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Videogame Intervention for Improved Control of Type 1 Diabetes in Adolescents

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VIDEOGAME INTERVENTION FOR IMPROVED CONTROL OF TYPE 1 DIABETES IN ADOLESCENTS

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Abstract

Type 1 diabetes is a metabolic disease characterized by an inability to produce insulin, leading to hyperglycemia and other serious complications. Type 1 diabetes can be managed with exogenous insulin and careful dietary monitoring. However, adolescents with type 1 diabetes often have difficulty adhering to optimal treatment regimens, resulting in poorer diabetic control than patients in any other age group. **In this study, we will test the efficacy of a serious videogame for increasing adherence to effective treatment regimens.** We hypothesize that this intervention will lead to a significant reduction in glycosylated hemoglobin A1c, the standard assessment of diabetic control. We will randomize patients to the videogame intervention or a control group and measure hemoglobin A1c levels before and after intervention. This study will evaluate an engaging, age-appropriate tool to allow clinicians to connect with adolescent patients with the goal of decreasing their incidence of future diabetes-related complications.

Chapter 1 – Introduction

Proposal Background

Although many potential factors have been identified that may lead to elevated Hemoglobin A1c (HbA1c), a blood test used to estimate three-month glycemic control, the challenge of implementing a solution that will appeal to adolescent patients and overcome these obstacles persists. Potentially modifiable factors that negatively impact glycemic control include limited continuous glucose monitor (CGM) uptake,[1-3] missed or poorly timed insulin boluses,[4-6] the effects of psychiatric issues common in adolescence,[7] and alcohol use.[8-10] While some research groups have attempted to use traditional behavioral health care techniques, including motivational interviewing[11] and psychotherapy,[12] there remains an opportunity to approach the problem using more novel solutions. The use of videogames to promote behavioral modifications has shown to be promising with respect to asthma,[13-15] sexual risk reduction,[16] HIV prevention,[17] anxiety,[18] and tobacco use prevention.[19] These techniques have also been used for diabetes education and have shown the potential to improve knowledge and satisfaction outcomes, but previous studies have largely targeted educational outcomes and have not sufficiently addressed specific behaviors that have been shown to reduce HbA1c or diabetic complications.[20] In short, videogame interventions have shown promise in promoting specific behavioral changes in adolescents, and there is a paucity of literature studying videogames targeting specific diabetes management behaviors. As such, we propose a randomized controlled trial evaluating the effects of a videogame intervention intended to promote specific diabetes management behaviors, primarily the use of continuous glucose monitoring systems (CGM).

Prevalence and Pathophysiology of Type 1 Diabetes Mellitus

Type 1 diabetes mellitus (T1D) is a common metabolic disorder that presents in childhood or early adolescence. It is estimated that 96,000 children and adolescents under the age

of 15 are diagnosed each year.[21] The prevalence is increasing over time and has been estimated to affect just under 1 individual per 500 worldwide[22] and as many as 1 in 300 in the United States.[23] T1D is typically caused by autoimmune-mediated destruction of pancreatic beta cells, the body's source of insulin. Insulin is the primary hormone involved in permitting transport of glucose from the blood into metabolically active tissue and is necessary for this process to occur. While the pancreas can initially compensate for this destruction, leading to a clinically silent period in which the cellular changes go unnoticed, symptoms of T1D begin to present after about 90% of the pancreatic beta cells have lost function.[21] As this process continues, circulating levels of blood glucose increase and the blood vessels are exposed to large amounts of glucose without a way to process the excess sugar molecules.[24] The cellular changes that occur in the pancreas are currently irreversible.

Diabetes Complications

At initial diagnosis, patients with T1D typically present with symptoms of polyuria, fatigue, weight loss, and may have further metabolic derangement leading to diabetic ketoacidosis (DKA), which is the leading cause of death among young patients with T1D.[25-27] A lack of insulin can lead to DKA because the body perceives low insulin as representing a fasting state, even though high levels of glucose are present—unutilized, given the absence of insulin—in the blood. This leads to increased production of counterregulatory hormones and the mobilization of other energy sources, such as fatty acids, to correct the perceived fasting state. This leads to glucosuria, dehydration, metabolic acidosis, and in severe cases can lead to coma, cerebral edema, and death.[28,29] In order to mitigate these symptoms and restore a quasi-normal metabolic state, patients must be treated with exogenous insulin. This can be administered in several forms but is most effective when a basal insulin (either a long-acting insulin injection or

a continuous insulin infusion) is supplemented with pre-prandial insulin boluses to simulate the physiologic insulin response.[30]

In addition to acutely life-threatening complications, such as DKA, T1D is associated with numerous long-term sequelae that are predictive of poor long-term outcomes. These include nephropathy, peripheral neuropathy, retinopathy, arterial disease, and altered growth.[31-36] The earliest physiologic changes of many of these pathologies begin to develop during childhood and adolescence, even before noticeable symptoms are present.[32] Ultimately, cardiovascular disease is the leading cause of death in patients with T1D over the age of 40.[27] However, with intensive treatment, these deleterious effects can be delayed and, in some cases, prevented.[37]

Given the potential for both acute and chronic complications if blood glucose is not managed effectively, frequent monitoring is necessary throughout the life of a patient with T1D. Blood glucose must be monitored several times a day, either via self-monitored blood glucose readings (SMBG) or using a CGM, with CGM being the most effective for improving metabolic control, especially when combined with use of a subcutaneous insulin infusion system.[38-40] The preferred clinical measure of consistent metabolic control is hemoglobin A1c (HbA1c), which measures the percentage of glycosylated hemoglobin in the blood and, as such, provides an estimated blood glucose across the lifespan of the erythrocytes (about 3-4 months). HbA1c goals are generally set on an individual basis between patients and their clinicians, but the International Society for Pediatric and Adolescent Diabetes (ISPAD) generally recommends that goals should be to reduce HbA1c below 7.0 except in populations in which hypoglycemia is a significant concern.[41] Another useful measurement of glycemic control, made practical by the advent of CGM technology, is the time spent within a target blood glucose range, which is typically defined as 70-180 mg/dL.[42,43]

Challenges in Adolescents with T1D

Unfortunately, despite the extensive literature illustrating both the short-term and long-term benefit of strict glycemic control, average HbA1c levels in the United States continue to exceed the recommended targets. This effect is especially pronounced among adolescents with T1D, with the mean HbA1c level among youth aged 13-17 years being > 9.0%.[44] Indeed, elevated HbA1c and adolescence are both correlated with increased risk of DKA.[45] Additionally, while this population may be more likely to appear "healthy" compared to an aged population with similar HbA1c levels, they are already prone to experience subclinical microvascular complications, especially neuropathy, in the absence of strict glycemic control during childhood and adolescence. Diabetic retinopathy may present symptomatically during this time as well, although current therapies and surveillance strategies have decreased its incidence.[32,46] Furthermore, a prospective cohort study of 720 children and adolescents with T1D conducted over 24 years in Denmark found that elevated HbA1c in childhood or adolescence (at the start of the study) was the only statistically significant predictor of increased death rates across the 24 years of the study.[47] As such, it is paramount to identify and address barriers to decreasing HbA1c in adolescents.

As treatment for T1D is known to be effective and is similar across all age groups—insulin therapy, adjusted for carbohydrate intake and blood/sensor glucose levels—the most promising areas for exploration are improving monitoring of blood glucose and adherence to the prescribed regimen, including lifestyle choices. Numerous studies have illustrated the benefit of consistent use of CGM, especially in conjunction with use of subcutaneous insulin infusion systems.[38,39,44,48] However, CGM uptake remains below 30% across the Type 1 Diabetes Exchange Registry (T1DX), which is sampled from endocrinology centers across the USA specializing in diabetes care.[44] Most importantly, CGM uptake and compliance remains

suboptimal across the adolescent and young adult population, with patients aged 13-26 representing the lowest proportion of individuals using CGM across the T1DX (24% among ages 13-18, 22% among ages 18-26).[1-3,44] Several possible reasons for poor CGM uptake and compliance have been considered. Certainly, cost and access to this technology is a consideration. Cross-sectional data suggests that the use of CGM is less frequent in racial minority populations and low-income environments.[2,3] However, low rates of uptake in the T1DX (representing patient populations with access to specialized endocrinology care) suggest that additional factors are involved in the rejection of CGM. Thus, the question of how to motivate youth to use this technology and create a durable change in behavior to improve glycemic control persists.

Targets of the Proposed Intervention

The videogame strategy to intervention is especially promising in the adolescent population as over 90% of these individuals report playing videogames.[49] Serious videogames have been used extensively to improve health-related education and promote specific disease-modifying behaviors because they allow the player to be entertained by and thus enjoy the intervention. While other aggressive interventions may require frequent clinician follow-up, videogame interventions have the advantage of being accessible anywhere the patient has a mobile device. Components of the proposed game will be designed to allow the patient to learn about and simulate situations which allow them to practice situations that affect glycemic control, including common barriers to CGM uptake, effects of insulin dose timing strategies, and social alcohol use.

Our first goal of the proposed game will be to address and overcome obstacles that prevent adolescents from utilizing CGM systems. One barrier to CGM uptake is that adolescents

may be more inclined to value their personal preferences as being more important than the benefits of CGM, especially if there is no noticeable effect on individual symptoms. Some concerns identified include the hassle of managing another device, a dislike of wearing the sensor on the body, being nervous that the technology will fail, not wanting to have others notice and ask questions about the device, and finding the device aesthetically displeasing.[50] Depressive symptoms and higher diabetes distress at baseline (prior to prescription of a CGM) have also been correlated with infrequent use or refusal of CGM.[7] While studies have shown extensively the efficacy of CGM, there remains the potential for a few negative effects that must be considered as well, including interruption of sleep cycles by alarms for out-of-range blood glucose readings and increased parental anxiety secondary to the increase in available information relative to SMBG.[51]

Beyond use of CGM, there are several other components that may be contributing to the increase in HbA1c in adolescents relative to other demographics. Adherence to an optimized insulin regimen is important; however, adolescents may deprioritize the timing of insulin, waiting until after eating or even forgetting to bolus altogether. Postprandial insulin dosing (compared to pre-prandial dosing) of insulin is associated with higher HbA1c levels, larger insulin doses, and greater prevalence of both hypoglycemia and DKA.[4] When comparing children and adolescents in the T1DX, those with "poor control" (defined as HbA1c > 9.0%) were more likely than those with "excellent control" (HbA1c < 7.0%) to dose insulin postprandially, used more insulin given in fewer boluses, and were less likely to administer insulin for day-time snacks, in addition to performing SMBG checks less frequently.[5] When interviewed, adolescents most often cite "lost focus" as the reason for missing meal-time insulin

boluses. This is especially true among those who dose postprandially, as they may forget to administer insulin during the course of the meal.[6]

Additionally, elevated HbA1c in adolescents can be connected to puberty and its biopsychosocial correlates. The HbA1c elevation has been linked to an increase in insulin resistance due to pubertal changes in hormones, but is also correlated with decreasing self-care.[52] Some evidence has linked behavioral problems to elevated HbA1c, an association that is most likely mediated by low self-confidence and subsequent mismanagement of T1D during adolescence. Suboptimal adherence to the diabetes regimen may be considered a type of risk-taking behavior that is a part of this problem.[53] In the same vein, these T1D patients are similar to their healthy adolescent counterparts in that they are frequently afflicted with comorbid psychiatric conditions.[54] Mood, anxiety, and behavioral psychiatric disorders have been linked with impaired metabolic control.[55]

Finally, addressing alcohol use and promoting risk reduction strategies would be especially beneficial for adolescents with T1D. While alcohol use is illegal in the USA under the age of 21, the prevalence of alcohol use among adolescents is still significant. About half of all adolescents report having consumed alcohol at least once in or prior to the 8th grade (ages 13-14), with 20-30% reporting having used alcohol within the prior month.[8] It is worth noting that these numbers may underrepresent the truth given the illicit status of underage alcohol use. Unfortunately for T1D patients, at-risk alcohol use in the adolescent population is strongly associated with elevated HbA1c as well as an increased risk of DKA. This association dissipates into adulthood, suggesting that this is a potential target for an adolescent-specific intervention.[9] Beyond its impact on HbA1c, social alcohol use by adolescents has also been associated with increased short-term glucose lability and blunted awareness of hypoglycemia.[10]

Goals and Objectives

The goal of the proposed study is to evaluate the efficacy of a well-designed videogame intervention in increasing adherence of adolescents with T1D to the treatment and behaviors recommended by their clinicians and ISPAD. The primary objective of the study is to use the videogame intervention to produce a reduction in HbA1c at 3 months from the initiation of the study. Secondary objectives for the study are to **(1)** maintain this HbA1c reduction at 6 months; **(2)** increase the proportion of adolescents using CGM $\geq$ 6.0 days per week; **(3)** increase the proportion of adolescents adhering to preprandial meal-time insulin bolus; **(4)** improve scores on validated scales measuring diabetes distress and diabetes-related self-efficacy, and **(5)** decrease incidence of hospitalization due to DKA or other diabetes-related complications.

