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Depression in type 1 diabetic youth: insulin injections vs. pumps

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BOSTON UNIVERSITY
SCHOOL OF MEDICINE

Thesis

**DEPRESSION IN TYPE 1 DIABETIC YOUTH: INSULIN INJECTIONS VS.
PUMPS**

by

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PUMPS**

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ABSTRACT

Type 1 diabetes is an autoimmune disease that involves destruction of pancreatic cells that produce insulin. The disease typically presents in children and adolescents. The burden of disease management, fear of complications, and disruption of normal childhood that the disease causes place youth with type 1 diabetes at increased risk for developing depression compared to peers without the disease. The presence and severity of depression correlates with disease outcomes. Use of continuous subcutaneous insulin infusion pumps has been shown to improve youth's quality of life compared to use of multiple daily insulin injections. Although quality of life measures are associated with the risk of developing depression, no studies have compared depression symptomatology in youth using insulin pumps to those using multiple daily insulin injections. The proposed project will assess relative depression symptomatology in youth ages 10-17 using insulin pumps and multiple daily insulin injections. The results of this proposed project could help inform clinicians' decisions about whether to initiate type 1 diabetes therapy in youth with either insulin pumps or insulin injections. Given the financial burden of depression, it could also potentially encourage insurance companies to increase coverage of insulin pumps.

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LIST OF ABBREVIATIONS

CDI.....	Children’s Depression Inventory
CES-D.....	Center for Epidemiological Studies Depression Scale
CGM.....	Continuous glucose monitoring
CSII.....	Continuous subcutaneous insulin infusion
DKA.....	Diabetic ketoacidosis
MDI.....	Multiple Daily Injections
SMBG.....	Self-monitoring of blood glucose
T1D.....	Type 1 Diabetes Mellitus
T2D.....	Type 2 Diabetes Mellitus

INTRODUCTION

Background

Type 1 diabetes (T1D) is an autoimmune disease in which the immune system attacks and destroys the cells in the pancreas that produce insulin.¹ Insulin is a hormone that allows the body's cells to uptake glucose from the blood to use for energy.¹ With T1D, there is inadequate production of insulin by the pancreas and, consequently, less glucose is taken up by cells.¹ This results in hyperglycemia, or elevated blood glucose, which can lead to both acute and chronic complications.¹

Both genetic and environmental factors, including viruses, diet, and the gut microbiome, have been implicated as potential causes of T1D.² It is thought that environmental factors may trigger the disease in genetically predisposed individuals.²

T1D typically presents in children and adolescents.³ The majority of youth with new-onset T1D present with polyuria, polydipsia, and weight loss and many present with diabetic ketoacidosis, a serious complication of the disease.³

Given that T1D is characterized by insufficient insulin production and, consequently, elevated blood glucose levels, management of the disease involves frequent checks of blood glucose levels and administration of exogenous insulin, which increases cellular uptake of glucose in the blood, thereby keeping blood glucose levels within acceptable physiological boundaries.⁴ Methods for monitoring blood glucose levels include multiple daily fingersticks (also termed self-monitoring of blood glucose, or SMBG) and continuous glucose monitors (CGM).⁴ Methods for insulin administration include multiple daily injections (MDI) via syringes/needles or insulin pens, continuous

subcutaneous insulin infusion pumps (CSII), and closed-loop insulin pumps (also called the “artificial pancreas”).⁵

Statement of the Problem

The prevalence of psychiatric disorders is quite high in youth with T1D⁶ and youth with T1D are at increased risk for developing psychiatric disorders compared to peers without T1D.^{7,41,42} In particular, depression has been found to be the most prevalent psychiatric disorder in youth with T1D.⁸ The significant burden of living with and managing a chronic, complex disease like T1D, the fear of acute and chronic complications, and the disruption in normal childhood activities and peer group interactions that T1D causes all contribute to the increased risk of depression in youth with T1D.^{9,43} Additionally, the presence and severity of depression symptoms are associated with clinical outcomes in youth with T1D, as depression symptoms can impede a youth’s ability to motivate themselves to manage the disease and carry out tasks required to manage the disease.^{10,45,46,47} Depression in youth with T1D is also associated with increased hospitalizations for T1D complications.¹¹

In recent years, use of CSII has become increasingly prevalent.¹² Results from a limited number of studies suggest that CSII improves youths’ quality of life when compared to MDI.^{13,14,51,52} Although these quality of life measures are associated with the development of depression, there are no studies that specifically address the effect of CSII on the development of depression symptoms in youth compared to MDI.

Hypothesis

The burden of disease management, the fear of acute and chronic complications, and the disruption in normal childhood activities that T1D causes all place youth with T1D at increased risk for depression.^{9,43} The use of CSII has been shown to mitigate these factors.^{13,14,51,52} Therefore, the hypothesis is that youth who use CSII will develop decreased depression symptomatology compared to youth who use MDI.

Objective and Specific Aims

The proposed prospective cohort study will compare depression symptomatology in youth with T1D who use CSII versus those who use MDI. Specific aims of the proposed study include:

- Assess relative depression symptomatology in youth with T1D using CSII versus MDI via the Children's Depression Inventory (CDI)

REVIEW OF THE LITERATURE

Pathophysiology of Type 1 Diabetes

The pancreas plays a key role in maintaining glucose homeostasis in the body.¹ Increased blood glucose levels (for example, following food intake) are sensed by beta cells in the pancreas.¹ In turn, these beta cells secrete the hormone insulin into the blood. Insulin binds to receptors on cells throughout the body, which ultimately results in uptake of glucose by these cells and consequently a decrease in blood glucose levels.¹

Type 1 diabetes (T1D) is an autoimmune disease.¹⁵ Normally, the immune system is regulated so that it only recognizes and attacks pathogens.¹⁵ However, autoimmune diseases occur when the immune system recognizes, attacks, and destroys healthy tissue.¹⁵ T1D involves an autoimmune attack on pancreatic beta cells.¹⁵ When these cells are destroyed by the body's immune system, their ability to secrete insulin is compromised.¹⁵ As a result, the ability of glucose to enter cells is diminished and, consequently, blood glucose levels remain elevated.¹⁵

Risk Factors and Potential Causes of T1D

Both genetic susceptibility and environmental factors are believed to be involved in triggering T1D.¹⁶ The prevailing hypothesis on the cause of T1D is that exposure to one or more environmental agents in a person with genetic susceptibility triggers and/or potentiates an autoimmune attack on pancreatic beta cells, the underlying pathophysiology of T1D.¹⁶

There are several genes that have been found to be associated with an increased risk of developing T1D. These genes can be divided into two groups: MHC genes and non-MHC genes. MHC, or major histocompatibility complex, genes encode a set of proteins that are located on cell surfaces.¹⁷ Due to the role these proteins play in immune system activation and regulation, MHC gene/protein variants have been found to be associated with autoimmune disease, although the specific mechanisms behind this association are not well-understood.¹⁷ More than 40 non-MHC gene variants have been identified that increase susceptibility to T1D.¹⁸

Although susceptibility to T1D appears to be inherited, the specific transmission pattern is unknown.¹⁸ The general population has an estimated 0.55% chance of developing T1D.¹⁸ Offspring of fathers with T1D have an approximately 12% chance of developing the disease, while offspring of mothers with T1D have an approximately 6% chance.¹⁸ Siblings of individuals with the disease have a 5-10% chance of developing the disease by age 20, a 15-fold greater risk than the general population.¹⁸ Studies among twin siblings found that if one has the disease, a monozygotic twin has a 13-33% chance of having it as well, whereas a dizygotic twin has 6-10% chance.¹⁸

