trial (S. Wang et al., 2024). The chemically induced pluripotent stem cells were derived from the patient adipose tissue cells, then differentiated into islet-like cells. These stem cell-derived islets were then transplanted under the anterior rectus sheath and the patient was observed for 12 months. 75 days after transplantation, the patient achieved insulin independence (Figure 9) (S. Wang et al., 2024). The investigators observed that improvements such as insulin independence, an increase in TIR from 43.18% to above 98%, an HbA1C decrease to about 5%, and elimination of severe hypoglycemia events were sustained one year after transplantation. This trial is ongoing to determine the long-term safety and efficacy and has included two other participants (S. Wang et al., 2024).

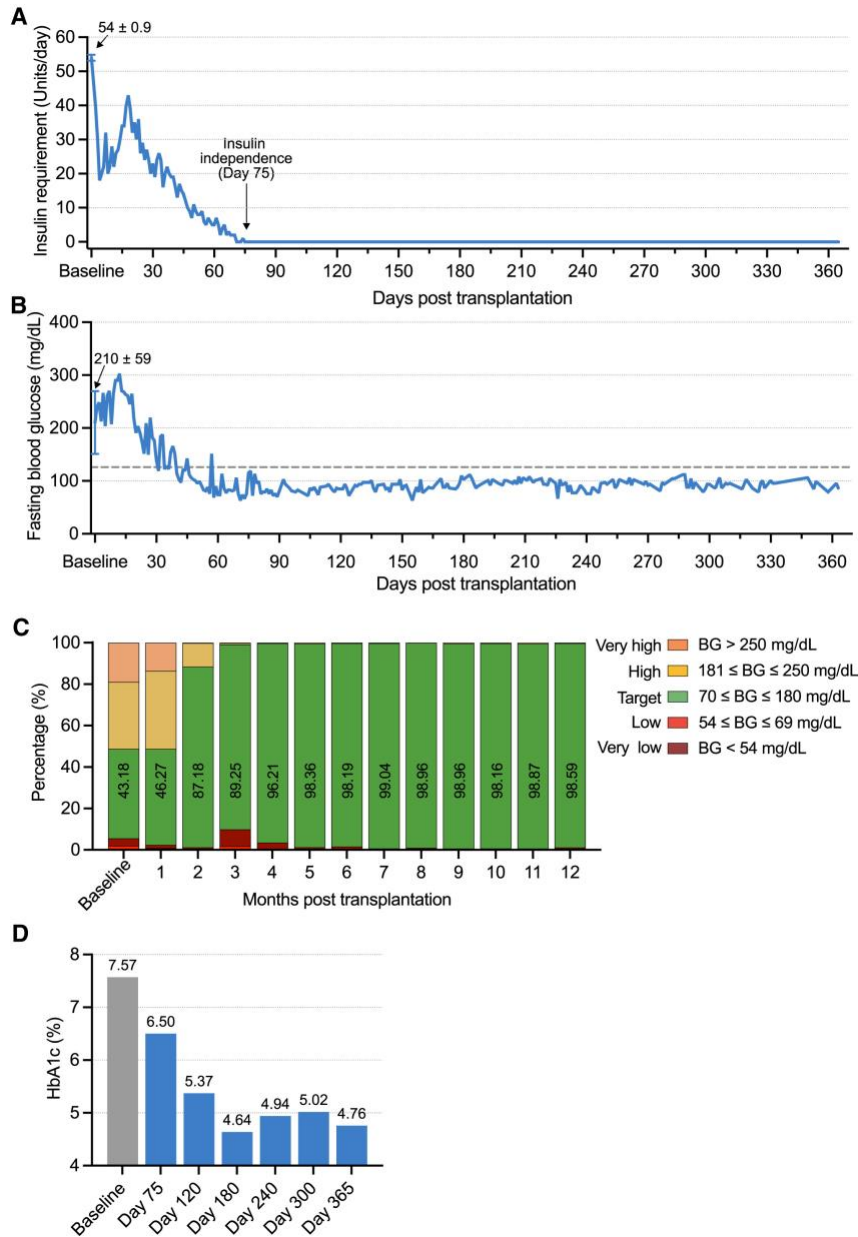


Figure 9. Glycemic outcomes post-transplantation. A) Insulin requirement at baseline up to 365 days after transplantation. B) Fasting blood glucose at baseline to 1-year post-transplantation. The patient was able to achieve levels below the American Diabetes Association (ADA) recommended level of 126 mg/dL. C) TIR before and after transplantation. Twelve months after transplantation, patient achieved and maintained TIR >98%. D) Patient HbA1c levels before and after transplantation (S. Wang et al., 2024).