Hypothesis

We hypothesize that adolescents (defined as patients aged 13-17) with T1D assigned to play our videogame for 60 minutes once weekly for 12 weeks, in addition to receiving ongoing treatment from their endocrinologists, will lead to a difference of at least 0.5% in the treatment group mean HbA1c at 3 months from beginning the study relative to a control group assigned to play other unrelated videogames (and continue their ongoing endocrinology treatment regimen, as in the treatment group). We expect that this effect will primarily be achieved through increased CGM uptake and consistent CGM use but will also be augmented by improved preprandial insulin bolus adherence and alcohol-related risk reduction.

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Chapter 2 – Literature Review

Introduction

A comprehensive literature review was conducted from June to December 2019 to identify previous studies examining the relationship between videogame interventions and diabetes education or management. Additionally, relevant studies pertaining to both the planned intervention and the outcomes of interest were identified individually in order to evaluate potential confounding variables and review the optimal methodology for the study. This literature review was performed using the Cochrane library, PubMed, Scopus, and OVID databases (including OVID Medline, EMBASE, and AMED). Search terms used for examining the relationship between the dependent and independent variables included [("video game" OR "videogame" OR "electronic game" OR "serious game") AND ("diabetes mellitus, type 1" OR "type 1 diabetes" OR "juvenile diabetes" OR "insulin-dependent diabetes") AND "adolescent"]. MeSH terms for this search were "video game," "adolescent," and "diabetes mellitus, type 1." Additional searching was performed using MeSH terms "blood glucose self-monitoring" (combined with keywords "CGM" and "continuous glucose monitor"), "adolescent," and "treatment adherence and compliance" to review factors contributing to CGM uptake, our primary outcome of interest. Several additional terms were used to identify additional studies, determine appropriate methodology, and identify potential confounding variables including "glycemic control," "hemoglobin a1c," "diabetes-related self-efficacy," "diabetes education," and "logic model." Finally, manual citation searching of references included in articles already reviewed was performed to identify additional relevant studies that may have been outside the scope of the initial searches. The results of this review process as it pertains to this research proposal are outlined below.

Videogame Interventions for Diabetes in Children and Adolescents

Overall, there is a paucity of available literature that effectively applies the use of serious videogames to improving outcomes for patients with type 1 diabetes. Although several small-sample, short-duration pilot studies have shown promising results, only a few randomized controlled trials have been published on this topic. The existing literature prior to 2010 was effectively summarized in a review written by DeShazo et al.[1] This review identified 11 games that were designed and tested with results published in nine different studies. Of these nine studies, three were randomized controlled trials (RCT). The remainder consisted primarily of smaller pilot studies designed to determine the utility of further developing these videogames and implementing them as tools for the treatment of T1D. Further evaluation of the specific studies reviewed by DeShazo et al. will be given individually in subsequent sections, but the review highlights a few broad factors that are relevant in approaching this topic.

First, this study identified the primary teaching methods used in each of the games reviewed. The most commonly used teaching methods involved presentation of didactic material and situational problem solving. Unfortunately, DeShazo et al. also noted that didactic presentation is "thought to be the least effective" of the many possible teaching techniques. Situational problem solving is likely more helpful, but it does exhibit the efficacy of tools such as goal setting and empowerment, which the authors noted have been shown to be key components of interventions producing changes in behavior. Only one study reviewed by DeShazo et al. utilized goal setting as part of their design.

Additionally, the content of the games was reviewed and classified into broad categories. While all 11 games targeted appropriate dietary choices, and five emphasized the importance of self-monitoring blood glucose, only one game—studied in 1997—was designed to impact psychosocial components of diabetes treatment. This illustrates one of the key gaps in the

literature surrounding this topic: even in approaching diet and blood glucose monitoring, which the games studied had done, psychosocial factors should be considered and explicitly addressed in designing a useful game.

DeShazo et al. concluded by noting that, while the cumulative results of these studies suggest potential benefits towards improving diabetes-related self-efficacy, decreasing hyperglycemia and diabetes-related emergent doctor's visits, and several scales of diabetes-related knowledge and skills, there is much to be studied and several areas for improvement in future research. Only one study was clearly identified as being built upon theoretical frameworks that connect the ideas of the game to tangible behavioral changes. None of the studies reviewed identified clear "dose" requirements for use of the videogames studied.

RCTs Evaluating Videogames and Diabetes in Children and Adolescents

The earliest RCT evaluated in DeShazo et al.'s review was a study by Brown et al. in 1997, in which the game *Packy & Marlon* was evaluated for its ability to improve self-care and metabolic control among kids and adolescents with T1D.[2] This game focused primarily on the effect of food choices on blood glucose but also required players to appropriately dose insulin and provided a multi-player option that forced collaboration in order for both players to maintain diabetic control. 59 subjects were randomized to play either *Packy & Marlon* or an unrelated pinball videogame on the same gaming platform. No instructions were given with regards to frequency or duration of game play. Participants and their parents were then interviewed at three months and six months by trained technicians blinded to exposure status to assess enjoyment of the game, diabetes-related communication between the child and parent, parents' assessment of the child's self-care, and number of emergent doctor visits since the last appointment. Additionally, the child's HbA1c was measured at the initiation of the study and at the time of each follow-up interview.

The control and treatment group were similar at baseline in reported characteristics, although the control group did report more diabetes-related communication with parents than the treatment group when the study began (mean questionnaire score of 18.85 vs. 9.77, no p-value calculated). In spite of these baseline similarities, however, a significant potential for information bias exists within this study as much of the data was collected via interview with participating children and their parents. Given the nature of the intervention, these participants were not blinded to exposure status. This potential information bias is even more notable in the context of the study's results, which showed only two statistically significant results for the treatment group: increased diabetes-related communication with parents (change of 9.50 vs. -3.89 in control group, p-value 0.025) and diabetes self-care as rated by parents (change of 0.28 vs. -0.38, p-value 0.003). These statistically significant results were the only two outcome measures that were subjectively reported by parents, who could have been influenced by the knowledge that their child was playing the educational videogame.

Aside from these statistically significant results, researchers did identify two positive trends associated with the treatment group. Diabetes-related self-efficacy, as reported by interview with the child, improved from a mean of 5.55 to 6.00 in the treatment group and from 5.68 to 5.85 in the control group (change of 0.45 vs. 0.17, p-value 0.07). Additionally, urgent diabetes visits appeared to decrease in the treatment group (-0.43 vs. 0.04 increase in the control group, p-value 0.08). These changes could plausibly have been statistically significant had the study been powered to assess them; however, power to detect differences in these outcomes was limited by the cost of giving each participant a Nintendo gaming system (in turn, limiting sample size) as well as the infrequency of urgent diabetes visits in both groups. Additionally, the authors noted that these patients were all part of the Stanford and Kaiser Permanente health

systems and had been receiving gold-standard care and education for years prior to beginning the study. As such, Brown et al. felt that their participants may have been predisposed to benefit less from this intervention than the general population would have been.

This study showed that, even with the limited videogame technology available in 1997, there was potential to improve diabetes self-efficacy, communication, and adverse outcome frequency through these interventions. They did this successfully despite their own concern for a "ceiling effect" associated with selecting research subjects from elite providers of diabetes care within the Stanford and Kaiser Permanente health systems. Unfortunately, the study is limited by small sample size and a lack of tangible behavior changes that could be quantifiably observed. Improvements on this study would ideally use standardized questionnaires and objective outcome measurements in place of subjective interview data, especially considering the possible information bias as parents report their perception of their child's abilities. Modern videogame technology and internet connectivity will also provide practical means by which to monitor some of these outcomes using in-game performance metrics that would have been unfeasible in 1997.

The second RCT included in DeShazo et al.'s review was published in 2004 by Kumar et al.[3] This study, the DAILY trial, used a program called *DiaBetNet* to take a different approach toward the use of games in diabetes management. Their program was a very simple game, wherein test subjects uploaded blood glucose data, carbohydrate intake, and insulin injection, after which the game would display the data graphically. After three blood glucose checks during a single day, the game would prompt players to guess what their fourth reading would be. Points were awarded for completing this fourth reading and for accuracy in blood glucose prediction.

For this study, 40 subjects from a single clinic in Boston were stratified by age into groups of 8-12 year-old children and 13-18 year old adolescents, then randomized to use either

the *DiaBetNet* game (n=19) or to a control group (n=21) given the same equipment for monitoring blood glucose, insulin, and carbohydrate intake without access to the game. The trial lasted 4 weeks. The DAILY trial identified that those randomized to the game checked their blood glucose more frequently (1662 total checks in the treatment group vs. 1471 in the control group, $p < 0.001$), consumed fewer carbohydrates per day (154 g/day vs. 214 g/day, $p < 0.05$), and had fewer episodes of hyperglycemia, defined as glucose readings greater than 250 mg/dL (318 episodes vs. 377, $p < 0.001$). Furthermore, using a two-tailed paired t-test to evaluate scores on the Diabetes Knowledge Survey, Kumar et al. calculated that there was a significant increase in diabetes-related knowledge for the game group ($t=3.27$, $p < 0.05$) but not for the control group ($t=1.79$, $p = 0.09$). Finally, although not statistically significant, they did note a trend among those randomized to the game group to be more likely to achieve or maintain HbA1c < 8.0% (63% vs 33%, $p = 0.06$) at 3 months after the study began. As this was not the primary outcome of the study, the DAILY trial was not powered to determine statistical significance of this outcome; however, this is a strong trend that could have been statistically significant with a slightly larger sample size.

One potential pitfall associated with this study is the possibility of selection bias associated with selecting test subjects from a single clinic in Boston; this could limit the generalizability of the results as the population studied may not represent the overall population of adolescents with T1D. Aside from this small concern, the biggest flaw in this study is the short duration: none of the measured outcomes except HbA1c were evaluated again after the four-week mark. Outcome measures such as number of glucose checks and carbohydrates per day can only be clinically meaningful if the change persists; this study could have been improved

without substantial additional cost by re-evaluating these outcome measures at 3 months when the HbA1c was rechecked.

The strengths of the DAILY trial lie in its ability to effect quantifiable behavioral change in its participants: while the duration was short, these patients checked their blood glucose more frequently on average, consumed fewer grams of carbohydrates, and experienced fewer episodes of hyperglycemia. One explanation for this is the integration of the patient's personal diabetes data instead of using a simulated game character who happens to have diabetes. An additional strength of this trial was that the game was relatively simple and did not require much time beyond that which would normally be spent performing self-monitoring activities. This would be an appealing feature for any participants who, while open to the idea of an enjoyable diabetes-related game, may not be willing or able to dedicate long amounts of time to playing a videogame.

Lastly, the third RCT mentioned by DeShazo et al had not yet been completed at the time of their review but is currently published and available for detailed evaluation. This trial was published by Baranowski et al. in 2019.[4] While the games studied by Baranowski et al. (*Escape from Diab* and *Nanoswarm: Invasion from Inner Space)* did not directly target patients with T1D, this research was performed with an eye towards diabetes prevention and encompassed similar factors as games made specifically for T1D. Additionally, their study highlights several key elements in designing a game and carrying out the type of trial that we are proposing in this study.

To perform this study, 200 volunteers ages 10-12 who were overweight (BMI range 85th-99th %ile) were recruited and post-recruitment power calculations were performed. They determined that, with 200 test subjects, they would be able to detect an effect size of $f = 0.13$

with 80% power and an $\alpha = 0.05$. These subjects were then randomized to play the two games mentioned above or to a control group. The control group was put on a "waitlist" and then given the games after outcome measurement had been completed. No specific instructions for how frequently to play the game were given, but there were research assistants instructed to contact participants if it took longer than expected to complete the next level. Outcomes were evaluated by blinded observers at times of three months (at which point, both games should have been played to completion of the story) and at five months. The primary outcome for this study was fasting insulin levels, with secondary outcomes of BMI, dietary choices, time spent in physical activity, and time spent in sedentary behavior.

Statistical analysis was performed using ANOVA and χ^2 testing. Additionally, Baranowski et al. controlled for several potential confounders using mixed linear regression models: baseline fasting insulin, age, gender, ethnicity, and BMI. Unfortunately, their study did not identify any significant difference between the treatment and control group with respect to the key outcome of interest, fasting insulin levels (at t = 3 months, ANOVA estimate 24.373 in the treatment group vs. 21.747 in the control group, $p = 0.307$; at t = 5 months, 22.381 vs. 21.268, $p = 0.681$). Similarly, the secondary outcomes measured failed to achieve statistical significance in this study.

