iDECIDE: An Evidence-based Decision Support System for Improving Postprandial Blood Glucose by Accounting for Patient's Preferences

by

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ABSTRACT

Type 1 diabetes (T1D) is a chronic disease that affects 1.25 million people in the United States. There is no known cure and patients must self-manage the disease to avoid complications resulting from blood glucose (BG) excursions. Patients are more likely to adhere to treatments when they incorporate lifestyle preferences. Current technologies that assist patients fail to consider two factors that are known to affect BG: exercise and alcohol. The hypothesis is postprandial blood glucose levels of adult patients with T1D can be improved by providing insulin bolus or carbohydrate recommendations that account for meal and alcohol carbohydrates, glycemic excursion, and planned exercise. I propose an evidence-based decision support tool, iDECIDE, to make recommendations to improve glucose control by taking into account meal and alcohol carbohydrates, glycemic excursion and planned exercise. iDECIDE is deployed as a low-cost and easy to disseminate smartphone application.

A literature review was conducted on T1D and the state-of-the-art in diabetes technology. To better understand self-management behaviors and guide the development of iDECIDE, several data sources were collected and analyzed: surveys, insulin pump paired with glucose monitoring, and self-tracking of exercise and alcohol. The analysis showed variability in compensation techniques for exercise and alcohol and that patients made unaided decisions, suggesting a need for better decision support.

The iDECIDE algorithm can make insulin and carbohydrate recommendations. Since there were no existing in-silico methods for assessing bolus calculators, like iDECIDE, I proposed a novel methodology to retrospectively compare insulin pump

bolus calculators. Application of the methodology shows that iDECIDE outperformed the Medtronic insulin pump bolus calculator and could have improved glucose control.

This work makes contributions to diabetes technology researchers, clinicians and patients. The iDECIDE app provides patients easy access to a decision support tool that can improve glucose control. The study of behaviors from diabetes technology and self-report patient data can inform clinicians and the design of future technologies and bedside tools that integrate patient's behaviors and perceptions. The comparison methodology provides a means for clinical informatics researchers to identify and retrospectively test promising insulin blousing algorithms using real-life data.

This dissertation is dedicated to my beloved husband and children,

for their patience,

sacrifice,

support,

and

unconditional love.

Joel, I love you

Ezra, I love you

Anastasia, I love you

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ABBREVIATIONS

ADA	American Diabetes Association
apps	smartphone/mobile applications
ASU	Arizona State University
BCa	applied bolus calculator
BCp	proposed bolus calculator
BG	blood glucose
carbs	carbohydrates
cBG	current blood glucose
CDSS	clinical decision support system
CF	correction factor
CGM	continuous glucose monitor
CGMS	continuous glucose monitoring system
CSII	continuous subcutaneous insulin injection
FDA	Food and Drug Administration
HIMSS	Health Information Management Systems Society
IB	insulin bolus
ICR	insulin to carbohydrate ratio
ICU	intensive care unit
iDECIDE	patient-centered decision support based on device data
IHI	intermittent high intensity
IOB	insulin on board

IP	insulin pump
IPBC	insulin pump bolus calculator
ISF	insulin sensitivity factor
lbs	pounds
MDI	multiple daily injections
mg/dL	milligrams per deciliter
OS	operating system
PDA	proposed decision aid
SD	standard deviation
SMB	self-management behavior
SUS	system usability scale
S-TOFHLA	short test of functional health literacy in adults
tBG	target blood glucose
TDD	total daily dose
T1D	type 1 diabetes
T2D	type 2 diabetes
UML	unified modeling language

1 INTRODUCTION

1.1 Lack of Diabetes Management Technologies that Account for Lifestyle Preferences

Diabetes is a complex disease that affects 29.1 million US citizens and type 1 diabetes (T1D) is a subtype that affects 1.25 million people in the US [1]. T1D is a chronic condition with no known cure in which a person's pancreas does not produce insulin, a hormone required to regulate carbohydrate and fat metabolism in the body. The lack of insulin causes hyperglycemia, also referred to as high blood glucose. The state of hyperglycemia leads to long term complications, such as damage to kidneys, eyes, heart and nervous system, as well as increased mortality rates from heart disease [2,3].