Vertex Pharmaceuticals has developed fully differentiated stem cell-derived insulin-producing cells (VX-880). A phase I/II/III clinical trial is underway and preliminary results for two patients administered half of the recommended dose have been positive (Ghoneim et al., 2024; Hoglebe et al., 2023; Keymeulen et al., 2024). Improved glycemic control and insulin production were reported in both patients and one patient progressed to insulin independence post-transplantation with an HbA1C of 5.2% (Ghoneim et al., 2024; Keymeulen et al., 2024) The company is currently recruiting for phase III of this clinical trial assessing the effectiveness and safety of VX-880 in adults with T1DM who also experience severe hypoglycemia (Vertex Pharmaceuticals Incorporated, 2025a) (NCT04786262). A separate phase II clinical trial by Vertex Pharmaceuticals will begin recruiting in 2025 aiming to assess efficacy and safety of VX-880 in T1DM patients who have previously undergone a kidney transplant procedure (Vertex Pharmaceuticals Incorporated, 2025b) (NCT06832410).

Genome editing of pancreatic islets, whether derived from stem cell populations or donor tissue has been proposed as a resolution to safeguard transplanted cells from immune attack (Ghoneim et al., 2024; Hoglebe et al., 2023; Holt et al., 2021). Carlsson and collaborators, Sana Biotechnology, are currently recruiting patients for a clinical trial testing the safety and efficacy of genetically modified islet of Langerhans (UP421) from an organ donor without additional treatment of immunosuppressive agents (NCT06239636). This study will be the first of its kind completed in human subjects and is scheduled to be completed in 2025 (Carlsson, 2024).

Physical barriers have also been proposed for protecting transplanted cells from immune destruction (Ghoneim et al., 2024; Hoglebe et al., 2023; Holt et al., 2021; Keymeulen et al., 2024). There have been unsuccessful attempts at creating immunoprotective devices. ViaCyte created such a device, the PEC-Encap (VC-01), in which pancreatic progenitor cells were encapsulated in an impermeable membrane, but initial results showed a small amount of viable cells post-transplantation and fibrosis surrounding the capsule, leading to discontinuation of the trial (Ghoneim et al., 2024; Hoglebe et al., 2023). ViaCyte reimaged the device to create the PEC-Direct (VC-02), which contained pores in its membrane (Ghoneim et al., 2024; Hoglebe et al., 2023). This updated device showed improvements in graft viability and vascularization, however, host cells could now enter the device, so the immune protection function of the device was lost, necessitating the use of immunosuppressive drugs in conjunction with transplantation (Ghoneim et al., 2024; Hoglebe et al., 2023). A clinical trial utilizing the PEC-direct device showed that only 3 out of 10 participants reached the primary outcome of C-peptide secretion greater than 0.1 nmol/L (Keymeulen et al., 2024).

Although there have been many improvements, important hurdles still remain. Unfortunately, these stem cell-derived insulin-producing cells are still susceptible to immune attack necessitating the continued use of immunosuppressive agents (Ghoneim et al., 2024; Holt et al., 2021). Risks, such as infection, versus benefits for trading insulin administration for administration of immunosuppressive drugs should be assessed before

considering any method of transplantation. Stem cell-derived insulin secreting cells are also not up to par with the functional standard of insulin secretion in human islets, for example most of these cells lack biphasic insulin secretion, which is characteristic of human β cells (Hogrebe et al., 2023). Biphasic insulin secretion consists of a primary rapid phase and a secondary sustained phase in response to changing blood glucose level and intracellular Ca^{2+} concentration (Henquin et al., 2002). However, many of the currently available therapies do not mimic this aspect of physiological insulin secretion although insulin pump devices have made efforts to (Berget et al., 2019; Hogrebe et al., 2023; Kesavadev et al., 2020).