The authors proposed several reasons for these disappointing results after what they described as a very promising pilot study. First, there was significant loss to follow up (only 155 of 200 subjects completed the study, a 22.5% drop-out rate), associated in many cases with technological difficulties while trying to play the game. Second, there was a significant culture shift in popular videogames during the elapsed time from the pilot study to this RCT. Both *Diab* and *Nano* had been designed in the decade of the 2000's, but the style of popular game changed

dramatically in the ensuing years; in fact, the game developing client supporting these games was discontinued, limiting the researchers' abilities to make the games playable for participants. Third, as in other studies, there was no clear dose or instructions for gameplay frequency. Finally, and perhaps most importantly, the researchers noted that they discovered a serious concern late in the process of conducting the study. Evidently, some research staff had failed to conduct follow-up, provide promised incentives to research subjects, document use of accelerometers that were measuring physical activity, or correctly file data. While the principal investigators of the study indicate that they made every effort to rectify these errors, this significantly undermines what was otherwise a very well-designed and promising trial.

Despite these weaknesses, and its failure to identify a statistically significant result with respect to its outcomes of interest, the Baranowski et al. trial provides considerable insight into key theoretical frameworks for designing an effective game. The reported successes of their pilot study that inspired the trial suggest that, while their intervention was unsuccessful, their frameworks are useful models for building an effective serious game. They relied on Self Determination Theory (which states that autonomy, competence, and relatedness lead to intrinsic motivation)[5] and Social Cognitive Theory (which highlights the effects of an individual's interaction with their environment, as well as the need for self-efficacy in order to alter behavior)[6,7] to develop key features of the games in hopes that participants would be motivated to play the game, change behaviors, and practice self-control. These are key theoretical frameworks for establishing a link between the game and the behaviors we hope for participants to develop. Furthermore, Baranowski et al. used games that change in response to player's input, which, according to the Elaboration Likelihood Model, will increase player's interest and mental

investment in the game. This model further suggests a utility for incorporating a patients' own diabetes metrics, as suggested by the DAILY trial.[3]

Other Study Designs Evaluating Videogames and Diabetes in Children and Adolescents

Given the limited selection of systematic reviews and RCTs regarding this subject, there is still much to be learned by briefly discussing some of the published pilot studies that provide insight into the relationship of videogame interventions and T1D management. As a key example, a 2016 study by Joubert et al. called the LUDIDIAB pilot study conducted in France used a game called *L'Affaire Birman* (Mr. Birman's File) in an attempt to improve carbohydrate-counting and insulin-titration skills in adolescents with T1D.[8] For this study, 47 participants with T1D aged 11-18 were assigned to play this game in which they had to manage the T1D of the main character while conducting a playful investigation. Game use was, again, unstructured without a recommended dose, although participants were encouraged to play the game to completion. During the study, they also were seen for routine three-month follow-up visits, according to usual T1D standards of care. The study lasted for nine months overall, with data measurements carried out 1-3 months prior to starting the game, 1-2 weeks after starting the game, and six months after free use of the game. Primary outcome was scores on the PedCarbQuiz (PCQ), a validated questionnaire that assesses skills in counting carbohydrates and titrating insulin. Secondary measures included scores on the Diabetes Self-Management Profile (DSMP), HbA1c, and a 10-point Likert scale evaluating desire to modify self-care behavior.

Children in the study reported having played the game 3.3 ± 2.8 times, with 60% able to successfully describe the end-of-game scenario. After six months, the 38 participants who completed the LUDIDIAB study (though not necessarily the game) did show an increase in PCQ scores (31.6 ± 4.9 at baseline, 36.0 ± 4.0 at 6 months; $p < 0.05$). Subgroup analysis of participants whose PCQ scores increased the most ("high effect" group defined as > 8.33 point

increase, the median value of change) suggested that those with poor control initially were more likely to have a high effect (HbA1c in the high effect group was 9.0 ± 1.4% vs 7.8 ± 0.9% in the low effect group; p-value = 0.006). There were no significant changes detected in the secondary outcome measures. Notably, however, these changes in competency did not correlate with desire to modify self-care behavior: the mean score for desire to modify self-care behavior was only 1.4 ± 1.9 (out of 10). This speaks to the importance of using the theoretical frameworks discussed previously to impact participants' self-efficacy and actual behavior change. Additionally, the durability of the measurable effect to six months with just a few bouts of gameplay is impressive; if this were to be combined with game features that are more able to motivate behavioral change, this could enable real clinical differences to be achieved.

Klingensmith et al. tested the accuracy of the Didget system, which enabled participants to connect their blood glucose meters to a separate gaming device and obtain points for having measured their blood glucose.[9] While this study was primarily designed to evaluate the technical machinery involved and assure the Didget system was viable for use as a blood glucose monitor, a few notable conclusions were reached. 147 patients ages 5-24 from four clinical sites in the USA were given this system to use for 3-5 days and, in addition to comparing its accuracy with previously validated glucose monitoring technology, were asked several questions regarding their opinion of the device. 96% reported liking the system, 75.4% indicated that they "agree" or "strongly agree" that it would help build good habits, and 58.6% said that they "agree" or "strongly agree" that it would motivate them to monitor their blood glucose more regularly. While this study did not have a control group, was very short-term, and was not designed with any robust means of measuring psychological or behavior change associated with the intervention, it does highlight that connecting videogame technology to glucose monitoring is

something patients are interested in and that they feel as though it would be helpful. Engaging the patient in their own care is a critical aspect of any diabetes management program, so this data should not be overlooked.

Insulot was a cell-phone based game built to resemble a slot machine used by Aoki et al. to teach patients the relationship between blood glucose, food choices, and insulin dosages.[10] While this game was not studied extensively, Aoki et al. described briefly a small test of 30 subjects with T1D, ages 12-24, at a Japanese summer camp who utilized the game. At the end of the camp, participants were given a 13-question survey to evaluate the game (where a response of one signified significant disagreement, whereas a response of seven indicated strong agreement). The results showed that participants agreed that the game was interesting (5.57 ± 0.22) and more than 80% of the participants agreed the game was useful as a learning tool (5.44 ± 0.29). Aoki et al. also performed a similar study using Nintendo GameBoy instead of cell phones in 2004 with three additional games: *Egg Breeder*, *Detective,* and *Buildup Blocks.*[11] 58 participants found these games to be relatively fun and useful over the course of a 1-week summer camp. No additional data was ascertained regarding specific outcome measures. While these studies do not provide any actionable data, owing to short duration, lack of control group, and absence of diabetes-specific outcome measures, they do illustrate that people with T1D can be engaged in simple cell phone and handheld-based interventions. If principles from the more comprehensive studies evaluated above are incorporated, the cell phone and other handheld devices can be powerful tools that are accessible to more participants than a formal videogame system.

The DeShazo review and the additional studies reviewed in detail above provide the most robust insight into the relationship between serious videogames and improving control of T1D in

adolescents. Notable conclusions drawn from this review include the utility of involving patients' own data in the course of game play, the importance of building on known theoretical frameworks to effect behavioral change, and the potential for these games to influence a variety of diabetes-related outcomes. These outcomes include self-efficacy, glucose monitoring frequency, diabetes-specific knowledge, and frequency of hyperglycemia. Connecting these principles into a single unified trial, coupled with increased specificity of instructions in terms of videogame "dose," would advance the literature surrounding this subject and has the potential to positively influence the care of adolescents with T1D. Additionally, there is a wealth of additional information and research that connects serious game play to improved outcomes in other disease processes. The studies below are not intended to be a comprehensive review of all videogame-related disease interventions for adolescents; rather, the studies selected further inform our methodology as it pertains to use of videogames for the proposed study and highlight many of the possible benefits we hope to achieve.

Selected Videogame Interventions for Other Disease States in Adolescents

In 2013, Hieftje et al. performed a systematic review of the literature and were able to identify 19 studies, including the Brown et al.[2] study outlined previously, that tested the ability of videogames to promote specific behavior changes.[12] Upon detailed analysis, only five of these studies were considered to be high-quality research designs; however, four of these five did indicate statistically significant behavior change associated with the videogame group. These findings emphasize the importance of using high-quality, robust research methods to evaluate future videogame interventions.

The published protocol from an RCT by Fiellin et al. provides a very thorough framework and rigorous design after which we plan to model many components of our videogame intervention.[13,14] In the RCT, Fiellin et al. hypothesized that the game *PlayForward:*

Elm City Stories could be used to delay initiation of sexual activity in adolescents ages 11-14. 333 participants across 12 after-school and school-based programs were recruited, stratified by age group and gender, and randomized to play *Elm City Stories* or other games devoid of content related to the intervention for 60-75 minutes, twice weekly for six weeks. The game was built on established theoretical frameworks including Social Learning Theory and principles of self-efficacy, and it included five minigames that specifically addressed targeted behaviors and skills. Data was collected at numerous timepoints with a primary endpoint of sexual initiation at 12 months from the beginning of the study. Additional data were collected including but not limited to knowledge, attitudes, and intentions to delay intercourse.

The study found that, over 12 months, there were significant improvements in sexual health attitudes (least squares mean 0.37, 95% CI 0.01-0.72, $p = 0.04$) and sexual health knowledge (least squares mean 1.13, 95% CI 0.64-1.61, $p < .001$). While this study was unable to detect a difference in delay of initiation of intercourse between the experimental (94.6%, 95% CI 89.1-97.8%) and control group (95.4%, 95% CI 90.2-98.3%), the researchers proposed several possible explanations. There could have been an unwillingness of participants to disclose their sexual activity. However, Fiellin et al. noted that they optimized disclosure of this sensitive information by using face-to-face data collection and carefully ensuring complete privacy and confidentiality of all participants. While there has been mixed data surrounding the optimal method of collecting sensitive information, the researchers noted that face-to-face collection of data led to fewer skipped questions and that no advantage to web-based data collection has been identified in the literature. Thus, they were confident that they had minimized any potential effect of participants' hesitancy to disclose their sexual activity. More likely, the difference may simply have been imperceptible due to overall low rates of initiating sexual activity in this young

population. Based on the positive outcomes with respect to both health attitudes and knowledge, it is likely that a greater effect on sexual initiation could have been observed under different circumstances, such as a longer trial or with a slightly older population. Any combination of these factors may have limited the ability of the study to detect a measurable decrease in sexual initiation.

Important strengths of this study are its use of established theoretical frameworks connecting Social Cognitive Theory and self-efficacy to patient outcomes, the clearly defined "dose" of the intervention, and the large sample size relative to other videogame trials. Specifically, with respect to the theoretical frameworks, the researchers created the method of a "Game Playbook," outlined by Duncan et al.,[15] to ensure that communication between the research team and the game developers was consistent with the intentions of the intervention. The Game Playbook concept outlines the goals of the game, curriculum content, the targeted variables, the theoretical framework for effecting change, and the game design. It is an iterative process that requires frequent communication between game developers and research scientists in order to allow for optimization of intervention content in an enjoyable manner. Furthermore, the paper clarifies the concept of a "logic model," a graphical illustration of the connection from gameplay to research outcome. This ensures all parties involved in the research are working effectively towards the common goal of the primary outcome.

In fact, a 2010 RCT conducted by Tortolero et al. was able to demonstrate that electronic interventions could be effective in delaying sexual activity.[16] 536 subjects in ten middle schools were randomized to a computer game intervention or to be placed in a comparison group. Those in the intervention group completed 24 45-minute lessons across two years in which they interacted in a virtual world, answered quiz questions, discovered fact sheets, etc. They found

that, by 9th grade, 29.9% of those in the control group compared to 23.4% of those in the intervention group (ARR 1.29, 95% CI 1.02-1.64) had initiated sexual activity. The duration of the intervention is a major strength of this study and may have contributed to its ability to detect a statistically significant outcome. Given this finding, in contrast to the 6 weeks used by Fiellin et al., we propose to deliver intervention content for the entire 12-week period between study enrollment and primary outcome measurement. One caveat, however, is found in data from the *PlayForward* trial published by Montanaro et al.[17] The data revealed that it was the number of levels completed, not the amount of time spent playing the game, that was most strongly correlated with increased knowledge (at three months, R^2=.528, p = .001 for correlation between levels beaten and knowledge compared to R^2=.205, p = .03 for correlation between time played and knowledge). As such, we plan to stretch the gameplay schedule initially utilized by Fiellin et al. (twice weekly for six weeks) to once weekly for 12 weeks. This allows us to perform the study over a 12-week period, consistent with other interventions targeting HbA1c.

Another interesting model to consider when planning a videogame intervention study for T1D is provided by Kato et al. in a study evaluating the ability of the game *Re-mission* to increase adherence to cancer treatment regimens.[18] As in diabetes, where there is a need to perform daily activities (e.g. insulin injections, blood glucose monitoring), cancer patients need to engage in specific behaviors (e.g. taking a prophylactic antibiotic or their chemotherapy dose) that can be instantaneously unpleasant but critically important. In this multicenter RCT, 371 patients ages 13-29 were randomized to the game *Re-mission*, in which participants control a nanobot to destroy cancer cells using tools such as their daily antibiotic, or an otherwise similar game with no cancer-related content. Of note for our study, 324 of these 371 participants were

adolescents aged 13-18. Those assigned to the intervention played for one hour per week for three months, as we propose for our study.