It is believed that environmental factors trigger and/or potentiate an autoimmune reaction against pancreatic beta cells in genetically susceptible patients.¹⁶ While much uncertainty remains regarding the specific environmental agents that are responsible, there is evidence that environmental factors are indeed involved in the pathogenesis of T1D. Firstly, a very small portion of genetically susceptible people develop T1D, suggesting that some factor beyond genetics is required to develop the disease.¹⁶ This is

further supported by the aforementioned data from studies on genetically identical twins.¹⁸ Furthermore, there are drastically different incidence rates among people of the same genetic background living in different geographic regions. For example, among Caucasian children under 15 years old, the incidence rate is 3.2/100,000 in Macedonia, while in Finland it is 63/100,000.¹⁶ Moreover, studies of migrants have shown that the incidence of the disease increases when they move from a region of lower incidence to a region of higher incidence, further implicating environmental conditions as triggers of the disease.¹⁶

While no specific environmental agents have been proven to trigger T1D, there has been research on the association of different agents, in particular viruses, dietary factors, and the gut microbiome, with the disease. Viruses may trigger an autoimmune response against pancreatic beta cells via molecular mimicry.¹⁶ The enterovirus genus has been particularly implicated in the development of the disease.¹⁹ Several dietary factors, including exposure to cow's milk, breastfeeding, Vitamin D levels, and Omega-3 fatty acid levels, have been studied in the setting of T1D.^{16,20} Data from multiple studies suggest that Omega-3 fatty acids protect against the development of pancreatic beta cell autoimmunity and T1D,^{16,20} but the effect of other dietary factors on the pathogenesis of T1D remains controversial and unclear. Studies suggest that imbalances in gut microbiome composition may play a role in the development of T1D,^{16,20} but causative associations between specific intestinal microbes and/or specific microflora compositions and T1D have not been established.

Epidemiology of T1D

T1D accounts for 5-10% of cases of diabetes mellitus worldwide with type 2 diabetes (T2D), a form of diabetes that involves insulin resistance due to obesity and insufficient exercise, accounting for the other cases.²¹ Although T2D is becoming more prevalent in children and adolescents, T1D remains the most common type in these age groups, accounting for more than 85% of diabetes mellitus cases in people younger than 20 years of age worldwide.²² Two large studies have investigated the epidemiology of T1D in children and adolescents: the World Health Organization's DIAMOND Project looked at trends worldwide, while the SEARCH Study, an ongoing multicenter study, has looked at trends in the United States.

Published in 2000, the DIAMOND Project²³ investigated the incidence of T1D worldwide in children less than or equal to 14 years of age between the years 1990-1994. Among the populations that were studied, they found an approximately 350-fold difference in incidence rates. For example, in China and Venezuela, incidence rates were 0.1/100,000 per year, while in Sardinia, Italy the incidence rate was 36.8/100,000 per year. Countries with the lowest incidence rates (<1/100,000 per year) included China and South American countries and countries with the highest incidence rates (>20/100,000 per year) included the Scandinavian countries, Italy, Canada, and New Zealand. The incidence rates in different US populations ranged from 10-20/100,000 per year. The study also found that, in most populations, incidence rates increased with age with the highest incidence rates in those 10 to 14 years old. Finally, the study also found that

between 1990 and 1994, there was an average annual increase in incidence rates worldwide of 2.8%.²³

The SEARCH for Diabetes in Youth Study is an ongoing, multicenter study investigating the epidemiology of T1D in the United States. One sub-study from SEARCH found that the overall prevalence of T1D in people less than 20 years old in 2001 was 1.82/1,000 people.²⁴ Another sub-study investigated T1D incidence in people younger than 20 years old and found that the incidence rates were highest in non-Hispanic white youth, slightly higher in females compared to males, and highest in the 5-9 and 10-14 age ranges.²⁵ Another study that used data from the SEARCH Study found that the incidence of T1D increased from 14.8/100,000 people per year in 1988 to 23.9/100,000 people per year in 2004.²⁶ Lastly, a sub-study estimated that from 1978-2004, the overall incidence of T1D increased by approximately 2.3% per year.²² Together these studies suggest that the incidence of T1D among children and adolescents is increasing both in the US and worldwide.

Clinical Presentation of T1D

T1D is a disease of youth: approximately $\frac{3}{4}$ of people with the disease are diagnosed prior to their 18th birthday.³ Patients can present with signs and symptoms of T1D or diabetic ketoacidosis (DKA), a serious complication of the disease, or the disease can be discovered incidentally in an asymptomatic patient.³ A prospective study by Roche et al³ investigated the presenting features in patients under 15 years old with incident cases of T1D in Ireland in 1997 and 1998. The study found that across all age

categories, the combination of polyuria and polydipsia was the most common presentation scenario with 66-75% of patients, depending on age ranges, presenting this way. The study found that weight loss was the next most common presenting sign with 22-45% of patients, depending on age, presenting with this. The study also found that 25% of patients presented in moderate to severe diabetic ketoacidosis.³

A retrospective study by Al Rashed et al²⁷ investigated clinical presentation patterns in children and adolescents with T1D in Saudi Arabia. Similar to Roche et al, the study found that the most common presenting signs and symptoms were polyuria, polydipsia, and weight loss. Al Rashed found that 92% of patients presented with polyuria and 88.8% presented with polydipsia. Of note, these percentages are slightly higher compared to Roche et al's results. Al Rashed found that 32.9% of patients presented with weight loss, which is similar to what Roche et al found. Additionally, Al Rashed found that 47.2% of patients presented with moderate to severe DKA, which is higher than what Roche et al found, which may reflect a relative lack of healthcare knowledge in the study region.²⁷

These two studies highlight that the most common presenting signs/symptoms in a child or adolescent with new onset T1D include polyuria, polydipsia, and weight loss and that a quarter to half of patients with new onset T1D will present in some form of diabetic ketoacidosis.

Diagnosis of T1D

Any of the following criteria can constitute a diagnosis of diabetes of any type, including T1D and T2D: 1) classic symptoms of diabetes, such as polyuria, polydipsia,

and unexplained weight loss, and a random plasma glucose level of greater than or equal to 200 mg/dl; 2) a fasting (no food intake for at least 8 hours) plasma glucose level of greater than or equal to 126 mg/dl on two consecutive days; or 3) a plasma glucose level of 200 mg/dl or greater 2 hours after an oral glucose tolerance test.²⁸

Once a diagnosis of diabetes has been confirmed, the provider must determine whether the patient has T1D or T2D because the treatment of these two types could be different. In the past, children and adolescents who were diagnosed with diabetes nearly always had T1D.²⁸ However, the incidence of T2D is rapidly increasing in children and adolescents, which complicates the diagnosis of diabetes in this age group.²⁸ The presence of autoantibodies to pancreatic autoantigens points toward T1D, but cannot be used to definitively diagnose T1D because these autoantibodies can also be present in patients with T2D.²⁹ Therefore, providers have to consider a variety of other factors, including the patient's age, body habitus, and family history, to help distinguish T1D and T2D.²⁸ The vast majority of youth with T1D present before the age of 14, while the vast majority of youth with T2D present at the onset of puberty or later.²⁵ Non-obese youth with diabetes typically have T1D, while obese patients with diabetes typically have T2D.³⁰ Up to 10% of patients with T1D will have a first-degree family member who also has the disease, while up to 90% of patients with T2D will have a first-degree family member with the disease.³¹

Management of T1D: Blood Glucose Monitoring

Given that T1D is characterized by the insufficient production of insulin and, consequently, the potential for elevated blood glucose levels, management of T1D

involves frequent monitoring of blood glucose levels and the administration of exogenous insulin to maintain appropriate glucose homeostasis. Both hyperglycemia and hypoglycemia are associated with multiple complications^{28,39} so the goal for patients with T1D is to maintain blood glucose levels within a particular range that minimizes the risk of these complications.