Pancreatic Organoid Models

Pancreatic organoid models are 3D in-vitro cultures derived from pluripotent stem cells or patient-derived cells that aim to recreate the spatial organization, structure, and function, such as insulin production, of the pancreas (Beydag-Tasöz et al., 2023; Candiello et al., 2018). These models provide a novel method for studying pancreas development, the early stages of T1DM pathophysiology, and drug safety and efficacy for treatment of T1DM (Beydag-Tasöz et al., 2023; Candiello et al., 2018; Jiang et al., 2022).

Yesildag and colleagues created three in-vitro spheroid models demonstrating immune injury to pancreatic islets. Pro-inflammatory cytokines, such as $\text{TNF}\alpha$ and $\text{IL-1}\beta$, stimulated anti-CD3/CD28 peripheral blood mononuclear cells, and HLA-A2-

restricted preproinsulin-specific cytotoxic T lymphocytes were added to culture in order to induce immune-mediated destruction of β cells (Figure 10) (Yesildag et al., 2022). All three models exhibited decreased GSIS and intracellular insulin content, which is representative of declining β cell function, a hallmark of T1DM (Yesildag et al., 2022). Using this model, Yesildag and colleagues evaluated the efficacy of a GLP-1 RA, liraglutide, in T1DM. They found that liraglutide is able to reduce the loss of GSIS seen in T1DM, preserving β cell function under immune stress, as well as decreasing immune cell infiltration (Yesildag et al., 2022). This represents a functional disease model that can be successfully used to test drug efficacy.

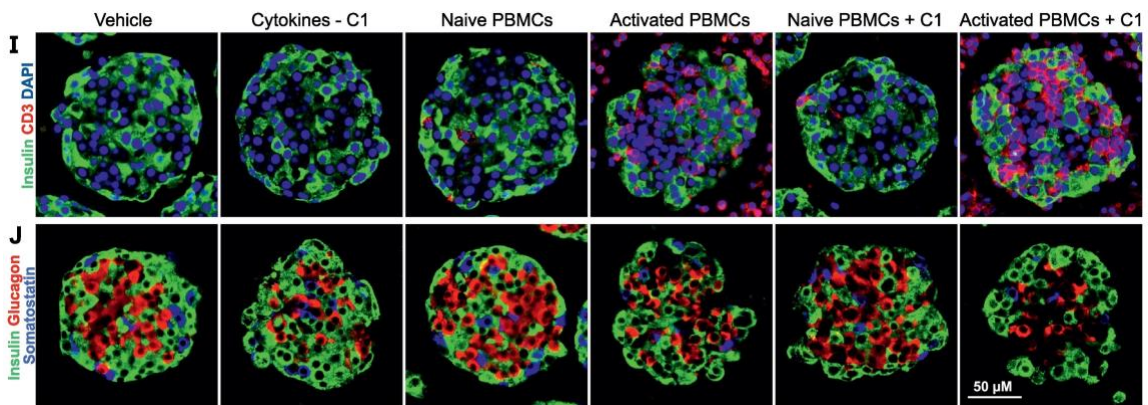


Figure 10. Pancreatic organoid models. I) Immunostaining of paraffin embedded islet organoids using insulin (green), DAPI (blue), and CD3 (red) antibodies. This figure shows that the addition of a cytokine mix of 2 ng/mL of IL-1 β , 10 ng/mL of IFN- γ , and 10 ng/mL of TNF- α (C1) decreased the insulin content in the pancreatic β cells. The red CD3 staining shows the increased immune infiltration that occurs when activated peripheral blood mononuclear cells (PBMCs) and cytokine mix is added or when activated PBMCs are added alone. J) Immunostaining of paraffin embedded islet organoids using antibodies towards the pancreatic hormones insulin (green), glucagon (red), and somatostatin (blue). A decrease in intracellular insulin content is shown with the addition of activated PBMCs and cytokine mix (2 ng/mL of IL-1 β , 10 ng/mL of IFN- γ , and 10 ng/mL of TNF- α) or activated PBMCs alone. PBMCs, peripheral mononuclear blood cells (Yesildag et al., 2022).