T1D requires that individuals self-manage blood glucose and administer insulin therapy to compensate for the lack of insulin produced by the pancreas. Insulin pump therapy mimics a normal functioning pancreas by delivering preprandial (i.e. before mealtime) bolus insulin and continuous basal insulin to compensate for carbohydrate loads and out of target blood glucose levels. Bolus insulin doses are calculated based on: carbohydrate load, insulin to carbohydrate ratio, the actual blood glucose level, the target blood glucose level, insulin sensitivity factor, and the insulin on board [4,5]. While self-management of blood glucose can be empowering, the amount of data that must be tracked can be overwhelming [6]. Because the calculation to determine an insulin bolus is complex and error prone, insulin pumps and blood glucose meters often have embedded bolus calculators which use proprietary algorithms to lessen the cognitive burden on patients by automating the computation of bolus insulin doses. Even with assistance from consumer health informatics applications, such as clinical decision

support systems, patients still fail to meet glycemic goals [7]. In addition to delivering insulin at mealtimes, patients on intensive insulin therapy are recommended to consume 3 meals a day and to check blood glucose 4-10 times a day, which includes checking before every meal and before bedtime. At least 150 minutes of moderate exercise spread over several days a week is also recommended for all types of diabetes, particularly with T2D in order to manage obesity [8]. Those with type 2 diabetes may have different pharmacologic approaches to maintain glycemic control, such as daily oral medications. Barriers to initiating insulin therapy in both T1D and T2D have been identified, such as fear of hypoglycemia and reluctance to accommodate the timing of insulin doses [9].

While bolus calculators have been shown to lead to better glucose control [10], they have limited capabilities as they currently only account for out-of-target blood glucose levels and planned carbohydrate loads. Although there are many variables that can influence glucose levels, e.g. stress, illness, medications, etc., in this work we will focus on two lifestyle preferences that are known to affect blood glucose: alcohol and exercise [11–17]. While the immediate effects of the carbohydrates in some types of alcoholic beverages may increase blood glucose, the alcohol itself may cause delayed hypoglycemia. Exercise generally results in lowering blood glucose levels during the activity and may cause delayed hypoglycemia as well. Allowing for flexibility is important, as it is known that regimented, invariant self-management care is not effective in diabetes care [18–20], and can lead to therapeutic non-adherence in the absence of accounting for individual lifestyle preferences.

Closed-loop devices (a.k.a. artificial pancreas) are based on complex mathematical models that aim to improve glycemic control by automating insulin delivery and other hormones related to controlling blood glucose. These closed-loop devices are not ready for commercial use and there are few studies that have reported specifics on how the proposed algorithms perform when compensating for exercise or alcohol. Similarly, existing mobile applications (apps) are sub-optimal for meeting evidence-based guidelines for glucose control as they do not account for exercise or alcohol consumption. In the US, there are few FDA-regulated mobile apps that provide bolus calculators. Of the apps that do provide such calculators, they do not account for exercise and alcohol [21].

Clearly, better tools are needed to assist type 1 diabetes patients with insulin dosing, particularly when trying to account for multiple factors simultaneously that may impact glucose control. The hypothesis is postprandial blood glucose levels of adult patients with T1D can be improved by providing insulin bolus or carbohydrate recommendations that account for meal and alcohol carbohydrates, glycemic excursion, and planned exercise.

1.2 Research Aims

Aim 1: Review state of the art on relevant clinical evidence and technology

Conduct a literature review to understand how exercise and alcohol affect blood glucose absorption in adult T1D patients. Review current technologies available to self-manage glucose control, with particular emphasis on those that support patients as they decide how much insulin to take when consuming meals and/or alcohol and exercising.

Aim 2: Investigate self-management behaviors of adults on insulin pump therapy

Describe real-life self-management behaviors in T1D adults on insulin pump therapy. Contrast self-reported, self-management diabetes behaviors from patients versus behaviors recorded by diabetes technology (insulin pumps and glucose sensors) using a combination of qualitative and quantitative methods. Confirm the need for decisional support tools to help patients incorporate personal lifestyle choices, such as planned exercise and alcohol consumption, into diabetes self-management.