The most recent recommendations from both the American Diabetes Association (ADA) and the International Society for Pediatric and Adolescent Diabetes (ISPAD) suggest that adolescents ages 13-18 should have a target Hemoglobin A1C (HgA1C; a marker of average blood glucose levels over the prior 2-3 months) goal of <7.5%.^{28,32} The ADA notes that this number is higher than the target for adults (<7%) because of the physiological and behavioral challenges that adolescents face, which makes glycemic control more difficult to achieve. The ADA also notes that blood glucose and HgA1C targets should ultimately be individualized with the goal of maximizing glycemic control while minimizing the risk of severe hypoglycemia.³²

People with T1D need to monitor their blood glucose levels frequently each day so that they can appropriately adjust their dietary intake of glucose and can administer the correct amount of insulin to maintain their blood glucose level within a healthy range. There are two main strategies for blood glucose monitoring: self-monitoring of blood glucose (SMBG), which typically involves multiple daily fingersticks, and continuous glucose monitoring (CGM), which involves continuous measurement of blood glucose levels via a minimally invasive subcutaneous device.⁴ Per ISPAD recommendations, SMBG should be performed prior to meals, two hours after food intake, at bedtime,

during the night, and after the overnight fast to detect and prevent hypoglycemia and hyperglycemia and to optimize insulin dosing.⁴ Increased frequency of SMBG correlates with better glycemic control.⁴

In addition to eliminating the need for multiple daily fingersticks, which can be time-intensive and uncomfortable, a notable benefit of CGM is that these devices can be programmed to alarm when glucose levels trend towards dangerously low levels or when there are rapid fluctuations in glucose levels.³³ Hence, CGM is especially helpful for people who have hypoglycemia unawareness.³³ A study comparing SMBG and CGM with respect to changes in HgA1C found that adults (age 25 and older) who used CGM achieved a significantly greater reduction in HgA1C compared to those who used SMBG but found no significant differences in HgA1C among subjects between eight and 24 years old.³³ However, the study also found that frequency of CGM use was the best predictor of HgA1C lowering for all age-groups and, specifically, found that subjects age 25 and older wore the CGM devices significantly more than those younger than 25, which likely largely explains the differences in outcomes.³³ Therefore, insufficient use of/poor adherence to CGM devices is an important limitation to CGM in adolescents. Other barriers to CGM include cost, lack of insurance coverage, and lack of availability in some countries.³⁴

Management of T1D: Insulin

In addition to blood glucose monitoring, insulin therapy is the other cornerstone of T1D management. There are several different types of insulin based on their duration

of action in the body: short-, intermediate-, and long-acting.⁵ To achieve and maintain optimal glycemic control, the ideal strategy for insulin administration is “basal-bolus” therapy, which involves administering a long-acting insulin to maintain a basal level in the body and supplementing this with boluses of short-acting insulin to account for mealtime increases in blood glucose levels.⁵

There are several different methods for insulin administration. Multiple daily injections (MDI) is one method. This involves using either syringes and needles or insulin “pens,” which are prefilled with a certain amount of insulin, to administer basal and bolus doses of insulin at appropriate times during the day.⁵

Another method involves the use of an insulin pump, or continuous subcutaneous insulin infusion (CSII). These devices are programmed to continuously administer insulin at a set basal rate.⁵ However, users must check their blood glucose levels frequently throughout the day and manually adjust the insulin dose/infusion rate accordingly.⁵ Users must also manually increase the insulin dose/infusion rate to deliver mealtime boluses.⁵ Newer technology has integrated insulin pumps with CGM. With this “sensor-augmented pump therapy,” users monitor their blood glucose with the CGM device, then manually adjust their insulin dose/infusion rate via the insulin pump.³⁵ A newer variation of this technology, “sensor-augmented pump therapy with threshold suspension,” directly links the CGM with the CSII device and programs the insulin pump to terminate insulin delivery when the CGM device senses a preset low threshold blood glucose level.³⁶

The newest technology in insulin administration involves “closed-loop” insulin pumps, or the “artificial pancreas,” of which there are two types. The hybrid closed-loop

system is comprised of CGM technology and an insulin pump that uses an algorithm to automatically adjust basal insulin delivery based on CGM readings.³⁷ With this technology, users are still required to manually increase the insulin dose/infusion rate to deliver mealtime boluses.³⁷ Another type of closed-loop pump is the automated closed-loop system, which is similar to the hybrid closed-loop system, but which is fully automatic- users do not have to manually adjust the insulin dose/infusion rate at all.³⁸

Complications of T1D

There are multiple potential acute and chronic complications in patients with T1D. The most common acute complication is hypoglycemia, which is loosely defined as a blood glucose level less than 65 mg/dl.³⁹ In children, severe hypoglycemia can result in seizures and/or loss of consciousness.³⁹ Another acute complication is diabetic ketoacidosis (DKA), a life-threatening condition that results when, due to a shortage of insulin, the body is no longer able to use glucose as fuel and, therefore, starts metabolizing fatty acids.²⁸ This results in the production of ketone bodies, which increase the acidity in the blood.²⁸ Many patients with undiagnosed T1D often present with DKA and many T1D patients who fail to adhere to their insulin regimens rapidly develop DKA.²⁸

Vascular sequelae represent some of the most significant and burdensome long-term complications of T1D. Vascular complications include microvascular (nephropathy, retinopathy, and neuropathy) and macrovascular (coronary artery disease, cerebrovascular disease, and peripheral vascular disease) complications.⁴⁰ The

pathophysiology of how chronic/uncontrolled diabetes leads to these complications is not completely understood.⁴⁰ These complications typically take many years to manifest clinically and are rarely seen overtly in children and adolescents.⁴⁰ However, there is evidence that the pathophysiological processes underlying these complications begin around the time of disease onset and that these complications can be detected clinically and with laboratory data as early as 2-5 years after a patient is diagnosed.⁴⁰ Therefore, it is important that children and adolescents with T1D are regularly screened for these complications as part of disease management.

T1D in children and adolescents has also been shown to be a risk factor for a variety of psychiatric disorders. A prospective cohort study by Butwicka et al⁷ found that children and adolescents with T1D were 2.1 times more likely to be diagnosed with a psychiatric disorder compared to peers without T1D (HR = 2.1, 95% CI: 2.0, 2.2). Specifically, the study found that youth with T1D were at a significantly increased risk for mood disorders, anxiety disorders, eating disorders, substance misuse, ADHD, behavioral disorders, and intellectual disability compared to youth without T1D.⁷ Additionally, a retrospective cohort study by Cooper et al⁴¹ that looked at the incidence of psychiatric disorders in subjects who were diagnosed with T1D before age 18 found that subjects with T1D were 2.3 times more likely to be diagnosed with a psychiatric disorder compared to peers without T1D (HR= 2.3, 95% CI: 1.9, 2.7). Furthermore, a prospective cohort study by Dybdal et al⁴² found that youth with T1D were 1.55 times more likely to be diagnosed with a psychiatric disorder compared to peers without T1D (HR= 1.55, 95% CI: 1.38, 1.74). Like Butwicka et al, both Cooper et al and Dybdal et al

specifically found that youth with T1D were at a significantly increased risk for mood disorders, anxiety disorders, eating disorders, and behavior disorders.^{41,42} Ultimately, these studies all suggest that youth with T1D are at a significantly increased risk of developing a psychiatric disorder compared to youth without T1D.

Depression and T1D

As mentioned above, psychiatric disorders, and in particular anxiety, depression, and eating disorders, are common in children and adolescents with T1D.^{7,41,42} Multiple studies suggest that children and adolescents with T1D have increased rates of psychiatric disorders compared to peers without T1D.^{7,41,42} Additionally, there is evidence that suggests that the presence and severity of psychiatric disorders affect T1D monitoring, management, and clinical outcomes.^{10,45,46,47} Ultimately, the evidence suggests that psychiatric disorders are commonly present in children and adolescents with T1D and can significantly impact the clinical course of the disease. Depression, in particular, is a common psychiatric comorbidity in children and adolescents with T1D and can have a devastating impact on the management and clinical outcomes of T1D.