Improvements need to be made before pancreatic organoid models are widely used, including development of more mature β cells that are up to par with function of in vivo β cells (Beydag-Tasöz et al., 2023; Jiang et al., 2022). Future directions include building on these models by adding immune cells with patient-derived islets to observe interactions between β cells and immune cells as well as including vascularization and non-endocrine cells to make multi-cellular organoids that are more representative of the in vivo pancreas (Beydag-Tasöz et al., 2023; Candiello et al., 2018). These pancreatic organoid models should also be integrated with other organ-based organoid models to study communication between tissues in diabetic complications (Beydag-Tasöz et al., 2023).

Anti-CD3 Immunotherapies (Teplizumab)

There have been various immunotherapies tested in phase III clinical trials including oteelixizumab, daclizumab, antithymocyte globulin, alefacept, and abatacept, however, none of these have been as successful as teplizumab (Ajmal et al., 2024; Warshauer et al., 2020). CD3 is a protein complex of 6 molecules that is an integral part of the T cell receptor complex, therefore, anti-CD3 antibodies affect T lymphocyte signaling, leading to an inhibition of T lymphocyte cytotoxicity (Ajmal et al., 2024). Teplizumab is an Fc receptor non-binding anti-CD3 monoclonal antibody that has been shown to delay the onset of T1DM in at-risk individuals, particularly those in stage 2 T1DM (Ajmal et al., 2024; Herold et al., 2019; J. S. Hirsch, 2023; Holt et al., 2021;

Ramos et al., 2023). Teplizumab (Tziel) was approved by the FDA in November 2022 for the prevention of T1DM and represents a major milestone by being the first disease-modifying intervention for T1DM (J. S. Hirsch, 2023).

Teplizumab has been shown to maintain β cell functionality, evidenced by increased C-peptide secretion (Ajmal et al., 2024). A phase II trial published in 2019 evaluated a 14-day course of teplizumab in 76 non-diabetic, high-risk relatives of T1DM patients. The investigators observed the median times to diagnosis for the treatment group and the placebo were 48.4 months and 24.4 months respectively ($p = 0.006$), showing that the use of teplizumab in high-risk populations can delay the progression to clinical diagnosis of T1DM up to 2 years (Herold et al., 2019). Additionally, only 43% of participants randomized to teplizumab treatment progressed to clinical T1DM in comparison to 72% of participants in the placebo group (Herold et al., 2019). This effect was especially significant during the first year after treatment where only 7% of participants in teplizumab group received a T1DM diagnosis compared to 44% of the placebo group (Herold et al., 2019). In an extension of this study, the delay of T1DM onset continued with the median times to diagnosis of 59.6 months and 27.1 months for treatment and placebo groups, respectively ($p = 0.01$) (Sims et al., 2021). Fifty percent of the treatment group remained T1DM free after 5 years in comparison to 22% in the placebo group (Sims et al., 2021). This study also examined the long-term effects of teplizumab treatment on β cell function, which is represented by the levels of C-peptide secretion. Investigators observed that patients in the teplizumab group exhibited higher

levels of C-peptide secretion and early insulin secretion compared to participants in the placebo control group (Sims et al., 2021).

The phase III clinical trial, PROTECT, assessed the efficacy of two 12-day treatment courses of teplizumab in 217 children and adolescents who have been recently diagnosed with stage 3 T1DM (Ramos et al., 2023). This trial was conducted across 61 sites in the United States, Europe, and Canada. Investigators observed that the participants administered teplizumab had significantly higher levels of C-peptide, which represents the preservation of β cell function (Ramos et al., 2023). About 94.9% (95% confidence interval, 89.5 to 97.6) of participants in the treatment group continues to have clinically significant C-peptide levels of greater than 0.2 pmol/mL, while only 79.2% (95% confidence interval, 67.7 to 87.4) of the placebo group met this criteria (Ramos et al., 2023). An extension of this study is currently being conducted to evaluate long-term safety outcomes and is projected to be completed in 2026 (Provention Bio, a Sanofi Company, 2024a) (NCT04598893).