Aim 3: Propose iDECIDE, a novel evidence-based bolus insulin dosing decision aid that accounts for glycemic excursions, carbohydrates, planned exercise and alcohol

Refine the algorithms currently used by patients to compute preprandial insulin boluses to develop iDECIDE, an evidence-based bolus insulin decision aid that accounts for glycemic excursions, meal's carbohydrates, planned exercise and alcohol consumption.

Aim 4: Propose and apply novel methods for retrospectively evaluating the accuracy of the proposed iDECIDE insulin bolus algorithm

There is a lack of methods that use real-life data for evaluating the performance of insulin dosing algorithms. Current methods use data from controlled clinical environments (e.g. clinical trials) or simulators to evaluate the performance of insulin dosing algorithms. Retrospective, low-risk methods that use real life data could provide valuable preliminary results to inform future clinical trials. We propose a systematic approach to analyze the effectiveness of glycemic control interventions using real life

data and demonstrate the method by evaluating the performance of the iDECIDE decision aid.

Aim 5: Design and deploy the smartphone app iDECIDE

Design and deploy the proposed insulin bolus decision aid as an iOS smartphone application. Improve the application through usability testing.

1.3 Outline of Dissertation

This chapter provided a brief introduction to T1D and stated the lack of evidence-based decision support tools that account for personal lifestyle preferences such as exercise and alcohol, which are known to affect blood glucose levels. Chapter 2 delves deeper into the motivation of this work by reviewing in more detail the state of the art of current evidence on how carbohydrates, insulin, alcohol and exercise affect blood glucose. We also identify the current decision support systems available to help patients achieve better glycemic control. Chapter 3 focuses on understanding the challenges faced by those on insulin pump therapy and their self-management behaviors. Chapter 4 specifically targets self-management behaviors of patients on insulin pump therapy when compensating for exercise and alcohol. Chapter 5 describes the evidence-based decision aid, iDECIDE, and how it compensates for carbohydrates, blood glucose, alcohol and exercise. Chapter 6 introduces the novel methods that we propose for retrospectively comparing the efficacy of insulin bolus recommendations using real-life data. The results from retrospectively comparing iDECIDE against a conventional decision comprise Chapter 7. Chapter 8 addresses the steps required to design and deploy iDECIDE as an iOS smartphone app. A conclusion is provided in Chapter 9.

2 STATE OF THE ART ON CLINICAL EVIDENCE AND DECISION SUPPORT SYSTEMS FOR DIABETES MANAGEMENT

2.1 Introduction

This chapter summarizes the results of the completed literature review on: 1) relevant clinical evidence related to patient's daily lifestyle choices, including carbohydrates, alcohol consumption and exercise, as well as the effects of insulin on blood glucose, and 2) the state of the art on available technologies (decision support systems) to help diabetes patients compensate for everyday life preferences. The outcomes of this chapter correspond to Aim 1. Preliminary results of the completed literature review were presented as a poster at the American Medical Informatics Association Annual Symposium 2014 (APPENDIX A.1) and as a conference paper at MEDINFO 2015 [22,23] (APPENDIX B.1).

2.2 Background

Type 1 diabetes (T1D) is a chronic disease in which a person's immune system is involved in the destruction of insulin-producing β-cells (beta cells) in the pancreas [24]. T1D can be diagnosed at any age, but the disease is most likely to be diagnosed during childhood. There is no cure for T1D and what causes the disease is not well understood and there is no way to prevent the disease, but it is likely that both genetics and environment play a role [24]. Individuals with diabetes must engage in self-management to maintain glycemic control by regularly checking blood glucose levels with a meter or monitoring with a continuous blood glucose sensor. Patients must also deliver insulin with syringes, insulin pens or insulin pumps.