At the conclusion of the trial, the treatment group was compared to the control group with respect to their respective cancer regimen, compliance with dosing of trimethoprim-sulfamethoxazole (measured by electronic pill counting) or 6-mercaptopurine (measured by blood levels of metabolites). The treatment group was found to have complied with 62.3% of antibiotic doses compared to 52.5% in the control group ($p = .012$). Similar results were identified in mixed-effect linear model analyses of log-transformed 6-mercaptopurine metabolite concentrations (increased metabolite concentrations in the treatment group, $p = .041$). This highlights the ability of a game to encourage specific daily behaviors, even if unpleasant, in ways that other forms of treatment cannot easily mimic.

One flaw in this study, however, was the adherence to the intervention, particularly with low use in the African American subgroup ($p = 0.0086$). This can be a concern for any videogame intervention; if the game content is not applicable or relatable to the participants' life experiences, culture, or interests, they may not engage in the intervention and thereby be unable to benefit from it. Lu et al. addressed this in a novel study to determine whether story immersion in a videogame has a measurable effect on health outcomes.[19] They used *Escape from Diab*, in which none of the playable characters were Caucasian, to evaluate the effects of game play on several measures of activity, food choices, and healthy behaviors. 153 participants, ages 10-12, were randomized in a 2:1 ratio to play the game or to a control group. They played for 9 40-minute sessions and were given questionnaires to assess story immersion, food preferences, and self-efficacy.

Ultimately, this study produced a few notable findings: first, the story immersion did indeed differ across ethnic groups ($F = 9.8$, $p < 0.01$). The average story immersion score for Caucasian youth was 36.5 ± 1.3, while in African-Americans the score was 44.0 ± 1.4 and in Hispanics the score was 43.4 ± 1.5. The researchers surmised that this was because there were no playable Caucasian characters. Critically, this story immersion score was positively correlated with participants scores for fruit/vegetable preference ($r = 0.27$, $p = .014$), water motivation ($r = 0.29$, $p = .006$), vegetable self-efficacy ($r = 0.24$, $p = .027$), and physical activity self-efficacy ($r = 0.32$, $p = 0.03$). While this study has several weaknesses, including use of some unvalidated scales for its outcome measures and lack of ability to detect any causal relationships, it lends credence to the idea that participants should be able to imagine themselves inside the game situation if positive results are to be seen. Coupled with Kumar et al.'s findings that utilizing a patient's own blood glucose levels can be associated with videogame success,[3] which will impact the mechanics of game play, we also propose using customizable avatars that can be made to look like any of our potential participants. These two factors will allow our participants to feel more immersed and personally connected to the story of the game; in turn, we hope based on previous literature that this will lead to improved outcomes.

Finally, a small pilot study from Pentz et al. using a series of mini-games to provide education about cigarettes, e-cigarettes, and other tobacco products, demonstrates an important principle that is relevant to our proposal.[20] In this study, 80 subjects were assigned to play the mini-games for 60 minutes weekly for four weeks. This videogame intervention was able to improve knowledge ($t = 4.70$, $p < .001$), risk perception ($t = 3.49$, $p < .001$), and negative health beliefs ($t = 2.56$, $p < .05$) surrounding e-cigarettes. Mediational pathway analysis demonstrated that there was not a significant correlation between knowledge about these devices and intentions

to use them in the future. Instead, all changes in the participants' intentions could be explained by changes in their beliefs ($p < .001$). While this is a small study and not necessarily powered to demonstrate causality, it highlights a potential explanation for why some videogame interventions have had minimal effect: as discussed in the review of diabetes articles by DeShazo et al.,[1] too many games focus only on developing knowledge via didactic content delivery. However, as many of the non-diabetes videogame interventions have shown, these games must build upon theoretical constructs for enacting behavioral change such as Social Cognitive Theory (building self-efficacy), Self-Determination theory (developing intrinsic motivation), and principles of goal setting and empowerment. As Pentz et al. highlighted, a successful intervention must go beyond just increasing knowledge, and these established frameworks provide a mechanism by which participants' beliefs can be dynamically altered by the intervention.

CGM Uptake and Effect on HbA1c

Having reviewed the relevant research as it pertains to our intervention, it is important to briefly review a selection of the extensive research that has been performed surrounding CGM use and its effect on HbA1c. Cross-sectional data published in 2019 by Foster et al. from the T1D Exchange Registry (T1DX), a large sample of patients with T1D taken from endocrinology clinics across the USA, illustrates the scope of the problem in terms of both high HbA1c and low CGM use in the adolescent population we propose to study.[21]

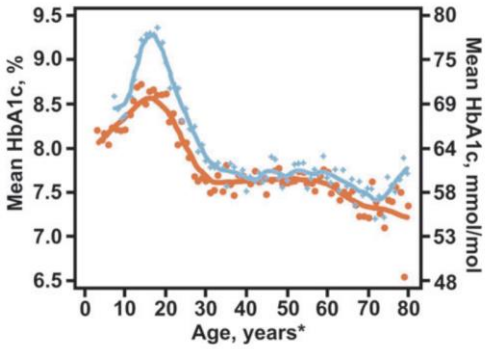

Figure 1: Mean HbA1c by age in the T1DX. From Foster et al.[21] The lower orange line represents data from 2010-2012, while the higher blue line represents data from 2016-2018.

As seen in Figure 1, the highest mean HbA1c of any age group is in our adolescent population, with Foster et al. reporting highest mean score of 9.3% in the 15-18 year-old age group. Furthermore, this article includes cross-sectional data regarding CGM use: 31.5% of 1313 6-12 year-old children, **18.3%** of 3183 13-17 year-old adolescents (our intended study population), 17.3% of 2445 18-25 year-old young adults, and 31.9% of 2143 26-49 year-old adults. Finally, to connect the two points, the study found that HbA1c is significantly lower in those using CGM alone or in conjunction with continuous subcutaneous insulin infusion systems (CSII) compared to those using standard self-monitored blood glucose measurements (SMBG) and manual insulin injections alone ($p < .001$ after adjusting for age, duration of diabetes, race, income, and SMBG frequency). While this registry data has some limitations—as cross-sectional data, it cannot provide evidence of a causal association, and the nature of the registry may disproportionately include patients with better access to diabetes care than the general population—it still suggests a potential target for an intervention.

Additional cross-sectional data collected by DeSalvo et al. focused on the <18 year-old population and expanded the data collection to include the DPV, a German/Austrian registry similar to the T1DX.[22] They reviewed data from over 28,000 patients collected at two

timepoints, in 2011 and 2016, with a specific focus on CGM use and its possible effect on HbA1c. They noted that CGM users in the T1DX had lower mean HbA1c levels at both time points (7.9 vs 8.6 in 2011, $p < .001$; 8.1 vs 9.0 in 2016, $p < .001$). The 2011 mean HbA1c levels of patients in the DPV were not different with respect to CGM use; however, the authors noted that widespread CGM insurance approval had not yet occurred in Germany in 2011. In 2016, the difference in mean HbA1c among DPV members was statistically significant (7.6 vs 7.9, $p < 0.001$). Finally, in 2016, CGM users in both groups were more likely to achieve established glycemic target goals than non-users (56% vs 43% in the DPV, $p < .001$; 30% vs 15% in the T1DX, $p < .001$). Notably, the mean HbA1c levels and the difference associated with CGM use were both greater in the American population of the T1DX, for whom we are proposing our intervention. Again, as cross-sectional data, this study does not provide evidence of a temporal correlation between CGM initiation and improved HbA1c. To obtain that evidence, we reviewed the results of several additional studies.

Floyd et al. performed a comprehensive comparative analysis using data collected from 14 RCTs with a total sample size of 1188, each of which compared CGM users to SMBG control groups.[23] Their data included a population with a mean age of 29.0 ± 14.3 years and a baseline HbA1c of 8.3 ± 0.8%. After combining and analyzing the data from all 14 RCTs, they found that regular CGM use was associated with a change in HbA1c of -0.3% (95% CI -0.2 to -0.4, $p < .0001$). While this differs significantly from the population we propose to study, it does establish a general basis for believing the causal effect of regular CGM use on improved HbA1c. This measured effect size is likely to be slightly lower than what we may see in our population due to several factors—notably, a lower baseline HbA1c than our population, control groups utilizing aggressive SMBG regimens, and the authors' inclusion of studies evaluating

retrospective CGM use (a method that allows for management changes by clinician but does not inform daily decision making for the patient).

A 2008 RCT from the Juvenile Diabetes Research Foundation CGM Study Group, published by Tamborlane et al.,[24] in addition to two follow-up studies using the same population,[25,26] provides even more specific data that is integral to the statistical expectations for our study. In the Tamborlane study, 322 patients at multiple centers were randomized to CGM or to SMBG and given intensive training on appropriate use of the devices. Participants were stratified into 3 age groups: 8-14, 15-24, or >25 and followed for 26 weeks (6 months). At the end of the study, HbA1c was measured as the primary endpoint. They identified a mean change of -0.53% (95% CI -0.71 to -0.35, $p < .001$) in the adult (>25) age group, but no significant change in the 8-14 or 15-24 groups. However, a key data point highlights the most important limitation of the study: CGM use, while part of group assignment, was not mandated or enforced as part of the trial. In fact, while 83% of the >25 group was using CGM at least 6.0 days/week at the end of the study, only 30% of the 15-24 group and 50% of the 6-14 group was using the CGM with this consistency. This concern was further validated by, at the end of the study, initiating CGM use in the control group without formal training or dedicated follow-up and measuring their HbA1c after six more months.[26]

This follow-up study, performed to simulate real clinical care environments, had predictable results given the data outlined above. There was no significant change in mean HbA1c in either the 8-14 (n=47) or 15-24 (n=56) age groups. At the end of the study, the average use of the CGM was 3.3 days/week in the 15-24 group and 3.7 days/week in the 8-14 group.

In contrast, Beck et al. further analyzed the data from the CGM users in the initial JDRF CGM Study Group trial with an important question in mind: how do the results change with

increasing CGM use?[25] Using a cut-off of minimum CGM use of 6.0 days/week at the end of the study, Beck et al. analyzed the 232 patients in the original treatment group with respect to other factors that correlate with successful use of the CGM. This article found that age (highest in >25 group, $p < 0.001$) and frequency of pre-CGM blood glucose monitoring ($p < 0.001$ in all age groups) were the strongest determinants of future CGM use. Furthermore, increased "time-in-range" (defined as blood glucose from 70-180 mg/dL) lead to more CGM use at the end of the trial ($p = .002$). Most importantly, their data showed that in all age groups, the change in HbA1c for those using CGM at least 6.0 days/week was significantly greater than any other group (-0.45 to -0.75 in all groups; $p = .002$ for 15-24 group, $p < .001$ in 8-14 group).

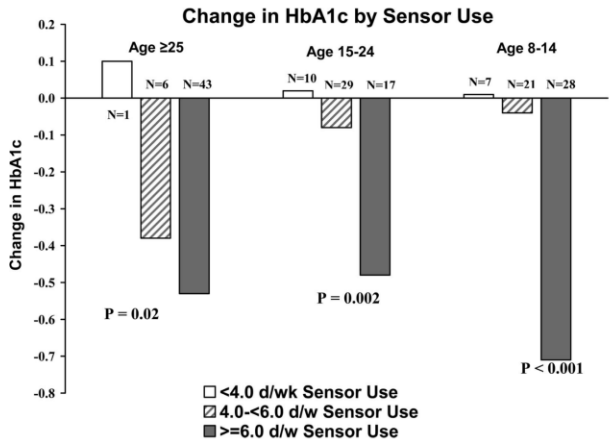

Figure 2: Change in HbA1c by Sensor Use. From Beck et al.[25] Data highlights significant effect size associated with >= 6.0 d/w CGM use.

This data provides strong support for causal associations of the findings in the cross-sectional data from Foster et al.[21] and DeSalvo et al.,[22] strengthening the hypothesis that an intervention able to promote CGM use ≥6.0 days/week would be able to produce a change in HbA1c of at least 0.5%. There are, of course, limitations to the study—this analysis was a post-hoc analysis, so the initial study was not designed to detect this specifically. Furthermore, the original design of the study did not emulate real-life clinic conditions (hence the need for the

follow-up study on the control group published by the JDRFCGM group). However, if able to recreate this ≥6.0 days/week CGM use in our study population, we predict a similar effect can be elicited. We predict CGM use to be the primary proximal event leading to our distal outcome of HbA1c reduction.