Epidemiology of Depression in Children and Adolescents with T1D

Multiple studies have found that depression is a common comorbidity in children and adolescents with T1D.^{7,8,41,42} For example, a study by Kovacs et al⁸ followed 92 youths who were diagnosed with T1D between the ages of 8 and 13. The study followed this cohort for 10 years and found that by the 10th year, 47.6% of the patients had

developed a psychiatric disorder. In particular, the study found that 27.5% of the group had developed major depression, the most prevalent psychiatric disorder among the cohort.⁸

The vast majority of the evidence also suggests that children and adolescents with T1D are at higher risk of depression than the general population of children and adolescents. A prospective cohort study by Butwicka et al⁷ used data from the Swedish Childhood Diabetes Register to identify patients younger than 18 with T1D. For each of these individuals, the study identified 100 controls matched for age, sex, and county of birth. The study then followed all subjects until their eighteenth birthday to investigate whether subjects developed psychiatric disorders. The study found that subjects with T1D were 2.1-times more likely to be diagnosed with a psychiatric disorder compared to controls and, in particular, found that patients with T1D were at increased risk for mood disorders, such as depression (HR= 2.0, 95% CI: 1.8, 2.3). Interestingly, this study determined the risk of developing a psychiatric disorder among siblings of both the cohort with T1D and the control cohort who did not have a diagnosis of T1D before age 18 and found no significant difference between these sibling groups,⁷ suggesting that genetics did not play a significant role in the development of mood disorders among the patients with T1D. This is a high-quality study: there were over 17,000 patients with T1D enrolled and the controls were well-matched. This study provides strong evidence that children and adolescents with T1D have a higher risk of depression than the general population of children and adolescents.

A prospective cohort study by Dybdal et al⁴² reached this same conclusion. The study identified 5,084 children and adolescents in two Danish national health registries who were diagnosed with T1D before their eighteenth birthday, then matched these individuals with controls (matched for age and sex). The study followed subjects to determine whether they developed psychiatric disorders, including depression. The study found that the incidence of mood disorders, including depression, in both boys and girls with T1D was higher than in matched controls (for boys: HR= 1.95, 95% CI: 1.52, 2.51, and for girls: HR= 1.55, 95% CI: 1.27, 1.89).⁴² Similar to Butwicka et al, this study was of high quality; it enrolled a large number of patients with T1D and had well-matched controls. It also reached the same conclusion as the Butwicka study: children and adolescents with T1D have a higher risk of depression than the general population of children and adolescents.

Another study from Australia supports the conclusions of Butwicka et al and Dybdal et al. A prospective cohort study by Cooper et al⁴¹ used the Western Australia Childhood Diabetes Database and identified 1,302 subjects who were diagnosed with T1D before their eighteenth birthday. The study then prospectively followed this cohort and 6,422 age- and sex-matched controls into early adulthood (average age at the end of follow up for both cohorts was 26.4 years). The study found that the incidence of depression in subjects with T1D was significantly higher than in controls (HR = 2.95, 95% CI: 2.3, 3.8).⁴¹ This study differs from the Butwicka et al and Dybdal et al in that it followed subjects past their eighteenth birthdays and into early adulthood, but it ultimately parallels the findings of these other two studies in demonstrating that children

and adolescents who are diagnosed with T1D are at increased risk of developing depression relative to the general population of children and adolescents.

Butwicka et al, Dybdal et al, and Cooper et al are all high-quality studies: they are population-based, prospective cohort studies that include thousands of youth with T1D and have well-matched controls. However, a notable weakness of these studies relates to their use of national registers to gather data on psychiatric diagnoses. It is likely that youth with T1D in these studies had more exposure to healthcare providers and, for this reason, it is possible that they were more likely to be diagnosed with a psychiatric disorder or be referred to a mental health clinician compared to non-diabetic peers. Individual assessment of all subjects for psychiatric disorders would have eliminated this referral and diagnostic bias. However, use of national registers precludes individual assessment of all subjects for psychiatric disorders and, therefore, each of these studies is limited by referral and diagnostic biases. Furthermore, although these three studies took place in three different countries and the results are similar across all three countries, the populations of Sweden, Denmark, and Australia are less diverse compared to other countries, which suggests that these results may not be generalizable across multiple countries or ethnicities.

A meta-analysis by Reynolds and Helgeson⁴³ in 2011 evaluated studies since 1990 that compared children and adolescents with and without T1D with regards to psychological well-being, including depressive symptoms and clinical depression. The study calculated aggregate effect sizes (Cohen's *d* values) for different variables (i.e. clinical depression), which reflected the magnitude of the difference between groups. The

study found that children with T1D had more depressive symptoms and clinical depression versus children without T1D and, based on the Cohen's *d* value, found the effect size to be "medium." Interestingly, the study found that the effect size decreased with more recent studies, perhaps suggesting that the prevalence and severity of depression in children and adolescents with T1D has been decreasing in severity in recent years. Nonetheless, the authors concluded that youth with T1D are at a slightly increased risk for psychological disorders, including depression, compared to peers without T1D.⁴³

However, not all studies have concluded that youth with T1D are at increased risk of developing depression compared to youth without the disease. Sivertsen et al¹² conducted a cross-sectional study of adolescents in a single county in Norway to compare the prevalence of psychiatric comorbidities, including depression, in youth with and without T1D. The study found that 6.5% of youth with T1D had depression, while 5.8% of youth without T1D had depression ($p = 0.28$). The authors concluded that there was no significant difference in the prevalence of depression among these two groups. They did note that their conclusion contrasted with the vast majority of prior studies, which had found an increased risk of depression among youth with T1D. They stated that this lack of difference might be due to the fact that the study was conducted relatively recently (2012) in Norway and that, at that time, a significant number of youths had started using CSII instead of MDI. They hypothesized that this might explain the lack of a significant difference in depression prevalence.¹² It is also possible that the lack of statistical significance is due to a beta error. Also, because only 40 patients with T1D were ultimately enrolled, the study may have been underpowered to detect a significant

difference in depression prevalence between those with and without T1D. Furthermore, this study has several significant limitations: it only enrolled patients living in a single county in Norway born between 1993 and 1995, which suggests that results are not generalizable; it allowed patients to self-report a diagnosis of diabetes without differentiating between T1D and T2D, then relied on reviews of medication lists to determine whether patients had T1D or T2D; and finally, no diagnoses were verified by clinicians and lab data were not available.

Ultimately, research findings suggest that youth with T1D are at increased risk of depression compared youth without T1D; Butwicka et al, Dybdal et al, and Cooper et al report significant hazard ratios between 1.55 and 2.95. The findings of Reynolds and Helgeson and Silvertsen et al do suggest that the incidence and prevalence of depression in youth with T1D may have started decreasing in recent years but, overall, the data suggest that there is a significant difference in the incidence and prevalence of depression in youth with and without T1D.

Explanations for the Increased Risk of Depression in Youth with T1D

Youth with T1D are at greater risk than their peers without the disease for developing depression and several studies have investigated reasons for this association. A diagnosis of T1D yields psychological stressors that can lead to depressive symptoms. For example, the knowledge that the disease is chronic/lifelong and the constant, looming threat of future complications can make youth more prone to depression.^{43,44} A diagnosis

can also result in decreased self-esteem, which can make an adolescent more prone to depression.⁴⁴

The nature of T1D management can also be a factor in the development of depression. Disease management is demanding and stressful.⁸ Youth with T1D have to check their blood glucose level multiple times throughout the day, keep track of their physical activity and carbohydrate intake, properly administer insulin, and quickly correct any abnormalities in their blood glucose levels.⁴³ This constant burden and stress, as well as the persistent fear of hypoglycemia, can lead to depression.⁴³ Additionally, the burden of diabetes management and poor control of diabetes can lead to family tension, as well as feelings of guilt and hopelessness in the adolescent, all of which can contribute to depression.⁹ The disease also has the capacity to disrupt normal childhood activities, such as school, sports, and peer group social interactions, which can make youth with T1D more prone to psychological disorders, including depression.⁴³

Grey et al⁴⁴ also note a new, hypothetical, physiological explanation for the development of depression in adolescents with T1D. Imbalances in GABA, a major neurotransmitter in the brain, are hypothesized to play a role in the pathophysiology of depression. Autoantibodies to glutamic acid decarboxylase, present in approximately 70% of adolescents with T1D, have been found to alter the synthesis of GABA. This suggests that autoantibodies involved in the pathogenesis of T1D may also play a role in the pathophysiology of depression.⁴⁴

The burden of living with and managing a chronic, complex disease and a potential biochemical association between diabetes and depression may explain why adolescents with T1D are at increased risk for depression compared to their healthy peers.