Providers are motivated to prescribe the best treatments to their patients in order to achieve better outcomes, but self-management behaviors have been found to have a greater impact on blood glucose levels than the decisions made by physicians [18]. Failing to provide patient-centered care, i.e. care that respects the wants, needs and preferences of the patient, places patients in a position where they must adapt to pre-existing treatment protocols and guidelines [25]. Patients with chronic diseases, like diabetes, are better motivated to make and sustain behavior changes if they receive patient-centered care [26]. Allowing for flexibility is important as regimented, invariant self-care routines are not effective and can lead to non-adherence [18–20]. One such self-care behavior that can empower patients with diabetes is self-monitoring of blood glucose. Self-tracking blood glucose data can be overwhelming for patients, as even those who are knowledgeable can fail to meet glycemic goals [27]. Many decision aids and technologies have been developed to enable patients to better integrate blood glucose data into the decisions they make as they engage in self-care. For example, Bluetooth technology supports data exchange between blood glucose meters and continuous glucose monitors with insulin pumps and smartphone apps, while patient portals allow patients to upload their data and grant access to their providers.

The objective of Aim 1 is to two-fold: 1) understand the current technologies available that provide decisional support to patients with diabetes as they self-manage the disease, and 2) understand two lifestyle preferences that have an impact on glucose levels: exercise and alcohol.

2.3 Methods and Materials

A literature search was conducted to understand the pathophysiology of diabetes and the effects of alcohol and exercise on postprandial blood glucose. The literature review described here applies to sections 2.4.1 – 2.4.4 and 2.4.6. PubMed, Google Scholar and insulin pump manufacturer manuals were used to identify articles and resources for inclusion. The Medtronic MiniMed, Inc. insulin pump user manual was identified and included in the literature review [28]. This insulin pump manufacturer was identified by the Mayo Clinic endocrinology clinicians as a widely-used device amongst their patient population. Google Scholar was used to identify guidelines and/or white papers on type 1 diabetes. The search criteria for guidelines was "'guideline' OR 'standard of care' AND 'diabetes'" and the search criteria for white papers was "type 1 diabetes pathogenesis." For each search criteria, the dates of inclusion were limited from 2012 to 2016. The top 20 results for each search strategy were included in the search for a total of 40 results from Google Scholar. Two search strategies were used with PubMed to identify articles for the acute effects of exercise and alcohol. For exercise articles, the search included articles with exercise in the title and diabetes and glucose in the title or abstract. Articles were excluded if they included type 2 diabetes, risk, mortality or coronary in the title or abstract; the root words neuro and recommend were also excluded from the title or abstract. For alcohol, the articles were included if they had alcohol and diabetes in the title and excluded if the title or abstract contained type 2 diabetes, prevalence, mortality or smoking. Both exercise and alcohol searches were limited from 2010 to 2016 and restricted to human only studies.

In addition to the literature review, we met with an endocrinologist and diabetes care team to further understand diabetes and to discuss current clinical challenges that patients with diabetes encounter. We participated in a guided training session with a diabetes nurse educator at the Mayo Clinic Arizona Simulation Center that included hands-on experience with insulin pumps, meters and continuous glucose monitors. We also reviewed existing insulin pump technologies commercially available in the United States (US) that are approved by regulatory entities such as the Federal Food and Drug Administration (FDA).

2.4 Results

There were 229 identified articles from the search strategies of which all of the titles and abstracts were screened. Articles that described the short-term glycemic impact of alcohol and/or exercise were included in the review as well as guidelines and/or white papers about type 1 diabetes. There were 216 articles that were excluded, see Figure 2.1: Flow diagram of article and resource selection for literature review. for reasons for exclusion. During the full text review of the remaining 13 articles an additional 12 articles were identified from author citations that were not found in the literature searches and were included in the final review for a total of 25 resources.