Effects of Insulin Dosage Timing

Beyond CGM use, however, we intend to include content in the game that will help adolescents recognize the importance of dosing insulin prior to meals. Data from the T1DX, evaluated in Peters et al., provides clear reason to believe this is a valuable intervention.[27] 34% of adolescents ages 12-18 report regularly dosing their insulin postprandially.[27] Among 12,450 patients <18 years of age, Peters et al. found that children and adolescents who take insulin "immediately before meal" or "at least several minutes before meal" have significantly lower HbA1c levels (8.44 ± 1.69 vs 8.69 ± 1.48, $p < .0001$) and use less total daily insulin per kg of body weight (1.07 ± 0.69 vs 1.16 ± 0.72, $p < .0001$) than children who reported taking insulin "during meal" or "after meal" on their T1DX entrance surveys. They did note, incidentally, that preprandial insulin users were statistically more likely to have had a severe hypoglycemic event (4% vs 6%, $p = .0071$) or a DKA event (8% vs 9%, $p = .0243$) in the last 12 months. This does raise some concern for safety of preprandial dosing; however, this data—as noted previously—is not able to establish causality. It may be, for example, that children who have had these adverse events are more likely to be under stringent medical care and thereby more likely to have had preprandial insulin dosing recommended to them. Additionally, safety risks can be mitigated by use of CGM as users will be alerted of both low and high blood glucose levels.

A pair of studies conducted by Danne et al.[28] and Cobry et al.[29] sought to further characterize the importance of insulin timing. Danne et al. recruited 76 patients (ages 6-12 n=42, 13-17 n=34) and randomized them to conduct six weeks of administering insulin immediately

prior to a meal, then six weeks of administering insulin immediately after a meal (within 30 minutes of completion), or to complete these two six-week blocks in reverse order. Their study was powered to determine whether postprandial administration would be unsafe compared to preprandial administration; when the study was complete, they found no significant difference in safety outcomes among the two groups. However, they did record seven-point blood glucose profiles (before and two hours after each meal, plus at bedtime) and noted that there were higher post-breakfast glucose levels (37.5 ± 12.6 mg/dL, $p = .016$) associated with postprandial insulin use. There was also a trend toward higher pre- and post-dinner blood glucose values, but these were not statistically significant ($p > .05$). HbA1c was also measured and found to be similar at all time points (0 weeks, 6 weeks, 12 weeks) in both groups. However, given the nature of HbA1c as an estimation of 3-month blood glucose, these values do not isolate the effect of the intervention on HbA1c and do not detract from the data described by Peters et al.[27] Another interesting finding the authors highlighted is that, despite showing non-inferiority with respect to safety outcomes, parents were hesitant to recommend the postprandial regimen to others after completing the trial. Unfamiliarity with the regimen was cited by the authors as a possible explanation, but they also noted that parents complained of frequently forgetting postprandial insulin doses for their child. Even if there was no other data surrounding the benefit of preprandial insulin dosage, the possibility of forgetting to administer insulin is reason enough to encourage preprandial boluses.

That said, Cobry et al. effectively illustrated the immediate beneficial effects of preprandial insulin dosing using frequent blood glucose measurements in a controlled environment.[29] 23 subjects using CSII, ages 12-30 (age <18 n=11), completed three visits in which they would be given a meal and instructed to give an insulin bolus 20 minutes prior to

eating ("PRE" group), at the start of the meal ("START" group), or 20 minutes after eating ("POST" group). All participants were given a random order in which to complete these three conditions. Blood glucose was measured every 30 minutes for four hours after starting the meal. Measures of insulin effect included blood glucose area-under-the-curve (estimating a relationship between time spent and elevation of blood glucose), maximum blood glucose, and blood glucose at one hour and two hours post-meal. Blood glucose levels were similar prior to the meal in all conditions ($p = 0.8350$), but the PRE group showed improved blood glucose according to every measure calculated. Specifically, at 60 and 120 minutes, the PRE group had lower blood glucose (180.3 ± 66.4 at t=60min, 176.3 ± 70.7 at t=120min) than the START (222.0 ± 58.9 at t=60 min, $p = .0029$; 207.7 ± 48.5 at t=120 min, $p = .0294$) or the POST (235.7 ± 46.6 at t=60min, $p < .001$; 205.8 ± 50.7 at t=120min, $p = .0408$) groups. The PRE group also exhibited the fewest blood glucose readings above 180 ($p < .0001$ compared to each other group). While this is a small sample, it clearly illustrates the benefit that can be obtained from dosing insulin preprandially. We chose to review this study in detail because of its population overlap with our proposed study; however, its findings were also replicated in an adult population by Luijf et al.[30]

Alcohol Use in T1D

As a last area for intervention, we intend to address alcohol-related risk reduction as part of the curriculum content of our proposed videogame. We believe this to be a salient topic to include in the videogame given its conceptual proximity to previous game designs, such as *Play Forward: Elm City Stories*, upon which our methods have been developed. Additionally, the use of alcohol is relatively prevalent among adolescents and is known to affect many aspects of decision making and judgment.[31] Given the importance of decision making and conscious monitoring in the treatment of T1D, this would be a topic worth including even in the absence of

a direct correlation with metabolic outcomes. However, data from the DPV registry further supports its inclusion as a part of our curriculum.

Hermann et al. used data from this registry to analyze the relationship between alcohol use, glycemic control, and diabetes-related adverse events.[32] Data was collected for 29,630 patients between the ages of 10-30, the majority of whom were <18 (72.3%, median age 17.0, IQR 14.9-18.3). Using self-reported alcohol consumption data, this study found that HbA1c was significantly higher ($p < .001$) in those meeting diagnostic criteria for at-risk drinking (9.3 ± 2.3) than in those who abstain from alcohol (8.4 ± 1.9) or those who are low-risk drinkers (8.6 ± 2.0). Furthermore, the same at-risk alcohol use group had significantly more episodes of DKA (18.9 per 100 person-year, 95% CI 11.6-30.6) than the abstinent (6.4 per 100 person-year, 95% CI 6.0-6.8) or low-risk (7.5 per 100 person-year, 95% CI 6.5-8.8) groups.

As with the registry data reviewed previously, this data is unable to establish causality. It does support a strong trend in this association, albeit one that may potentially be mediated by other factors. At-risk drinking may be a behavior that those with suboptimal self-care tendencies may engage in more frequently than other groups. Additionally, as the data presented was self-reported, it is possible that those who are otherwise more vigilant (reflected in their better metabolic control and decreased incidence of DKA episodes) are less willing to confide in their health care providers regarding their alcohol use. Further, data collected in the German/Austrian registry (where, notably, legal drinking ages do not align with our American population) is not necessarily generalizable directly to our study. However, the causality of this association is not critical to its inclusion in our proposal; given the strength of the association and the independent salience of alcohol-related risk reduction in an adolescent population, we feel that this will provide sufficient benefit to our population to merit inclusion in our game design. While not a

primary outcome of our study, the additional curriculum will provide extra variety to the game and will help give participants insight into the relationship between alcohol and diabetes.

Potential Confounding Variables

As we are proposing an RCT, we hope to limit any possible effects of confounding through the randomization process, ensuring that the treatment group and control group are similar at baseline with respect to all relevant variables. We will exclude participants already using CGM at least 6.0 days/week in the last three months, as this is the primary means by which we predict to achieve our effect on HbA1c. Other demographic and clinical characteristics for which we would adjust in statistical analysis, if needed, are outlined in detail in chapter three of this proposal. Potential confounders including gender, race, socioeconomic status, and baseline diabetes characteristics have been identified primarily using both the videogame studies and CGM studies outlined above. We rely heavily on data from DeSalvo et al.,[22] Tamborlane et al.,[24] and Beck et al.[25] to identify diabetes-related confounders as these studies provide invaluable information with respect to CGM use. The demographic variables we plan to characterize are consistent with most of the trials reviewed, but extra note is made of results in Lu et al.[19] and Kato et al.[18] (regarding the effects of race) and of Fiellin et al.[13] (regarding the effects of both age and gender) as their findings suggest that these demographic characteristics may, in fact, be true confounding variables with respect to the potential benefits of videogame interventions.

Relevant Methodological Considerations

Much of the justification for our proposed methodology is contained in the literature previously reviewed. In chapter three, we will outline these methods in detail; however, there are several additional studies that influence our methodology that merit inclusion in our literature review. With respect to use of a videogame as a medium for intervention content delivery, the models set forth by Thompson et al. were instrumental in developing our game's logic model.[5]

This study relied on the theoretical frameworks discussed earlier in the literature review, primarily Social Cognitive Theory and Self Determination Theory, to identify a few causal pathways. First, knowledge leads to skill development, thereby leading to self-efficacy. This is necessary for promoting behavior change as well as self-regulation (which they further clarify to include goal setting, monitoring, and problem solving). Second, this study cites an idea from Self Determination Theory that autonomy, competence, and relatedness (of a person to the behavior in question) independently must be achieved in order to enhance intrinsic motivation. These models provide basic frameworks that allow us to build key intervention content for our proposal.

Additionally, several studies contributed helpful outcome measurements that we plan to use at the initiation and completion of the study. Messer et al. developed and validated two scales, BenCGM and BurCGM, that evaluated adolescents' perception of both benefits (BenCGM) and burdens (BurCGM) associated with CGM use.[33] Importantly, both were correlated with self-efficacy (positive correlation for BenCGM, $p = .001$, negative correlation for BurCGM, $p < .001$) as measured by the Self-Efficacy for Diabetes (SED) scale. This scale was identified by Rasbach et al. as the most common measurement of diabetes-related self-efficacy after an integrative review of 45 different articles using ten different measurement scales.[34] Van Allen et al. further evaluated the SED and its three sub-scales, SED-D (diabetes), SED-M (medical), and SED-G (general) in a population of 125 10-16 year-old adolescents with T1D.[35] The SED-D was identified as having the most consistent and statistically significant correlation to HbA1C ($r = -0.56$, $p < .001$) when compared to SED-M ($r = -0.20$, $p < .05$) or SED-G ($r = -0.22$, $p < .05$). With this data in mind, we intend to use questions from both the BenCGM and

BurCGM scales to develop CGM-related game content, and to measure participants' SED-D scores at the completion of the study.

Messers' scales were also correlated with measures of diabetes-related distress, as measured by the PAID-PEDS scale (Problems Areas in Diabetes), a scale validated by Markowitz et al.[36] McGill et al. found that, in a prospective cohort study of 120 8-18 year-olds with T1D, high scores on this PAID-PEDS scale were associated with infrequent CGM use (38 ± 26 in the 0-2 days/week group, vs. 27 ± 22 in the 3-7 days/week group; $p = .03$). Given this correlation, we intend to measure diabetes-related distress at the beginning and end of the study. However, Markowitz et al. also noted the validation of another, slightly different form of the PAID scale called PAID-T, validated for teens aged 11-19 by Weissberg-Benchell et al.[37] As the two scales are very similar in content, we plan to utilize the PAID-T scale because it was validated in a population more closely mirroring our own.

Conclusion

Collectively, the studies reviewed in this chapter provide the basis for our hypothesis. Many of these studies illustrate the work which has previously been done with respect to videogame interventions for adolescent pathologies, while the remainder detail key components of our proposed methodology and why we expect our intervention to be effective. We believe that our predicted effect of decreasing HbA1c can be achieved by building upon established theoretical frameworks for behavior change, primarily through promoting the use of CGM. Additional content will support preprandial insulin bolus and encourage alcohol-related risk reduction. If successful, this intervention would have the opportunity to positively influence the management of T1D in adolescents, leading to decreases in diabetic complications and, ultimately, the significant morbidity and mortality of this disease. Additionally, the studies reviewed above

provide extensive justification for and models of the methods that we plan to use in this study.

These methods are outlined in detail in chapter 3 of this proposal.

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Chapter 3 – Study Methods

Study Design Overview

We propose a randomized, controlled trial to be conducted over a period of two years following the completion of the videogame intervention development. Based on the theoretical frameworks discussed previously, we will work with our game development team to build a videogame that empowers participants to set goals regarding their diabetes care and to make choices—such as using CGM consistently, dosing insulin before meals, and reducing risky behaviors related to alcohol use—that will help them to achieve their goals. As in other studies, the game will be rooted in principles of Social Cognitive Theory and Self Determination Theory in hopes that a tangible effect on behavior change and personal motivation can be achieved. Participants in the study will be consented, enrolled, and administered questionnaires to collect data on their demographic characteristics as well as several baseline diabetes-related measures (see Table 1). Parents will also be consented given that all participants will be less than 18 years of age (see Appendix B for consent forms). If the participant does not already have a CGM, they will be prescribed a CGM by their diabetes care provider. Participants unable to obtain a CGM through this pathway (due to cost, insurance concerns, or any other reason) will be loaned a CGM system to use for the duration of the study. Baseline HbA1c will be collected from the electronic medical record. All participants will be given $20 in cash as incentive for completing the study questionnaires and personal access to the videogame at the completion of the study.