As discussed earlier, autoreactive T lymphocytes are the main effectors of β cell destruction (Ajmal et al., 2024; DiMeglio et al., 2018; Insel et al., 2015; Szablewski, 2014). The focus of immunomodulatory therapies, such as teplizumab, is to preserve β cell functionality by protecting them from immune attack through changing immune cell populations (Ajmal et al., 2024; Sims et al., 2021). The mechanism of action of teplizumab is thought to involve binding to a component of T cell receptor complex and

changing the phenotype of autoreactive CD8+ T lymphocytes (Ajmal et al., 2024; Herold et al., 2019; Warshauer et al., 2020). This change in phenotype leads to partially exhausted KLRG1+TIGIT+CD8+ T lymphocytes, which exhibit reduced secretion of the cytokines IFN- γ , TNF- α , and IL-1 β (Ajmal et al., 2023; Ramos et al., 2023; Sims et al., 2021). A study by Herold et al. showed that these partially exhausted CD8+ T lymphocytes were more commonly seen at 3 and 6 months after treatment in the teplizumab group than in the placebo group, however, no changes in other T lymphocyte populations were observed (Herold et al., 2019; Sims et al., 2021).

Side effects of teplizumab have been observed including headache, gastrointestinal issues, decrease in number of lymphocytes (lymphopenia), rash, and mild cytokine release syndrome, however, most of these effects self-resolved (Ajmal et al., 2024; Herold et al., 2019; Ramos et al., 2023). The modified Fc receptor of this antibody mitigates the potential immunosuppressive effect of the drug (Warshauer et al., 2020)(Warshauer et al., 2020). This is evidenced by the resolution of both COVID-19 infections and reactivations of Epstein-Barr virus (Ramos et al., 2023).

Longer-term studies evaluating safety and efficacy of teplizumab are needed. The PROTECT extension aims to evaluate long-term safety (Provention Bio, a Sanofi Company, 2024a). The PETITE-T1D clinical trial is currently running and aims to assess the safety and pharmacokinetics of a 14-day course of teplizumab in participants younger than 8 years of age with stage 2 T1DM (Provention Bio, a Sanofi Company, 2024b)

(NCT05757713). This trial will also be assessing the development of anti-teplizumab antibodies, which was not done in any of the studies discussed, providing more information on the long-term safety of teplizumab (Provention Bio, a Sanofi Company, 2024b). Teplizumab provides promising results for immunotherapies that could possibly lead to a cure for T1DM.

DISCUSSION AND CONCLUSION

There are around 2 million patients diagnosed in the United States and about 8.42 million people worldwide with T1DM as of 2021, however, therapies that halt or reverse the progression of T1DM are currently unavailable (Ajmal et al., 2023, 2024). There have been many promising developments in the treatment of type 1 diabetes mellitus including adjunctive therapies to insulin, the advent of fully closed-loop insulin delivery systems, the development of organoid models, stem-cell therapies, and immunomodulatory drugs. This thesis explores the current standard treatments for T1DM as well as new and emerging methods for treatment.

There was a lack of racial and ethnic diversity among many of the studies assessing therapies for T1DM. Many studies consisted of predominately non-Hispanic white participants (Herold et al., 2019; Lakshman et al., 2024; Ramos et al., 2023; Russell et al., 2022). There is a need for studies containing a more diverse patient population to assess the safety and efficacy of treatments across all races and ethnicities.

Cost is a significant barrier to uptake and continuation of treatment. The cost of insulin monotherapy has increased significantly in a short amount of time, and it continues to increase with the advent of new delivery methods (Crossen et al., 2020). Patients in underserved communities and low-income countries are less likely to utilize new diabetes technology, contributing to lack of glycemic control and increased mortality rates. Going forward, there needs to be a shift in focus to making diabetes care available to all patients.

Further exploration and characterization of the role of genetics and environmental factors regarding onset and progression of T1DM is needed. As more is discovered about T1DM, trials can be designed to better represent pathogenesis and risk factors, and future trials can be better targeted to patients who will benefit the most from the therapy or drug. This has already begun. This is exemplified by studies pertaining to biguanides and GLP-1 RAs (Garg et al., 2024; Libman et al., 2015; Moon et al., 2007). In these studies, participants were chiefly overweight and obese T1DM patients. However, these less diverse populations can limit the generalizability of their results.