Association between Depression, Adherence, and Glycemic Control

Given that depression is more prevalent in youth with T1D, it is important to consider the effect that depression has on adherence to monitoring and treatment regimens, as well as on clinical outcomes, in youth with T1D. A study by McGrady et al¹⁰ investigated the associations between depression and both blood glucose monitoring frequency (a marker of adherence to disease management) and HgA1C (a marker of glycemic control). This prospective observational study involved 144 adolescents (ages 13-18) with T1D. The study gathered baseline data on depression symptoms (via the Children's Depression Inventory, or CDI), blood glucose monitoring frequency, and HgA1C, and then gathered this same data six months later. The authors found that increased total CDI scores (indicating increased depression symptoms) correlated with decreased blood glucose monitoring frequency both initially ($r = -0.29, p < 0.001$) and at follow-up ($r = -0.16, p < 0.05$) and that increases in the specific depression symptoms of negative mood, ineffectiveness, and negative self-esteem correlated with decreased blood glucose monitoring frequency both initially and at follow-up ($p < 0.05$). Increased total CDI scores also correlated with increased HgA1C initially ($r = 0.26, p < 0.01$) and at follow-up ($r = 0.12, p > 0.05$), although the correlation at follow-up did not reach statistical significance. The authors concluded that increased depression symptoms,

particularly negative mood, ineffectiveness, and negative self-esteem, correlated with decreased frequency of blood glucose monitoring and worsened glycemic control.¹⁰

A study by Hood et al⁴⁵ reached similar conclusions but also identified an interesting three-way interaction between depression, blood glucose monitoring, and glycemic control. This was a prospective observational study that sought to determine the effect of depression on glycemic control in adolescents. The study enrolled 145 adolescents (age 13-18) with T1D. The study gathered data on depression symptoms, the frequency of blood glucose monitoring, and HgA1C at the initial study visit and again six months later. The results showed that increases in depression symptoms were associated with increases in HgA1C values. Specifically, every increase of 5 points on the CDI was associated with a 0.5% increase in HgA1C. Interestingly, in patients who experienced increased depression symptomatology, an increase in the frequency of blood glucose monitoring was associated with smaller increases in HgA1C. However, a decrease in the frequency of blood glucose monitoring acted synergistically with increased depression symptoms and resulted in notable increases in HgA1C.⁴⁵ The authors concluded that depression symptoms can predict HgA1C and that this relationship may be mediated by changes in the frequency of blood glucose monitoring.

McGrady and Laffel et al⁴⁶ also performed a study that found that depression worsens glycemic control and that the effect of depression on glycemic control can be mediated by blood glucose monitoring. They performed a cross-sectional study that involved 276 adolescents with T1D. They gathered data on depression symptoms using the CDI, blood glucose monitoring frequency, and HgA1C. They found that increases in

depression symptoms were associated with a lower frequency of blood glucose monitoring ($p = 0.02$) and higher HgA1C/poorer glycemic control ($p = 0.05$). However, when they looked at the effect of both depression symptoms and blood glucose monitoring frequency on glycemic control at the same time, the effect of blood glucose monitoring frequency was significant ($p < 0.001$), but the effect of depression symptoms was no longer significant ($p = 0.19$). This result led them to conclude that blood glucose monitoring can mediate the relationship between depression symptoms and glycemic control. They used the Sobel test to determine the magnitude of the mediation effect and concluded that blood glucose monitoring frequency can account for 37.5% of the link between depression and glycemic control ($p < 0.05$).⁴⁶ This means, for example, that the worse a patient's depression is, the poorer their glycemic control will likely be but if they monitor their blood glucose quite frequently, their glycemic control will be better than expected based on the severity of their depression.

A study by Hilliard et al⁴⁷ also found that depression severity correlates with poorer disease management and outcomes. This prospective observational study sought to determine which factors predict deteriorations in adherence to T1D management and glycemic control in adolescents. The study identified 150 adolescents (ages 13-18) with T1D, followed these subjects for 18-24 months, and separated them into three groups based on adherence to disease management (blood glucose monitoring frequency) and glycemic control (HgA1C). The three groups were "meeting treatment targets," "not meeting treatment targets," and "high risk." The study then sought to determine which variables predicted membership in each of these subgroups. A key finding was that, when

comparing subjects in the “meeting treatment targets” and “not meeting treatment targets” group, increased depression symptoms (based on CDI scores) predicted membership in the “not meeting treatment targets” group (OR = 1.07, $p < 0.05$). The study noted that an increase in a subject’s CDI score by one standard deviation made them 1.61 times more likely to be in the “not meeting treatment targets” group compared to the “meeting treatment targets” group.⁴⁷

The findings from these four studies suggest that in adolescents with T1D, increased severity of depression is associated with poorer adherence to disease management and poorer glycemic control. The data also suggest that the association between depression and glycemic control can be mediated by blood glucose monitoring frequency. Although these four studies reach the same conclusions and the majority of their findings on the association between depression, adherence, and glycemic control reach statistical significance, there are several limitations that the studies share. Firstly, the three prospective cohort studies had relatively short follow-up periods (6-24 months). They were able to show that worsening depression is associated with poorer adherence and glycemic control over 6-24 months but, given adolescence is a five-year period, it would have been interesting to see whether those associations and/or the magnitude of those associations held over a longer period of time. Additionally, each of the four studies employed the CDI score, which is based on self-reporting, to characterize the subjects’ depression. It would have been optimal to have a licensed clinician evaluate and score the subjects’ depression. Furthermore, the only variable used to assess adherence to the diabetes management regimen in each of the studies was blood glucose monitoring

frequency. There are several other important components to disease management, including appropriate dosing and timing of insulin administration and dietary factors, that were not considered. These could have had an effect on glycemic control independent of blood glucose monitoring. Finally, there was very little heterogeneity in the study populations - each of the studies noted that the vast majority of their subjects were Caucasian with intact families. This limits the generalizability of these studies' findings. Despite these flaws, the findings suggest that depression is associated with poorer adherence and poorer glycemic control in adolescents with T1D.

Explanations for Why Depression is Associated with Poorer Adherence and Glycemic Control

Several studies have put forth explanations for the association between depression symptoms and glycemic control in youth with T1D. Depression symptoms can include negative mood, loss of energy, hopelessness, indecisiveness, anhedonia, and pessimism.¹⁰ These symptoms may impede adolescents from finding the motivation to initiate and complete diabetes management tasks and can also make them believe their efforts will be unsuccessful.¹⁰ Depression can also lead to memory impairment, diminished concentration, and low energy, all of which can limit an adolescent's capacity to perform the complicated cognitive tasks required to manage their disease.⁴⁴ Decreased motivation and diminished cognitive capacity can result in poor disease management, and consequently, poor glycemic control.⁴⁵