Study Population and Sampling

This study will target adolescents, defined as individuals of ages 13-17 on the day of study enrollment, who have been diagnosed with T1D for a minimum of 1 year. We plan to recruit participants from pediatric endocrinology clinics in the Yale-New Haven Health (YNHH) system in Connecticut as well as the Intermountain Healthcare (IHC) system in Utah. These sites were chosen as they represent the expected physical locations of both the first author (Utah) and

the principal investigator (Connecticut) at the proposed start of the study, in January 2021. We will utilize convenience sampling of volunteers and use a rolling enrollment period until the calculated sample size of 150 is achieved. If we have not yet reached this sample size by 12 months, we will extend our recruitment to include other patients in New York, Massachusetts, Rhode Island, or Connecticut who participate in the T1DX registry and continue recruiting for an additional six months. All enrollment will be completed by 18 months from the completion of game development, allowing us to conclude all data collection within two years from initiation of the study.

Inclusion criteria for the study include age (13-17), documented diagnosis of type 1 diabetes mellitus, diabetes duration of at least one year, and participation in at least twice-yearly endocrinology follow-ups. Exclusion criteria for the study include consistent CGM use ($\geq$ 6.0 days/week for the last 30 days) prior to study enrollment, patients who have had more than one hospitalization for DKA in the past six months, and patients with additional medical conditions that require disease-specific diet or lifestyle adjustments, as determined by their diabetes care provider.

Intervention and Control Groups

At the time of enrollment, participants will be stratified by site (Utah or Connecticut) and randomized to the treatment or control group using a random number generator. Concealment of the allocated randomization will be performed using an off-site centralized allocation service that is not affiliated with the study. Participants will be randomized in a 1:1 fashion to play the intervention videogame on an iPad provided by the study personnel or to play other unrelated iPad games for 60 minutes, once weekly, for 12 weeks. They will be brought to designated study sites at each study location, where the iPads will be kept, and will play the assigned game under

the supervision of a trained research assistant. This research assistant will monitor that participants are able to access the game and that they continue to play for the assigned time; the intervention application will be designed such that the iPad locks into the game application for 60 minutes to prevent participants from using other applications. Outside of gameplay, both groups will be instructed to follow up with their diabetes care provider at three months and six months from study enrollment to retest their HbA1c levels. They will be instructed to log once daily, at breakfast, whether insulin was given prior to or after the meal. Additionally, they will be loaned a CGM if needed to complete the study; however, no additional instructions beyond the care provider's typical CGM-related counseling will be given to either group as to how frequently to use the device as it pertains to the study. If sufficient research staff is able to be obtained for the project, the trained research assistant supervising videogame play will not be involved in any data collection or medical record review. Ideally, all research personnel administering questionnaires, collecting demographic data, and reviewing medical records to collect HbA1c data will be blinded to group assignment. If this is not feasible, data will be deidentified before being given to a blinded outcome assessor to tabulate the overall results of the study.

Subject Protection and Confidentiality

The research protocol will be submitted to and approved by the Institutional Review Board (IRB) at YNHH and at IHC prior to recruiting or enrolling any participants for this study. Participants and their parent or guardian will both be asked to consent to the policies and required activities outlined in this proposal. The confidentiality agreement included in the consent forms in Appendix B will be reviewed with both the participant and their primary caregiver. No personal information will be stored on the gameplay iPads or in our data collection files except for a single file, kept separately from other data storage, that will allow us to connect

HbA1C from the electronic medical record with the patient's randomization assignment. The remainder of the data will be stored with a unique user ID for each patient. All staff assigned to review HbA1c from medical records will complete the associated health care system's mandatory Health Insurance Portability and Accountability Act (HIPAA) training and will sign agreements not to view any data that does not pertain to the study. CGM data will be immediately deidentified and saved only in secure spreadsheets with the participant's unique user ID. These sheets will be stored separately from data correlating the user ID with an individual's randomization assignment and accessed only when computing final results of the study. No individual data from the study will be given to the participants' health care teams. Finally, the "find-my-iPad" feature will be activated on all study iPads so that remote data deletion can be performed in the event of a stolen or missing device.

Intervention Content

Our game will consist of an explorable world in which a player's avatar, who will be customizable to look like the study participant, must solve a problem by completing several levels and minigames. The development of the problem-solving and the game's story will be determined in conjunction with game developers and adolescents recruited from the community to test and improve gameplay after the proposal is approved. However, specific content that we definitively plan to include—and the connection of that content to desired behavior change—is detailed in the logic model below. In our initial conceptualization of the game, the base game would enable the participant to enter that day's real-life blood glucose levels and apply them to the avatar to help determine the character's fitness to engage in the levels of the game. If blood glucose is not "in range" (70-180 mg/dL), the player would be able to direct their avatar to take corrective action (to administer insulin or eat a snack) to achieve an appropriate blood glucose level to participate in the next part of the story; the game would then pause automatically with a

reminder for the player to consider taking the same action in the real world. The player could then be guided through certain minigames, taught new skills, and given positive reinforcement by a guide character who would be programmed to match the character's avatar in both apparent gender and race. The game could also feature loading screens that will display "game tips" that also serve as real-life content, such as "If you turn on the CGM in the bottom right corner of the screen, you can correct a high blood sugar before your avatar even notices that they feel sick!" Additional minigames and levels without specific diabetes-related content may also be included in order to help attain a balance between enjoyability and curricular value; in fact, this could have some psychosocial value in that it would reinforce that there is more to the adolescent's life and identity than having T1D.

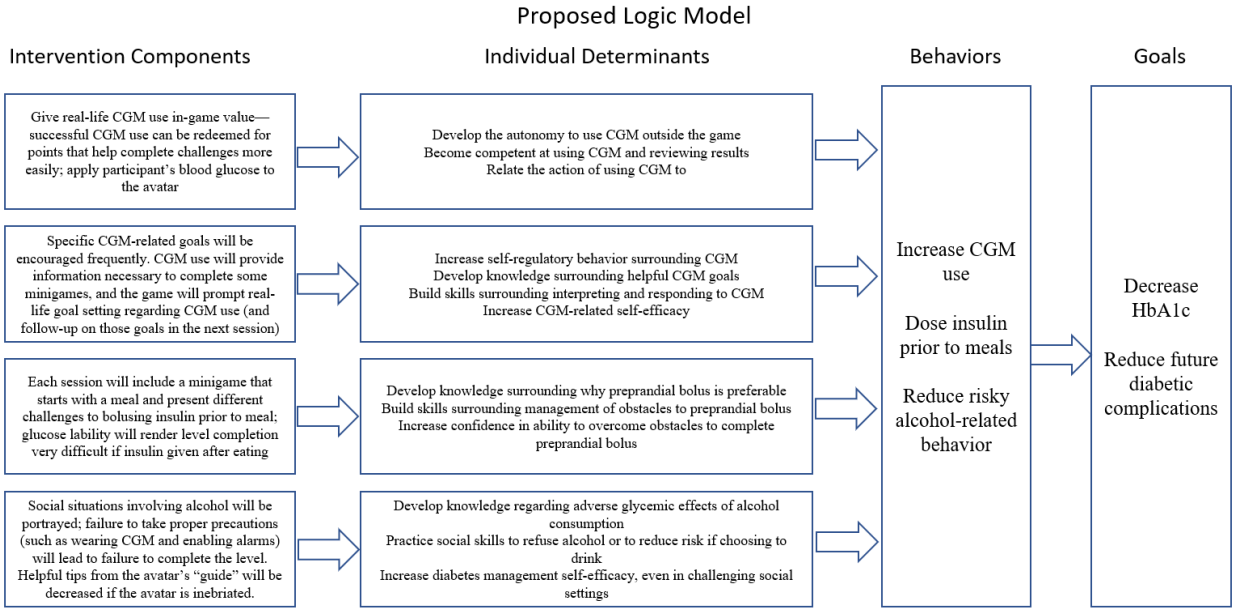

Figure 3: Proposed Logic Model.

Data Collection and Outcome Measures

All outcome measures we intend to collect are highlighted in Table 2. Baseline demographic characteristics, prior CGM use, diabetes duration, insulin pump use, and baseline

questionnaire scores will be ascertained by trained research personnel after consenting the participant and their parent or guardian to enroll in the study. HbA1c will then be obtained from the electronic medical record by the local HIPAA-certified research assistant. After completing the 12 week intervention, participants will have a follow-up appointment with their diabetes care provider, at which time HbA1c will be remeasured. They will then have a session with a research assistant, blinded to treatment allocation, to download CGM data and complete questionnaires, including additional questions regarding incidence of DKA event or other diabetes-related hospitalization or urgent care visits. Finally, at 6 months from enrollment, they will be re-evaluated by their diabetes care provider and HbA1c will be measured once again.

Statistical Analysis

Based on the literature reviewed in chapter two of this proposal, this study will be designed to achieve a sample size of 150 participants. This will enable us to test a two-tailed hypothesis with $\alpha = 0.05$ and power of 80% to detect a clinically significant effect size of 0.5% change in HbA1c[1] at three months from the initiation of the study (see Appendix A for detailed calculation). We plan to test this hypothesis using a student's t-test; however, this assumes that the baseline characteristics identified below in Table 1 are similar between the two groups. Given the limitations of working with a relatively small sample size and large number of potential confounders, there is the possibility that the randomization process does not produce treatment and control groups that are equivalent at baseline in all measured characteristics. In this setting, we would utilize multivariate linear regression analysis if the randomization process does not adequately control for any of these variables. Similar adjustments would be made for the other variables, using multivariate logistic regression in place of chi-square and multivariate ANOVA for the final HbA1c calculation. Finally, we intend to use an intention-to-treat approach to conduct our analysis. That said, if rates of loss to follow up are high, we will also use a per

protocol analysis and compare results with the intention-to-treat approach. This also applies specifically to calculation of the insulin-bolus timing outcome, as it is possible there will be a large quantity of incomplete data (due to participants forgetting to record data) even in the absence of significant loss to follow up. Tables 1 and 2 provide explicit detail with respect to all baseline characteristics and outcome variables we intend to use, including planned statistical tests. Note that, for the outcomes listed in Table 2, all data will be collected at three months except as otherwise specified.

Table 1: Baseline Characteristics of Study Participants. Statistical tests listed in this table will be used to compute a p-value to ensure the treatment and control groups are similar at baseline with respect to each variable.

Characteristic	**Treatment**	**Control**	**Statistical test**
Age	Mean (SD)	Mean (SD)	Student t-test
Gender	N male(%)	N male(%)	Chi-square test
Race Caucasian Black Hispanic Other	 N(%) N(%) N(%) N(%)	 N(%) N(%) N(%) N(%)	Chi-square test or Fisher exact test (if any N<5)
Household Income < $20,000/year $20,001-40,000/year $40,001-60,000/year $60,001-80,000/year $80,001-100,000/year > $100,000/year	 N(%) N(%) N(%) N(%) N(%) N(%)	 N(%) N(%) N(%) N(%) N(%) N(%)	Chi-square test or Fisher exact test (if any N<5)
Prior CGM use	N(%)	N(%)	Chi-square test
Diabetes duration	Mean months (SD)	Mean months (SD)	Student t-test
Baseline HbA1c	Mean (SD)	Mean (SD)	Student t-test
Insulin Pump Users	N(%)	N(%)	Chi-square test
SED-D score	Mean (SD)	Mean (SD)	Student t-test
PAID-T score	Mean (SD)	Mean (SD)	Student t-test

Table 2: Outcome Measures and Planned Statistical Tests.

Outcome	Treatment	Control	Statistical test
HbA1c	Mean (SD)	Mean (SD)	Student t-test
CGM use ≥ 6.0 days/week	N(%)	N(%)	Chi-square test
Adherence to preprandial insulin bolus	Mean % (SD)	Mean % (SD)	Student t-test
Time in BG 70-180 range	Mean % (SD)	Mean % (SD)	Student t-test
DKA episodes per person	Mean (SD)	Mean (SD)	Student t-test
Diabetes-related hospitalizations or urgent care visits per person	Mean (SD)	Mean (SD)	Student t-test
SED-D score	Mean (SD)	Mean (SD)	Student t-test
PAID-T score	Mean (SD)	Mean (SD)	Student t-test
HbA1c at 6 months	Mean (SD)	Mean (SD)	ANOVA for repeated measures

References

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Chapter 4 – Discussion

Study Advantages

This proposal as outlined provides the background and justification for a study that would have many advantages in light of the existing research. As previously noted, T1D is very common and typically is first diagnosed in childhood. Adolescents with T1D have the worst glycemic control, on average, of any age group.[1] This study would provide a way to test the delivery of an intervention via a videogame, a technology used by over 95% of adolescents.[2] These adolescent patients can be challenging to treat because, outside of physiological changes associated with puberty, there are numerous developmental and psychosocial factors that complicate adherence to diabetes regimens. In particular, this age group represents (along with young adults) the group least likely to utilize CGM, one of the most important advances in diabetes care technology of our time. As such, the most important strength of our study is that it uses an adolescent-friendly vehicle—the videogame—to deliver content designed not only to teach the patient why using CGM is effective, but to help them vicariously experience the benefits of CGM through the eyes of their game character and ultimately develop their own motivation to use the device.