Most of the noninsulin therapies used as adjunctive treatments to insulin are used off-label and are not approved for the treatment of T1DM. In the studies discussed, the safety and efficacy of these medications were only in comparison to insulin monotherapy and did not include evaluations of other adjunctive therapies (Boeder et al., 2024; Garg et al., 2024; Libman et al., 2015; Pasqua et al., 2022, 2025). A study by Anson and colleagues compared real-world outcomes of GLP-1 RAs and SGLT2 inhibitors. However, this study was conducted only by using coded medical data input by a variety of medical providers. This could have led to missing and inaccurate data points (Anson et al., 2023). This study also lacked a control group of patients using insulin monotherapy (Anson et al., 2023). Although these treatments may have benefits for an overweight and obese patient population, more randomized control trials are needed to make direct comparisons between these drugs based on efficacy and safety outcomes to determine which would be most beneficial for the treatment of T1DM (Libman et al., 2015; Moon et al., 2007; Warshauer et al., 2020).

In a study assessing a fully closed-loop insulin delivery system, Boughton and colleagues permitted the participants to use their normal insulin preparations, rapid or ultra-rapid acting during the control period (Boughton et al., 2023). In contrast, all participants were directed to use ultra-rapid insulin lispro with the closed-loop system (Boughton et al., 2023). This difference could have led to an overestimation of the perceived benefit of the closed loop system, especially since a minority of participants used ultra-rapid insulin lispro as their normal insulin preparation during the control period (Boughton et al., 2023). However, QOL was a major theme among studies assessing fully closed-loop insulin delivery systems. Most participants in these studies experienced an increased QOL when using a fully closed-loop insulin delivery system (Howard et al., 2024; Lakshman et al., 2024).

There are few studies that assess T1DM treatments in an elderly population. In the ones that exist, there are significant limitations. For example, studies assessing the usability and efficacy of insulin delivery devices in elderly patients, there was a lack of participants who met criteria for dementia, which could limit the generalizability of these results (McAuley et al., 2021).

Teplizumab has only been evaluated in high-risk relatives of patients with T1DM and patients with new-onset T1DM (Herold et al., 2019; Ramos et al., 2023; Sims et al., 2021). Two of these studies also included a small patient population of 76 high-risk relatives of T1DM patients (Herold et al., 2019; Sims et al., 2021). Due to these restricted patient populations, it is not certain if these benefits will translate to patients with long-

standing T1DM. However, this treatment provides the most promise in delaying the onset of T1DM and improving β cell functionality.

A study completed in China demonstrated the successful transplantation of autologous stem cell-derived islets. The patient achieved insulin independence and showed improved glycemic control (S. Wang et al., 2024). However, this study only consisted of one participant followed for 12 months post-transplantation. Patients who do achieve insulin independence only maintain independence for about 5 years post-transplantation and subsequently revert back to exogenous insulin monotherapy (Hogrebe et al., 2023; Holt et al., 2021; Keymeulen et al., 2024). However, transplantation still remains the only means of replacing lost β cell mass (Holt et al., 2021; Warshauer et al., 2020). Stem cell-derived islet transplantation still requires lifelong administration of immunomodulatory therapies. Efforts toward immune evasion of transplanted cells have been unsuccessful (Ghoneim et al., 2024; Hogrebe et al., 2023; Keymeulen et al., 2024).

Pancreatic organoids have been shown to be successful in testing the efficacy and toxicity of drugs for the treatment of T1DM (Yesildag et al., 2022). However, these organoid models need to be improved before they become widely used, such as the development of β cells up to par with the sophistication of in vivo, human β cells (Beydag-Tasöz et al., 2023; Jiang et al., 2022).

Future directions should include implementation of urgently needed changes such as further studies exploring causes and triggers of autoimmunity against β cells as well as in-depth and long-term studies assessing safety and efficacy of curative and preventative therapies. Immunotherapies, such as teplizumab show promise for those patients who

have been recently diagnosed or at a high risk of developing T1DM. On the other hand, for patients with long-standing T1DM, the fully closed-loop systems seem to provide the most promising results with the least amount of associated risk.

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CURRICULUM VITAE