Association Between Depression and Hospitalizations for T1D

T1D has acute complications, notably hypoglycemia and DKA, that can lead to hospitalization. Hypoglycemia and DKA can both result from failure to properly manage the disease (for example, inadequate carbohydrate intake or administration of too much insulin in the case of hypoglycemia, or failure to administer an adequate amount of insulin in the case of DKA). A couple of studies have investigated the effect of depression on hospitalizations for complications of T1D. Stewart et al¹¹ performed a prospective observational study that sought to determine whether depressive symptoms predict hospitalization in youth with T1D. The study enrolled 231 children and adolescents (ages 11-18) with T1D. The subjects self-rated their depression symptoms using the Center for Epidemiological Studies Depression Scale (CES-D). The CES-D score ranges from 0-60. The cutoff scores for detecting depression were 12 for boys and 22 for girls. The subjects were then followed for two years and their hospitalizations for complications from T1D were tracked. After controlling for gender, age, socioeconomic status, and HgA1C, each of which has been found to independently predict hospitalization in youth with T1D, subjects whose CES-D scores fell above the cutoff points were more than 2.5-times more likely to be hospitalized for complications from T1D compared to subjects whose CES-D scores fell below the cutoff points (HR = 2.58, 95% CI: 1.12, 5.98).¹¹ These results suggest that increased depression symptoms increase the likelihood that youth with T1D will be hospitalized due to complications from their disease. This study's limitations include recruitment from a single medical center, which limits the generalizability of the results; self-reporting of depressive symptoms, which

limits the validity of the results; and a short follow-up time period. However, the fact that a large number of youth (231) were enrolled and that the study controlled for several other variables that can predict hospitalizations point to the strength of this study.

Furthermore, a prospective cohort study by Garrison et al⁴⁸ sought to determine whether the presence of psychiatric disorders, including depression, has an effect on rehospitalization in youth who were hospitalized for complications of T1D. This study used the Pediatric Health System Database in the United States to identify 3,094 adolescents (ages 13-18) who were hospitalized due to diabetes complications. The presence or absence of comorbid psychiatric diagnoses at the time of discharge was noted, then the subjects were followed from the time of discharge for 24 months to look for rehospitalizations. The study found that 16% of the adolescents were rehospitalized at least once during the follow-up period and that internalizing disorders, including depression and anxiety, were associated with repeat admissions (OR = 1.79, 95% CI: 1.27, 2.52, $p < 0.01$). There was no significant association between externalizing disorders (i.e. impulsivity, aggression) and repeat hospitalizations.⁴⁸ The results ultimately suggest that comorbid internalizing disorders, including depression, are associated with a significantly increased risk of re-hospitalizations in adolescents with diabetes. Of note, the study included adolescents with both T1D and T2D, however, the study controlled for this potential confounder during analysis.⁴⁸ The studies by Stewart et al and Garrison et al suggest that depression significantly increases the risk of both hospitalizations and rehospitalizations due to complications of T1D.

T1D, Depression, and Suicide

Suicide is an important consideration in youth with T1D given that youth with the disease have access to insulin and administration of too much insulin can be lethal. There is evidence that T1D is a risk factor for suicide. A prospective cohort study by Goldston et al⁴⁹ found adolescents with T1D were more likely to experience suicidal ideation than the general population. The lifetime prevalence of suicidal ideation among the 91 adolescents with T1D in their study was 26.4%, more than double the prevalence found by two other studies on the general population of adolescents. However, the study did not find that adolescents with T1D were more likely to attempt suicide compared to the general population. This study also found that adolescents with T1D who had a history of suicidal ideation were three times more likely to be noncompliant with their medical regimen compared to adolescents with T1D who had never had suicidal ideation ($p < 0.001$).⁴⁹ Interestingly, a more recent prospective cohort study by Butwicka et al⁷ found that youth with T1D were 1.7 times more likely to attempt suicide compared to youth without T1D (HR = 1.7, 95% CI: 1.4, 2.0). The findings of these two studies suggest that adolescents with T1D are at higher risk for suicidal ideation and suicidal attempts compared to adolescents without T1D and that suicidal ideation can negatively impact adherence to treatment regimens.

Effect of Insulin Pumps on Quality of Life

To date, there have been no studies that have specifically investigated whether depression symptomatology is different between youth using MDI and CSII. However,

several studies have compared quality of life in children and adolescents using MDI and CSII. Hirose et al⁵⁰ noted that measures of quality of life in youth with T1D include lifestyle flexibility, feeling safe, perceiving positive and supportive relationships with family and friends, self-efficacy, anxiety, and fear of hypoglycemia and other complications. Many of these quality of life measures are associated with the development of depression. For example, fear of hypoglycemia has been identified as a cause of depression in youth with T1D.⁵⁰

Mednick et al⁵¹ (2004) performed a cross-sectional study to investigate quality of life in youth with T1D following transition from MDI to CSII. The study enrolled 22 youth ages 10-18 who had all been using MDI prior to transitioning to CSII. The study used surveys to gather data on satisfaction with CSII and quality of life; surveys were completed after the transition to CSII. The results of the CSII satisfaction surveys showed that subjects reported greatest satisfaction with the flexibility related to eating and sleeping that CSII provided relative to MDI. Quality of life survey results showed improvements in perceived quality of life after transitioning to CSII, mostly due to increased flexibility with diet and leisure activities. The results also showed that satisfaction with CSII was significantly positively correlated with quality of life ($r = 0.51$, $p < 0.05$).⁵¹ The cross-sectional design of this study is a limitation- subjects did not complete surveys while using MDI, which did not allow for comparison of quality of life data while using MDI versus CSII. Nevertheless, the authors did note that this pilot study identified specific areas of satisfaction associated with CSII use relative to MDI use and showed an association between CSII use and quality of life.

A prospective cohort study by McMahon et al¹³ (2004) found that children and adolescents with T1D who commenced CSII experienced statistically significant improvements in the quality of life measures “impact of diabetes on the patient” and “self-efficacy with diabetes” ($p < 0.05$) after six months of using CSII, which the authors attributed to the increased lifestyle flexibility and increased independence that pump therapy allows for relative to MDI. The results did not show statistically significant improvements in the quality of life measures “worries about diabetes” and “satisfaction with life.” A notable limitation of this study is that only approximately half of the subjects were using MDI prior to starting CSII, while the other half initiated therapy with CSII shortly after diagnosis. This calls into question the extent to which the improvements in quality of life measures were due to inherent benefits of CSII compared to MDI versus a novelty effect of starting a new treatment. Additionally, quality of life data was gathered via self-report questionnaires, which could limit the validity of the results. The authors noted that therapies that improve quality of life may have long-term benefits, including decreasing the risk of depression, and they noted that it would be important to determine the specific effect of CSII compared to MDI on depression over long periods of time.¹³

Nuboer et al¹⁴ (2008) performed a randomized controlled trial investigating the effects of CSII use compared to MDI use on quality of life. All subjects used MDI during a 3.5-month run-in phase, then subjects were randomized to MDI or CSII for 3.5 months, and then all subjects continued with CSII for another seven months. There was not a statistically significant difference in quality of life, measured by PedsQL (Pediatric

Quality of Life Inventory), when comparing the MDI group and the CSII group at the end of the 3.5 month randomization phase. However, those randomized to MDI experienced a statistically significant ($p < 0.05$) increase in quality of life from the end of the randomization period to the end of a subsequent 3.5 month period of using CSII. Additionally, an analysis of all children in the study showed a statistically significant increase in quality of life from the end of the randomization period to the end of the study ($p = 0.023$). This result suggests that quality of life improves after switching from MDI to CSII. Additionally, the study also used the Diabetes Quality of Life Questionnaire to measure the “impact of disease” on the subjects. A within-patient analysis of “impact of disease” scores showed that the “impact of the disease” decreased significantly from the end of the randomization period to the end of the study ($p = 0.0063$),¹⁴ which suggest that the “impact of disease” lessens after switching from MDI to CSII. Unlike in McMahon et al, all subjects in this study used both MDI and CSII at some point, which allowed for a much more accurate comparison of the relative quality of life impact of the two methods. Additionally, most subjects in the McMahon et al study were started on CSII by request, which represents a significant selection bias. In contrast, subjects in Nuboer et al were randomized into either the MDI or CSII group. Two weaknesses of this study are its limited power, given that there were only 19 subjects in each study arm, and its reliance on self-report questionnaires, which could limit the validity of the results. As discussed above, although the study does not specifically address depression, the PedsQL and Diabetes Quality of Life Questionnaire include measures of quality of life, which are associated with the risk of developing depression.