Furthermore, while other studies have attempted to use videogames as a content delivery method, this study would be the first to our knowledge to identify a specific behavior—consistent CGM use—that has already been shown to produce a measurable decrease in HbA1C.[3,4] By building this attribute into as many components of the game as possible, we believe our intervention would be very likely to produce a clinically meaningful improvement.

From a methodology standpoint, there are several strengths to the research design. First, the sample size has been specifically calculated to power the study to detect a clinically significant change in HbA1c of 0.5%. Where other studies have been powered to detect changes in more proximal outcomes, such as diabetes-related knowledge or self-efficacy,[5,6] ours would be

equipped to provide concrete data on measurable clinical outcomes. Second, the multicenter design would provide improved generalizability as Utah and Connecticut are demographically very different states, with very different family structures, social norms, and beliefs about health and illness. Third, while blinding the patient is impossible in our design, the careful blinding of the research personnel and the objective nature of our primary outcomes will be sufficient to ensure that the possibility of information bias is minimized. Finally, randomization in conjunction with the use of appropriate multivariate analyses (if necessary) will decrease the likelihood of confounding and allow us to detect the true effect of our intervention.

Limitations

Highlighting these strengths does not eliminate the potential limitations associated with our study design. Two of the primary limitations of the study are the accessibility of the intervention outside of study conditions and the unknown durability of the effect. While we would be able to provide research participants both the technology needed to play the videogame (an iPad) and to monitor blood glucose (a CGM), not every real-world patient will have access to these devices. As such, even if our intervention were to be successful, it is possible that clinicians would be reticent to utilize or suggest it to patients unless they feel confident that the patient is able to afford the needed devices. This could have the potential to increase health care disparities. However, data do suggest that nearly all adolescents live in a setting with a computer, videogame console, or smart phone.[2] As such, we feel that the benefit of such an adolescent-friendly adjunct to treatment outweighs this particular limitation and that clinicians should feel comfortable providing and recommending new technology, such as videogames, to all patients once it has been shown to be effective.

The second key limitation, the durability of the effect, is due to the duration of the study. While we plan to evaluate the effects on HbA1C at 6 months from study enrollment, T1D is a lifelong condition and even the adolescent period we propose to examine far exceeds the six-month study duration. Completion of the game may produce a temporary effect, but if it does not persist to any appreciable extent throughout adolescence, there will be minimal long-term clinical benefit for patients. As such, if this intervention is shown to be effective, it would be prudent to conduct further research following the treatment cohort forward through time, evaluating the effects of a series of booster sessions, or developing additional levels of game play that could age with the patient.

Finally, there are other modifiable factors associated with suboptimal HbA1C in adolescents, such as a high prevalence of depression.[7] While this would be a wonderful inclusion in the curriculum of a videogame for any adolescent population, including those with T1D, attempting to improve symptoms of depression is beyond the scope of our intervention. There is also limited research to support the efficacy of videogames as depression treatment; however, depression-specific curriculum would be a welcome addition to future iterations of the game if our study is successful.

Clinical Significance

T1D is a common disease process that requires lifelong monitoring and, if not well controlled, can lead to neuropathy, nephropathy, arterial disease, retinopathy, or any combination of these sequelae.[8] While effective treatment exists in the form of exogenous insulin, it requires diligent management and nearly constant vigilance for someone with T1D to maintain stable blood glucose levels. While HbA1c and mean levels of control typically level out after age 25-30,[1] treatment of adolescents presents a unique challenge to clinicians. Hormonal and biological

factors are certainly present and do contribute to glycemic lability, but this can be accounted for by providing adequate monitoring—ideally via CGM—and adjusting insulin dosage accordingly.

By developing an intervention that targets adolescents' interests, in the form of a videogame, our goal is that this intervention leads to creation of a tool that clinicians can utilize to connect with their adolescent patients and improve their glycemic control. If shown to be effective, the videogame could be disseminated on a larger scale and clinicians could recommend it to their adolescent patients to promote CGM uptake and other diabetes management behaviors. While it may be tempting to "treat" this challenging population merely by helping them avoid DKA and severe hypoglycemia, and temporarily ignore other consequences, it has been shown that childhood and adolescent HbA1C can be a marker of future complications, up to and including early death.[9] If a videogame allows these patients to experience a way to improve their diabetes and still live a normal adolescent life, they increase their likelihood of delaying or preventing altogether diabetes-related complications. This proposal and subsequent study are steps towards the goal of helping adolescents with T1D to improve their metabolic control and, by extension, their long-term prognosis as they reach adulthood.

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Appendix A: Sample Size Calculation

Sample size for comparison of two means with 1:1 randomization

$$n = 2 * \frac{\left[\sigma\left(z_{\frac{1-\alpha}{2}} + z_{\beta}\right)\right]^2}{\Delta^2}$$

Estimated Δ = 0.5% (from data in Floyd et al., Beck et al., Tamborlane et al.)
Estimated σ = 1.03 (average σ of 5 RCT evaluated by Floyd et al. with mean age 10-19)
See Chapter 2, "CGM Uptake and Effect on HbA1c," for full citations and description of these studies.

α = 0.05
β = .20

For a two sided hypothesis with these values for α and β:

$z_{\frac{1-\alpha}{2}} = 1.960$
$z_{\beta} = 0.84$

Therefore:

$$n = 2 * \frac{[(1.03)(1.960 + 0.84)]^2}{0.5^2}$$

$$n = 66.54$$

Rounding up, this calculation reveals that we need n = 67 for each group in order to achieve 80% power at the .05 significance level. Thus, we must recruit at least 134 participants for our study. If we plan for 10% loss to follow up, this increases to 150 participants.

Appendix B: Research Consent

The following consent forms have been adapted from sample forms provided by the IRB office of Human Research at Yale; original templates can be downloaded at: https://your.yale.edu/research-support/human-research/yale-irbs-yale-university-institutional-review-boards/forms-0

Parental Permission for Participation in a Research Project
310 FR. 2 (2016-1)
YALE UNIVERSITY SCHOOL OF MEDICINE
YALE-NEW HAVEN HEALTH SYSTEM
INTERMOUNTAIN HEALTH CARE

Study Title: *Videogame Intervention for Control of Type 1 Diabetes in Adolescents: A Randomized Controlled Trial.*
Principal Investigator: *Lynn Fiellin, MD*
Funding Source: _____

Invitation to Participate and Description of Project

We are inviting your child to participate in a research study designed to look at using videogames to help motivate teenagers to manage their diabetes and provide them with skills to do so. Your child has been asked to participate because he/she is in the appropriate age range, has had diabetes for over 1 year, and has expressed interest in our study. This study is being conducted in Connecticut and in Utah and will include approximately 150-200 youth.

In order to decide whether or not you wish your child to be a part of this research study you should know enough about its risks and benefits to make an informed decision. This permission form gives you detailed information about the research study, which a member of the research team will discuss with you. This discussion should go over all aspects of this research: its purpose, the procedures that will be performed, any risks of the procedures, and possible benefits of participation. Once you understand the study, you will be asked if you wish your child to participate; if so, you will be asked to sign this form.

Description of Procedures

If you agree to your child participating in this study, we will begin the study by having you complete a survey that will ask for demographic and diabetes-related information about your child (age, gender, race, household income, duration of diabetes, and whether your child has ever used a continuous glucose monitor or an insulin pump). Additionally, your child will be asked to complete 2 questionnaires that will measure their confidence in managing their diabetes and how much stress they experience related to diabetes care. Finally, a trained research assistant who has undergone appropriate confidentiality training will use your diabetes health care provider's electronic medical record to record your child's most recent Hemoglobin A1C (HbA1C). No other information will be viewed or collected from the medical record.

If your child's HbA1C has not been measured in the last 30 days, we will ask you to schedule an appointment with your diabetes care provider and have this checked. (This is important for our study, but also an important part of standard diabetes management.) If you do not have a continuous glucose monitoring system (CGM), you will also need to ask your provider for a prescription to get one at this visit.

We prefer that you obtain a CGM through this method because it will then be yours to keep and use after the completion of the study; however, if you are unable to obtain a CGM due to cost, insurance, or any other reason, we will be happy to provide one to use for the duration of the study.

After we collect initial information, your child will be asked to come to one or two appointments per week for 3 months in order to play a videogame. Half of the participants in the study will be randomly assigned by a computer program to play our new diabetes game, while half will be assigned to play other games without diabetes content. The games do not include any violent or gory content and will be age-appropriate. The diabetes videogame will simulate many situations your child may find him/herself in and will help teach and practice diabetes-management skills.

After 3 months are complete, we will ask you to schedule another follow-up appointment with your diabetes care provider and re-check your child's HbA1C. As in the beginning of the study, a trained research assistant will collect this information from the electronic medical record. Again, no additional information in the medical record will be viewed or collected. At this time, we will also have your child meet with another research assistant to repeat the questionnaires from the first meeting and to download data from your child's CGM. Finally, we will ask you to report any diabetes-related hospitalizations or urgent care visits, including any episodes of diabetic ketoacidosis (DKA).

As a last measure, we want to know if the effects of the study last after your child stops playing the videogame. Therefore, we will also ask you to schedule another diabetes follow-up appointment with your care provider 6 months from the beginning of the study. We will collect HbA1C data from this appointment as with the initial and 3 month appointments. After completing the study to this point, all children (in both groups) will be given access to the diabetes game for home use.

All information including medical records, blood glucose readings, and questionnaire results will be kept confidential and, in our data storage files, will not be specifically associated with you or your child's identity. This information will not be relayed back to you or to your child's diabetes care provider. It will not be shared with any other individuals outside of the research team; only the aggregate data for the two treatment groups will be reported.

You will be told of any significant new findings that are developed during the course of your child's participation in this study that may affect your willingness to continue to participate.

Risks and Inconveniences

Some questions or gameplay situations may make you or your child somewhat uncomfortable. This, to an extent, is within the expectations of the project as we hope to help some of these uncomfortable situations and feelings more manageable for your child; however, you should be aware of this possibility.

Despite exhaustive measures to protect the data we collect, there is always the possible risk of loss of confidentiality. Every effort will be made to keep your child's information confidential; however, this cannot be guaranteed.

You and your child should be aware that the health care provider's advice always takes precedent over what the child learns in the videogame. We have made every effort to ensure there is no content or activity in the game that would contradict established standards of care; however, in the event that there is content or an implication that contradicts what you have been told by your child's provider, please discuss the concern with your provider before implementing a sweeping lifestyle change.

There are minimal to no physical risks inherently associated with participation in this study for a child with type 1 diabetes and no other health concerns. If your child has any other chronic health conditions, you should speak to your child's primary care provider and discuss whether or not they would incur additional risk by participating in this trial.

As in any experimental trial, participation in this study may involve risks that are currently not known.

Benefits

We hope that this study demonstrates that the videogame we have created is able to help adolescents better control their diabetes. This may include experiencing fewer episodes of low or high blood glucose, a lower HbA1c, fewer forgotten insulin doses, and improved confidence in navigating social situations that complicate diabetes management. If successful, this may also be able to reduce future risks that can be associated with diabetes: kidney disease, nerve damage, vision loss, blocked arteries, heart attack, or death.

The research may have direct benefit to the research participants. All participants will be given access to the game at the end of the study, even if you or your child chooses to withdraw at any point during the research process). Additionally, if successful, this may offer the same benefits to the wider population of adolescents with type 1 diabetes.

Economic Considerations

We will provide $20 in compensation, in addition to free access to the videogame, for each study participant who completes the entire study.

This will be allocated as follows:
-$5 for completing the initial intake information and baseline HbA1C
-$10 for completion of questionnaires for 3-month data collection

-$5 for completing the 6-month HbA1C

If your child completes the 3-month data collection but does not complete the minimum 12 videogame sessions during the 3 month interval, the $10 will be prorated based on the number of sessions completed, with a minimum of $5 for completing the data collection.

According to the rules of the Internal Revenue Service (IRS), payments that are made to you or your child as a result of your/your child's participation in a study may be considered taxable income.

You will be responsible for any co-pays required by your insurance company for standard treatment, including regular diabetes follow-up appointments, testing HbA1c, typical management supplies such as insulin pens or pump equipment, and obtaining a CGM (unless you choose to borrow one for the duration of the study). Outside of these costs, which would be part of your standard diabetes management, there will be no additional costs associated with participation in the study. We will provide equipment for playing the videogame at each appointment free of charge. We will also loan CGM systems free of charge for the 6 month duration of the study if you are unable to obtain one for personal use.

Treatment Alternatives

This study does not propose any new treatments, but does use the videogame as an educational and motivational program as an adjunct to standard therapy. Alternative treatments would include any other educational or motivational class or program, including meeting with a diabetes educator or with a psychotherapist specializing in motivation or chronic disease management. You may choose to enroll in one of these programs instead of participating in this study.