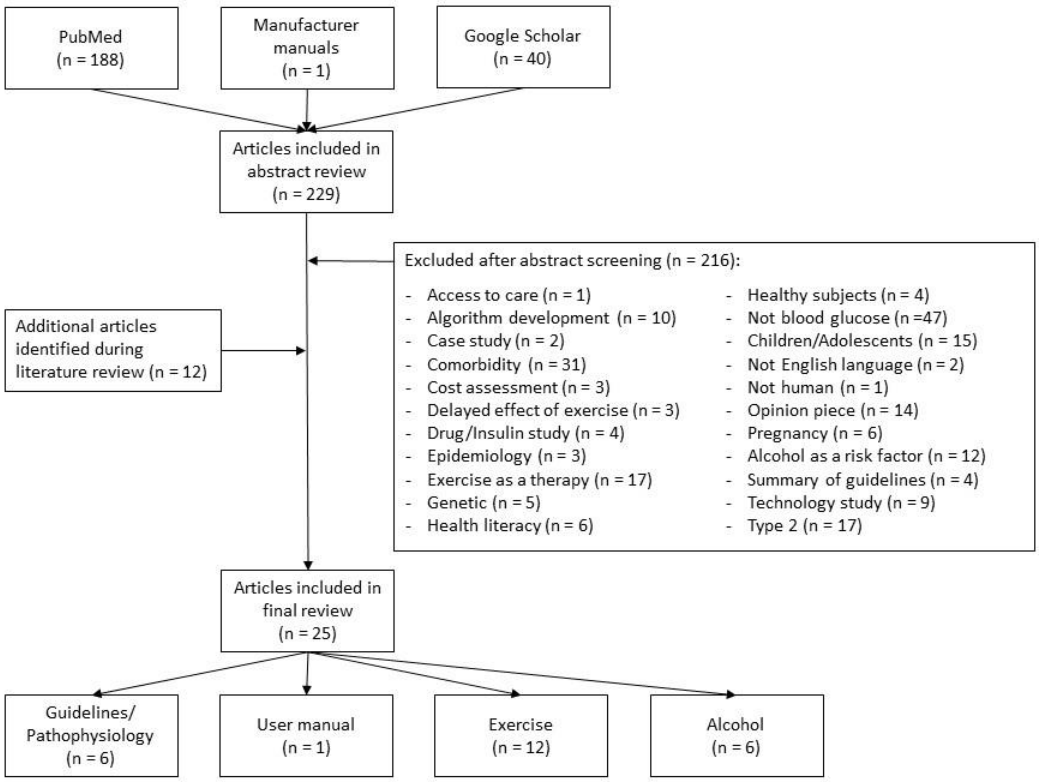


Figure 2.1: Flow diagram of article and resource selection for literature review.

2.5 Discussion

2.5.1 Effects of carbohydrates on blood glucose

Glucose is a simple sugar that is released into the bloodstream as a result of the digestion of food containing carbohydrates. When blood glucose levels are high, properly functioning β-cells in the pancreas secrete insulin into the bloodstream [24]. The secretion of insulin, along with other metabolic processes within the body, maintain tight glycemic control in healthy individuals. When the pancreas does not secrete insulin in response to increasing levels of glucose in the blood, as in the case of damaged β-cells in individuals with T1D, hyperglycemia, or high blood sugar, ensues. Chronic

hyperglycemia can lead to organ damage and other complications [2]. The goal of insulin therapy for individuals with T1D is to dose insulin in such a way that it mimics as closely as possible the secretion of insulin from healthy β-cells in the pancreas into the blood stream.

2.5.2 Effects of insulin on blood glucose

Insulin is a hormone that regulates the metabolism of carbohydrates, proteins and fats and is responsible for delivering glucose found in the bloodstream into cells, particularly adipose, liver and muscle cells [24]. Every individual reacts differently to carbohydrates and insulin, and as such, the amount of insulin required to offset the glycemic-load from food containing carbohydrates is different for each individual and its value is referred to as an insulin to carbohydrate ratio (ICR) [29]. The ICR indicates how many carbohydrates one unit of insulin will cover, i.e. the amount of glucose that insulin will move from the bloodstream into cells. This ratio can be coupled with carbohydrate counting, a method for estimating the carbohydrate content of foods, in order to adjust the amount of insulin for injection. Another important ratio to consider is the insulin sensitivity factor (ISF), which is also referred to as the correction factor (CF), which also is adjusted for each individual [29]. CF is described as how much 1 unit of fast-acting insulin will lower blood glucose levels over the course of 2-4 hours during a fasting or pre-meal state. Patients with T1D can use the following equation from Colin, et.al. (Equation 2.1) [29], to compute the amount of insulin needed to adjust for a carbohydrate load and/or an out of range blood glucose reading.