Alsaleh et al⁵² (2014) performed a study to investigate the impact of switching from MDI to CSII on quality of life in children and adolescents. The authors used face-to-face, semi-structured interviews to gather qualitative data from 34 youth ages 5-17. The authors found that 18 of the 34 youth reported increased comfort and autonomy with management of their disease with CSII compared to MDI; 25 of the 34 youth reported that CSII made it easier for them to take part in activities such as going to restaurants, parties, travelling, camping, and playing; 24 of the 34 youth reported CSII did not have a negative impact on education in school compared to MDI; 31 of the 34 youth reported using CSII at school did not negatively impact social interaction with peers compared to MDI; and 30 of the 34 youth reported CSII did not negatively affect participation in sports/extracurriculars. The authors concluded that use of CSII did not negatively impact quality of life compared to use of MDI and, in many ways, use of CSII improved quality of life compared to use of MDI. A notable limitation of this study is the use of semi-structured interview to collect data- questions may not have been asked in a uniform manner to all subjects, which could have skewed the data. However, the study is unique compared to other studies that have addressed this topic in that it gathered qualitative, not quantitative data. It also reached the same conclusion as Mednick et al, McMahon et al, and Nuboer et al: use of CSII can improve quality of life compared to use of MDI.

Weintrob et al⁵³ (2003) performed a randomized cross-over study to investigate treatment satisfaction and quality of life differences with use of MDI compared to CSII. The study enrolled 23 youth aged 8-14 with T1D who had been treated with MDI for at least two years. The 23 subjects were randomly assigned to use either MDI or CSII for

3.5 months, then subjects used the other mode of therapy for another 3.5 months. Subjects completed the Diabetes Treatment Satisfaction Questionnaire (DTSQ) and the Diabetes Quality of Life Questionnaire (DQOL) at the beginning of the study and at the end of each of the two treatment periods. The results showed a significant increase in treatment satisfaction at the end of the CSII treatment period compared to at the beginning of the study and at the end of the MDI period ($p < 0.001$). The results did not show statistically significant improvement in any of three quality of life measures at the end of the CSII period compared to at the beginning of the study and at the end of the MDI period. The authors noted that at the end of the study, 16 of the 23 youth said they would prefer to continue with CSII, due to the increased flexibility with mealtimes it allowed for compared to MDI and elimination of painful injections. The randomization of subjects into treatment groups and the use of both MDI and CSII by all subjects are strengths of this study. Nevertheless, the results of this study contrast with the four aforementioned studies in that they do not suggest that use of CSII results in improved quality of life compared to use of MDI. However, given that only 23 subjects were enrolled in the study, the study may not have been powered to detect a significant difference in quality of life.

Although the aforementioned studies that investigated quality of life in youth using MDI and CSII are limited by small sample sizes and reliance on self-report questionnaires, the majority of the studies suggest that youth using CSII may have a better quality of life compared to those using MDI.

A review by Hirose et al⁵⁰ provides several reasons for why CSII may improve quality of life. The authors note that T1D places significant demands on youth. These include: frequently monitoring blood glucose levels; frequently administering insulin via syringes, pens, or pumps; timing blood glucose monitoring and insulin administration with respect to meals, exercise, and bedtime; monitoring dietary intake; and avoiding acute fluctuations in blood glucose levels. They note that these demands can undoubtedly have an adverse effect on quality of life. However, they note that CSII gives patients the ability to make more precise adjustments to basal and bolus insulin doses compared to MDI, allows for more flexibility in timing of meals, and gives adolescents increased independence and responsibility for their management/treatment regimens, and that these factors may explain why CSII is associated with improved quality of life relative to MDI.⁵⁰

The findings discussed above suggest that CSII can improve quality of life relative to MDI. Although measures of quality of life are associated with the risk of developing depression, there do not appear to be any studies that specifically address differences in the effect of CSII versus MDI on depression symptomatology in youth with T1D. While the vast majority of studies suggest youth with T1D are at higher risk for depression compared to peers without the disease, the study by Sivertsen et al¹² in 2014 found no significant difference in prevalence of depression between adolescents with and without T1D. Although the study did not track how many adolescents used CSII or MDI, they did note that CSII had become very popular in the country the study took place in and hypothesized that this increased usage of CSII may explain the lack of a

significant difference in depression between the two cohorts. However, they did note that there are other plausible explanations for this lack of significant difference and they noted several significant limitations to their study.¹²

The majority of the data suggests that CSII improves quality of life compared to MDI: it decreases the burden of disease management, lessens the fear of acute and chronic complications, and leads to less disruption in normal childhood activities compared to MDI. Since there is an association between quality of life and the risk of developing depression, it follows that CSII may decrease depression symptomatology relative to MDI. However, there do not appear to be any studies that specifically address whether this is the case.

METHODS

Study Design

A multiple-center, prospective cohort study will be conducted to compare depression symptoms in youth ages 10-17 who have recently been diagnosed with T1D who are initiating therapy with either 1) multiple daily injections of insulin (MDI) or 2) continuous subcutaneous insulin infusion via an insulin pump (CSII). The Children's Depression Inventory (CDI-2) will be used to obtain data about subjects' depression symptoms at diagnosis, at six months, and at 12 months.

Study Population and Sampling

The source population from which the study sample will be drawn is youth ≥ 10 years old and ≤ 17 years old who have recently been diagnosed with T1D and who will be initiating therapy with one of two treatment regimens (see Exposure Groups). Inclusion criteria include a diagnosis of T1D according to the American Diabetes Association; age ≥ 10 and ≤ 17 years old; and initiating therapy with either MDI or CSII. Exclusion criteria include prior or current use of MDI, CSII, or closed-loop devices; initiating therapy with a closed-loop device; prior or current use of blood glucose monitoring devices; prior diagnosis of a psychiatric disorder (mood disorder including depression and bipolar disorder, anxiety, eating disorder, schizophrenia, ADD/ADHD); inability of the youth to read English at a second grade level; inability of at least one parent/guardian to demonstrate competence with management of their child's treatment regimen; and presence of another chronic disease (e.g. inflammatory bowel disease, cancer).

Subjects will be recruited from the SEARCH for Diabetes in Youth (SEARCH) study database. The SEARCH study is an ongoing, multicenter, observational study that began in 2000 with the goal of understanding more about diabetes in youth in the United States.⁵⁴ The study uses active surveillance to maintain a registry of youth under age 20 who have been diagnosed with diabetes (both T1D and T2D). This registry allows for the assessment of prevalence, annual incidence, and trends by diabetes type, age, race, and sex. The SEARCH study centers and registry have been used extensively for ancillary studies.⁵⁵ There are SEARCH study centers in five different states and some centers have multiple locations. These centers actively surveil certain geographically defined populations in each state: seven counties in (Southern) California, the entire state of Colorado, eight counties in Ohio, the entire state of South Carolina, and five counties in Washington. Overall, the study surveils 6.2% of the US population younger than 20 years old.²⁵

A study by Mayer-Davis et al that analyzed data from the SEARCH study found that the yearly incidence of T1D in people 0-19 years old in the geographical regions covered by the SEARCH study ranged from 916 to 1101 (with an average of 1022) between 2003 and 2012.⁵⁴ It has been found that approximately half of youth age 0-19 with type 1 diabetes will be diagnosed when ≤ 9 years old and approximately half will be diagnosed when ≥ 10 years old.²⁵ Thus, the SEARCH study identifies and enrolls approximately 500 incident cases of T1D in youth ages 10-17 per year.