Confidentiality

Any identifiable information that is obtained in connection with this study will remain confidential and will be disclosed only with your permission or as required by U.S. or State law. Examples of information that we are legally required to disclose include abuse of a child or elderly person, or certain reportable diseases. We will deidentify all data; it will be recorded only with a unique identifier code. This code will be associated with your name and no other personally identifying information on a separate computer so that it can be connected to HbA1C data from the EHR; only the designated HIPAA-trained research technicians will have access to this file. After HbA1c data is accessed and added to the deidentified data, this file will be destroyed so that, at the conclusion of the study period, the unique identifier will no longer be associated in any place with your personal information. Any paper research materials used will be stored in locked cabinets and computerized data will be accessible only with secure passwords. When the results of the research are published or discussed in conferences, no information will be included that would reveal your child's identity unless your specific permission for this activity is obtained.

Representatives from Yale University, the Yale Human Research Protection Program and the Yale Human Investigation Committee (the committee that reviews, approves, and monitors

research on human subjects) may inspect study records during internal auditing procedures. However, these individuals are required to keep all information confidential.

In Case of Injury

While this is unlikely, if your child is injured while actively participating in this study (e.g., during a videogame session), seek treatment and contact the study doctor as soon as you are able.

Yale School of Medicine, the Yale-New Haven Health system, and Intermountain Healthcare do not provide funds for the treatment of research-related injury. If your child is injured as a result of his or her participation in this study, treatment will be provided. You or your insurance carrier will be expected to pay the costs of this treatment. No additional financial compensation for injury or lost wages is available.

You do not give up any of your legal rights by signing this form.

Voluntary Participation and Withdrawal

You are free to choose not to have your child participate and if you do decide to have your child become a subject, you are free to withdraw him/her from this study at any time during its course. Refusing to participate or withdrawing from the study will involve no penalty or loss of benefits to which your child is otherwise entitled (such as your child's health care outside the study, the payment for your child's health care, and your child's health care benefits) If your child decides not to participate or if you withdraw him/her, it will not harm you or your child's relationship with your own doctors or with the organization at which you are participating in the study.

If you or your child decides to withdraw from the study, you may request the destruction of your personal data. We will make every effort to comply with this request; however, as the data will be deidentified in the process of recording, we cannot guarantee that we will be able to destroy your data in full. However, in this case, we can guarantee that the data would not be associated with any of your personal information and your participation in the study will not be recorded. There are no consequences to withdrawing from the study, but we will be unable to provide a copy of the diabetes videogame for your child if we destroy your data before the study is complete.

The researchers may withdraw your child from participating in the research if necessary. This is unlikely but could occur at the discretion of the research staff if the child is observed to be putting themselves or others at risk of injury or harm while participating in the study, including behaviors destructive to people or equipment.

Questions

We have used some technical terms in this form. Please feel free to ask about anything you don't understand and to consider this research and the permission form carefully—as long as you feel is necessary—before you make a decision.

Authorization and Permission

I have read (or someone has read to me) this form and have decided to allow my child to participate in the project described above. Its general purposes, the particulars of my child's involvement and possible hazards and inconveniences have been explained to my satisfaction. My signature also indicates that I have received a copy of this permission form.

By signing this form, I give permission to the researchers to use [and give out] information about my child for the purposes described in this form. By refusing to give permission, I understand that my child will not be able to be in this research.

Name of Child: _____

Parent/Legal Guardian Signature: _____

Date: _____

_____ _____

Signature of Person Obtaining Permission Date

If you have further questions about this project or if you have a research-related problem, you may contact the Principal Investigator, Dr. Lynn Fiellin, at 203-737-3347.

If after you have signed this form you have any questions about your privacy rights, please contact the Yale Privacy Officer at (203) 432-5919.

If you would like to talk with someone other than the researchers to discuss problems, concerns, and questions you may have concerning this research, or to discuss your rights as a research subject, you may contact the Yale Human Investigation Committee at (203) 785-4688.

Child's Assent for Being in a Research Study
Yale-New Haven Hospital/Yale University School of Medicine 310 FR.1

Title: A Videogame for Adolescents with Type 1 Diabetes

Why am I here?

We are asking you to take part in a research study because we are trying to learn more about how to use videogames to help adolescents (ages 13-17) manage type 1 diabetes. We are inviting you to be in the study because you have type 1 diabetes and have expressed interest in being part of our study.

Why are they doing this study?

We developed a videogame that is designed to teach teenagers about managing type 1 diabetes and give them an opportunity to practice skills needed to keep blood sugars under control. The game also simulates situations that teenagers are likely to encounter with their friends and helps to figure out what to do in these situations in real life. We hope that people who play this game will be able to keep their blood sugars in the "normal range" (70-180) more often and may even lower hemoglobin A1C levels.

What will happen to me?

If you agree to be in the study, you will be asked, first, to commit to going to routine diabetes follow-up appointments every 3 months for a total of 6 months (at the beginning of the study, then another 3 months later, and the last visit 6 months from the first one). At each visit, you will have your A1C checked as part of your normal diabetes care. You will go to these appointments as usual and follow your diabetes specialist's instructions. At the first visit, you will get a continuous glucose monitor (CGM) if you don't have one already.

After the first visit, a computer will randomly assign you to play our diabetes videogame or other games that are not related to diabetes. You will come to our office to do this once to twice weekly, for 1 hour each session, until your second visit with your diabetes specialist.

After the first and second visits, you will sit down with one of our research assistants, who will give you some questionnaires. You will be asked several questions about your confidence regarding managing your own diabetes as well as some of the things about diabetes that may cause you stress. At the second visit, the research assistant will also download information from your CGM to see how often you used it and what your blood sugars have been.

Will the study hurt?

The study will not hurt. As you already know, getting your A1C checked can be uncomfortable, but this should be a normal part of your diabetes care whether you are in the study or not. There should not be any other physical pain or discomfort as part of the study.

That said, it is possible that some questions on the questionnaires or some of the events in the videogame will make you nervous or anxious. This is important, because they represent things that can happen in real life that may also make you nervous or anxious. We hope that the game will help you to become less nervous or anxious so that you will no what to do if these situations occur in real life.

Will the study help me?

The study may help you have better control of your blood sugar. It may even help you lower your A1C. Additionally, it may help you build confidence in your skills to manage your own diabetes, especially when you are at school or with your friends. If it does, you may begin to feel healthier and safer as a result of participating in the study. Lowering your A1C can also help protect you from the damage that diabetes can do to your body as you get older, such as damaging your eyes or your ability to feel things with your fingers and toes. Even if you get assigned to play the non-diabetes games during the study, you will be given your own copy of the diabetes game when you finish the study.

What if I have any questions?

You can ask any questions that you have about the study. If you have a question later that you didn't think of now, you can call Dr. Fiellin (203-737-3347), who is in charge of the study, or ask me next time. You can also call (or have your parent call) your diabetes specialist to ask any questions about your diabetes treatment.

Do my parents know about this?

This study was explained to your parents and they said that you could be in it. You can talk this over with them before you decide.

Do I have to be in the study?

You do not have to be in the study. No one will be upset if you don't want to do this. If you don't want to be in this study, you just have to tell them. You can say yes now and change your mind later. It's up to you.

Writing your name on this page means that that you agree to be in the study, and know what will happen to you. If you decide to quit the study at any point, all you have to do is tell the person in charge.

_____ _____

Signature of Child Date

_____ _____

Signature of Researcher Date

Appendix C: Outcome Questionnaires

PAID-T (Problem Areas in Diabetes-Teens)

Age _____ Sex _____

How old were you when your diabetes was diagnosed? _____

Today's Date _____

Directions: Living with diabetes can sometimes be difficult. In day-to-day life, there may be many problems and hassles with your diabetes. The problems may range from minor hassles to major life difficulties. Listed below are a variety of possible problem areas which people with diabetes may have. Think about how much each of the items below may have upset or bothered you DURING THE PAST MONTH and circle the appropriate number.

Please note that we are asking you how much each item may be bothering you in your life, NOT whether the item is merely true for you. If you feel that an item is not a bother or a problem for you, you would circle "1." If it is very bothersome to you, you would circle "6."

		Not A Problem		Moderate Problem		Serious Problem	
1.	Feeling sad when I think about having and living with diabetes.	1	2	3	4	5	6
2.	Not knowing if the mood or feelings I am having are related to my blood sugar levels.	1	2	3	4	5	6
3.	Feeling overwhelmed by my diabetes regimen.	1	2	3	4	5	6
4.	Feeling angry when I think about having and living with diabetes.	1	2	3	4	5	6
5.	Feeling constantly concerned about food and eating.	1	2	3	4	5	6
6.	Worrying about the future and the possibility of serious complications.	1	2	3	4	5	6
7.	Feeling upset when my diabetes management is ''off track.''	1	2	3	4	5	6
8.	Feeling ''burned-out'' by the constant effort to manage diabetes.	1	2	3	4	5	6
9.	Feeling that I am not checking my blood sugars often enough.	1	2	3	4	5	6
10.	Feeling unclear about exactly what or how much I should be doing to take care of my diabetes properly.	1	2	3	4	5	6
11.	Not feeling motivated to keep up with my daily diabetes tasks.	1	2	3	4	5	6
12.	Feeling discouraged or defeated when I see high blood sugar results on my meter.	1	2	3	4	5	6
13.	Feeling that my friends or family act like ''diabetes police'' (e.g. nag about eating properly, checking blood sugars, not trying hard enough).	1	2	3	4	5	6
14.	Feeling like my parents don't trust me to care for my diabetes.	1	2	3	4	5	6
15.	Feeling I must be perfect in my diabetes management.	1	2	3	4	5	6
16.	Missing or skipping blood sugar checks.	1	2	3	4	5	6
17.	Feeling that my blood sugars are often swinging wildly, no matter how hard I try.	1	2	3	4	5	6
18.	Feeling that I am often failing with my diabetes regimen.	1	2	3	4	5	6
19.	Feeling like my parents blame me for blood sugar numbers they don't like.	1	2	3	4	5	6
20.	Feeling that my friends or family don't understand how difficult living with diabetes can be.	1	2	3	4	5	6
21.	Feeling that I can't control my eating.	1	2	3	4	5	6
22.	Worrying about my weight.	1	2	3	4	5	6
23.	Worrying that diabetes gets in the way of having fun and being with my friends.	1	2	3	4	5	6
24.	Fitting my diabetes regimen into my day when I'm away from home (e.g. school, work, etc.).	1	2	3	4	5	6
25.	Worrying about getting low during a sports activity.	1	2	3	4	5	6
26.	Feeling like my parents worry about complications too much.	1	2	3	4	5	6

Adapted from Weissberg-Benchel et al.; see chapter 3 references for full citation.

SED-D (Self-Efficacy for Diabetes scale)

For each of the following items, indicate how confident you are in your ability to:

1 Least confident (… I CANNOT do) 3 | 4 Most confident (… I CAN do) 6

For example, choosing "4" to the first item would mean you are SURE that you CAN be the one in charge of giving yourself an insulin injection.

Item	Very sure		Sure	Sure		Very sure
Be the one in charge of giving my insulin injection to myself	1	2	3	4	5	6
Figure out my own meals and snacks at home	1	2	3	4	5	6
Figure out what foods to eat when I am away from home	1	2	3	4	5	6
Keep track of my own blood sugar levels	1	2	3	4	5	6
Watch my own sugar levels in my urine	1	2	3	4	5	6
Change the amount of time I get insulin when I get a lot of extra exercise	1	2	3	4	5	6
Judge the amount of food I should eat before activities	1	2	3	4	5	6
Figure out how much insulin to give myself when I am sick in bed	1	2	3	4	5	6
Prevent having reactions	1	2	3	4	5	6
Avoid or get rid of dents, swelling, or redness of my skin where I get my shot	1	2	3	4	5	6
Suggest to my parents changes in my insulin dose	1	2	3	4	5	6
Sleep away from home on a class trip or at a friend's house where no one knows about my diabetes	1	2	3	4	5	6
Keep myself free of high blood sugar levels	1	2	3	4	5	6
Know how to make my urine tests look better or worse than they are	1	2	3	4	5	6
Avoid having ketones	1	2	3	4	5	6
Feel able to stop a reaction when I am having one	1	2	3	4	5	6
Tell a friend I have diabetes	1	2	3	4	5	6
Prevent blindness and other complications from my diabetes	1	2	3	4	5	6
Tell my boyfriend or girlfriend I am diabetic	1	2	3	4	5	6
Get as much attention from others when my diabetes is under control as when it isn't	1	2	3	4	5	6
Regularly wear a medical alert tag or bracelet which says I have diabetes	1	2	3	4	5	6
Sneak food not on my diet without getting caught	1	2	3	4	5	6
Believe that I have the ability to have control over my diabetes	1	2	3	4	5	6
Run my life the same as I would if I didn't have diabetes	1	2	3	4	5	6

Adapted from Van Allen, et al.; see chapter 3 references for full citation.

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