Equation 2.1: Standard Insulin Dosing Equation

$$U = \frac{carbs}{ICR} + \frac{cBG - tBG}{CF} - IOB$$

In Equation 2.1, the variable *U* represents the units of insulin to deliver. The first fraction of the equation, "*carbs/ICR*", calculates the relationship between the grams of carbohydrates (*carbs*) intended to be consumed covered by insulin, or the *ICR*. *ICR* is calculated as 450/TDD, where the total daily dose of insulin (TDD) = body weight (lbs.) x 0.23. The second fraction in the equation calculates the difference between the actual, or current blood glucose (*cBG*) level and the target blood glucose level (*tBG*) and divides the difference by the *CF*. *CF* is calculated as 1700 mg/dL divided by TDD. The final segment of the equation subtracts the insulin on board (*IOB*), i.e. the theoretical amount of insulin remaining in the body from previous insulin boluses. Adjusting for previous boluses avoids insulin stacking, or dosing more insulin than is needed, which can lead to hypoglycemia, or low blood sugar levels. Hypoglycemia is an acute situation that if left untreated can result in neurologic damage and even death. Hypoglycemia can be averted by reducing the bolus insulin, increasing food intake, or a combination of both [30]. While hypoglycemia poses immediate danger, hyperglycemia, has delayed effects that can lead to cardiovascular disease and organ damage. Hyperglycemia can be managed by dosing insulin [31].

2.5.3 Effects of exercise on blood glucose

The American Diabetes Association (ADA) Standards of Care guidelines from 2016 state that regular physical activity is important for maintaining health and fitness for

those diagnosed with diabetes [8]. The guidelines suggest that people with diabetes should participate in 150 minutes of moderate intensity (50% to 70% of maximum heart rate) physical activity per week. The guidelines caution that taking insulin and engaging in moderate exercise may cause hypoglycemia, but in the case of intense exercise blood glucose levels may rise [8].

García-García, et.al. conducted a systematic review and meta-analysis in 2015 on ten studies to find the rate of change of glucose during exercise [32]. The meta-analysis showed that continuous exercise at moderate intensities resulted in a rapid decrease in glucose. Fewer studies were available for the analysis of intermittent high intensity (IHI) exercise and the results were conflicting showing either a rapid decrease in glucose or a slight increase in glucose. Guelfi, et.al. conducted an observational study with 7 participants with type 1 diabetes on the difference in blood glucose response between moderate exercise and IHI exercise [33]. Each participant was monitored at rest and during 30 minutes of moderate exercise and IHI exercise. Moderate exercise decreased glucose levels an average of 80 mg/dL while IHI exercise decreased glucose levels 52 mg/dL when compared to resting. Another review was done in 2015 by Bally, et. al. found corollary results that high intensity exercise may lead to hyperglycemia and that incorporating an IHI exercise routine may produce more predictable declines in blood glucose [34].

The most common study design amongst the literature on exercise was a randomized crossover design with 7 to 12 participants that was often preceded by obtaining a baseline measurement for reference, such as rest, peak heart rate or VO_{2max}

(peak oxygen uptake, an indicator or cardiorespiratory endurance) with 2 of the 6 studies being a specific subtype where the timing of meals and/or insulin were controlled as well [35–38] and [39,40].

In a recent study in 2015, Tonoli, et. al. used an exhaustion test to obtain VO_{2max} on 7 participants and a baseline of blood glucose at rest [35]. Each participant then exercised twice for 22 minutes, with the order of the type of exercise randomized between continuous moderate exercise at 70% VO_{2max} or IHI with 1 minute of intense intervals at 90% VO_{2max}. This study found that there was a significant drop in blood glucose between rest and exercise, and although the moderate exercise reduced blood glucose an average of 50 mg/dL and IHI exercise an average of 35 mg/dL, the differences between the types of exercise were not found to be statistically significant. A randomized crossover study by Shetty, et.al. in 2015 identified an inverse u-shape between exercise intensity and glucose requirements [36]. A euglycemic clamp was used as 9 participants engaged in exercise on four occasions randomized at various levels of VO_{2max} (35, 50, 65 and 80% VO_{2max}) and glucose requirements were recorded during the exercise. Glucose infusion rates increased for exercises with intensities up to 65% of VO_{2max} with statistical significance up to 50% VO_{2max}. This study found that glucose was not required at when participants engaged in exercise at 80% VO_{2max}.