A study by Miller et al in 2015 found that 65% of 6-12 year-olds and 58% of 13-17 year-olds with T1D in the United States were using CSII, while the rest were using

MDI.⁵⁶ A review by Prahalad et al in 2018 found that 47% of 9½-15 year olds with T1D in the United States were using CSII.⁵⁷ Given this, we estimate that approximately 50% of 10-17 year-olds with newly diagnosed T1D will initiate therapy with MDI and 50% will initiate therapy with CSII.

Given that the SEARCH study identifies and enrolls approximately 500 incident cases of T1D in youth ages 10-17 per year, we estimate that of these 500 cases, approximately 250 youth will initiate therapy with MDI and approximately 250 will initiate therapy with CSII. Extrapolating these data over three years, we expect there to be approximately 750 youth in the SEARCH study initiating therapy with MDI and 750 youth initiating therapy with CSII. Given the limited time requirements of this study and the ease of participation, we expect at least 80% of potential subjects to consent, so we expect to enroll approximately 600 youth initiating therapy with MDI and 600 youth initiating therapy with CSII.

Using these estimates, as well as an alpha of 0.05 and a beta of 0.2, this study will have 80% power to detect an effect size of 0.162 standard deviations in CDI-2 score, which is considered a “small” effect size based on Cohen’s *d* calculations.⁵⁸

Exposure Groups

There will be two exposure groups, or cohorts, in this study. Both cohorts will include youth ≥ 10 and ≤ 17 years old who were recently diagnosed with T1D. One cohort will include youth who are initiating therapy with MDI. The other cohort will include youth who are initiating therapy with CSII.

Study Variables and Measures

The primary outcome is severity of depression symptoms. Depression symptoms will be measured by the Children's Depression Inventory 2 (CDI-2), a self-report questionnaire that is widely used to evaluate depression symptoms in youth ages 7-17.¹⁰ Youth rate 27 items on a scale from 0 to 2. The total score can range from 0-54. Higher scores indicate more depression symptomatology.⁴⁶ While different cutoff scores for clinically significant depression have been proposed, a cutoff score of ≥ 13 is considered to be sensitive for detecting clinically significant depression.⁴⁵

Recruitment

The SEARCH registry will be reviewed daily by research assistants to identify youth with a new diagnosis of T1D. These youth and their families will then be contacted by telephone to introduce and describe the study and to gauge interest. If there is interest in enrolling in the study, a research assistant will meet with the youth and their family at the youth's next scheduled follow-up appointment, which will likely involve meetings with a multidisciplinary team and the initiation of a treatment regimen for T1D. The research assistant will further describe the study and assess the youth for inclusion/exclusion criteria. If the youth meets inclusion/exclusion criteria and they and their family wish to proceed with the study, informed consent will be obtained from a parent and assent will be obtained from the youth.

Data Collection

Demographic data including age, gender, race/ethnicity, state and county of residence, and center the patient was recruited from will be obtained from the SEARCH database and will be entered into an Excel spreadsheet on an encrypted computer by a research assistant. Additionally, the exposure group that the patient is in will be entered into the spreadsheet by a research assistant.

Subjects will fill out a paper-based version of the CDI-2 around the time of their diagnosis and again at follow-up visits six and 12 months later. A research assistant will be present to provide the subjects with the survey and will be present while the subject is filling out the survey. The research assistant will then collect and score the survey and enter the score into the Excel spreadsheet using an encrypted computer. The paper-based CDI-2 will then be stored in a locked cabinet in the research assistant's office space.

Data Analysis

For each of the two cohorts, a mean (with standard deviation) CDI score will be calculated at diagnosis, six months, and 12 months. At each of the three time intervals, a Student's t-test will be performed to compare CDI scores between the two cohorts.

Of note, we will review each subject's medical chart prior to them completing CDI-2 surveys at six and 12 months. If they have switched to a new method of insulin administration since they completed the last survey, they will be excluded from analysis.

Timeline and Resources

We expect IRB approval will take approximately 1 month. Recruitment of subjects will take place over a three year period (which will allow for a total sample size of approximately 1,500 subjects) and since subjects will be followed for one year, the total length of time that the study will be following subjects will be approximately four years. We expect data analysis will take approximately 1 month. Study personnel will include the primary investigator, a statistician, and five research assistants (one for each of the SEARCH study centers). The study will also require three paper-based CDI surveys for each of the subjects, as well as statistical software.

Institutional Review Board

We will submit this study proposal for review by the IRB at each of the SEARCH centers and the Boston University Medical Center IRB. Given that this study involves administering surveys to children under the age of 18, we will apply for a full board review.

CONCLUSION

Discussion

The proposed prospective cohort study will compare depression symptoms in youth ages 10-17 who have recently been diagnosed with T1D who are initiating therapy with either MDI or CSII. The study will seek to determine whether the use of CSII results in decreased depression symptomatology compared to the use of MDI.

A key strength of this study is that it will be the first to investigate the association between method of insulin administration and depression symptomatology. Another strength is that it will employ the SEARCH study sites and surveillance data. The SEARCH study surveils an estimated 6.2% of the US population under 20 years old and its surveillance range includes five different states across the US. Thus, the results will be quite generalizable to the entire US.

The study design does have limitations. First, we are measuring depression symptomatology over time, not presence or absence of clinically significant depression. Although different threshold CDI scores have been proposed to indicate clinically significant depression, we are gathering data on depression symptomatology. We are not determining whether subjects have clinically significant depression. Therefore, although we may observe a statistically significant difference in depression scores between groups by the end of the study, the results may not actually be clinically significant.

We must also consider the hypothetical physiological explanation that has been proposed to explain why individuals with T1D are at higher risk for depression- autoantibodies to GAD, which are involved in the pathogenesis of T1D, may cause an

imbalance in GABA, which could then result in depression.⁴⁴ Further research is needed to determine the role of this hypothetical phenomenon, but we must note that if this phenomenon plays a role in the pathogenesis of depression in youth with T1D, we may not see as large a difference in depression symptomatology in our two cohorts as we expect to.

Closed-loop insulin pumps are the newest insulin administration technology for patients with T1D. Given the limited use of this technology compared to MDI and CSII at this time, this study will not investigate the effect of closed-loop pumps on depression symptomatology. However, given that closed-loop pumps theoretically decrease the burden of disease management compared to MDI and CSII, an important follow-up study will be to investigate the effect of closed-loop pumps on depression symptomatology compared to MDI and CSII.

Summary

T1D is an autoimmune disease that involves destruction of pancreatic beta cells and, consequently, hyperglycemia. The disease typically presents in children and adolescents. Management of the disease involves frequent monitoring of blood glucose levels and administration of exogenous insulin. Youth with T1D have been found to be at increased risk of depression compared to peers without T1D, which is thought to be due to the burden of disease management, disruption of normal childhood activities, fear of complications, and decreased self-esteem that the disease brings. The presence and severity of depression symptoms in youth with T1D have been shown to correlate with

clinical outcomes, hospitalizations and rehospitalizations for disease complications, and suicidal ideation. In recent years, CSII has emerged as an option for management of T1D, in addition to MDI. Results from a limited number of studies suggest that use of CSII improves youths' quality of life compared to use of MDI. Although these quality of life factors are associated with the development of depression, there are no studies that specifically address the effect of use of MDI compared to CSII on depression symptoms in youth with T1D. This proposed project will seek to compare depression symptomatology in youth using MDI and CSII over the course of a year.

Clinical Significance

There are several factors that inform a clinician's decision about whether to use MDI or CSII. If the results of this study show that depression symptomatology is significantly lower in those using CSII compared to MDI, clinicians could use this to inform their decision about whether to start youth on MDI or CSII.

Additionally, not all insurance companies currently cover insulin pumps. However, if the results of this study show that depression symptomatology is significantly lower in those using CSII compared to MDI, insurance companies may be more inclined to pay for pumps, as the extra cost of the pump may be offset by a decrease in mental health clinic visits and a decrease in prescriptions for anti-depressive medications. However, this would require further analysis of the data to determine if there was a clinically significant difference in depression symptomatology.

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