In 2007 Guelfi, el. al. conducted a similar study in which they determined VO_{2max} for 9 participants and then randomized the order of 45 minutes of rest, IHI exercise and moderate exercise at 40% VO_{2max} [37]. During each type of activity blood glucose levels were maintained with glucose infusion delivered intravenously. Although exercise did

require significant amounts of glucose infusion to maintain blood glucose, the differences in the amount of infused glucose were not significantly different between the two types of exercise. In 2013, Yardley, et.al failed to establish a difference in the reduction of blood glucose between 45 minutes of continuous exercise at 60% VO_{2max} and resistance training in their study that included 8 participants [38]. In their study, aerobic exercise reduced blood glucose by 60 mg/dL while resistance training had a reduction of 28 mg/dL, but the differences were not significant.

Campbell, et.al. conducted a study in 2014 where 8 participants engaged in 45 minutes of exercise at 70% VO_{2max} with the order of the insulin delivery 1 hour before exercise randomized between no change in the regular bolus to a 75% reduction in the regular insulin bolus accompanied with a meal [39]. This study identified a 120 mg/dL drop in glucose for both arms of the study, with the insulin reduction arm having a lower risk for hypoglycemic events. Mauvais-Jarvis, et.al. used a relatively large cohort with 12 participants and determined the VO_{2max} [40]. Then 60 minutes of exercise at 70% VO_{2max} was held constant while the amount of insulin delivered before mid-morning exercise was randomized between a regular bolus or a 90% reduction of the regular insulin bolus. Sucrose was provided partway through the exercise event for 8 of the participants during the regular insulin bolus arm of the study while the bolus reduction arm did not experience any hypoglycemic events. This study found that blood glucose levels fell an average of 90 mg/dL during both arms of the study.

Although the study conducted by Mallad, et.al. focused on the use of glucose tracers, they recorded the glucose levels of 75 minutes of moderated exercise (estimated

50% VO_{2max}) for 16 participants and found that the average drop in glucose was 120 mg/dL [41].

In a review of the current literature on exercise and type 1 diabetes, Kourtoglou synthesizes the findings from various studies to describe the biological mechanisms at play that effect glucose levels during exercise [11]. Kourtoglou explains that insulin sensitivity increases during physical activity while glucose production from the glucagon stores in the liver increases as well. While this response generally leads to hypoglycemia, it can produce hyperglycemia in certain types of intense exercise. Most types of exercise, including light, moderate, and some types of vigorous exercise will cause blood glucose levels to drop, which may cause hypoglycemia during or after completion of the physical activity. Exercise-induced hypoglycemia can be mitigated by consuming carbohydrates when engaging in exercise.

2.5.4 Effects of alcoholic beverages on blood glucose

The ADA guidelines suggest that for patients who drink alcohol they should do so in moderation, that is 2 or fewer drinks per day for men and 1 or fewer drinks per day for women [8]. The difficulty with alcohol and diabetes is the risk of hypoglycemia, which has been documented to contribute up to 6% of hypoglycemic admissions in the emergency department amongst patients treated with insulin [42]. Depending on the specific content of the drink, alcoholic beverages can be a source of carbohydrates and/or can cause hypoglycemia due to the metabolic effects of alcohol. Evidence on alcohol and type 1 diabetes is sparse, difficult to compare due to differences in study design and beverage types used, and results are often contradictory. Although most studies show

that consuming alcohol with a meal increases the risk of hypoglycemia the next day [17,43–45], the results at 2-3 hours following the ingestion of alcohol vary. Studies by Koivisto et.al. and Gin et.al. show that there is no postprandial difference when consuming alcoholic beverages with an appreciable carbohydrate content (e.g. red wine) in conjunction with a meal [43,45]. Both studies had a small number of participants (n=10, n=5, respectively) when participants were given identical meals on two different occasions with one served with alcohol. Two other studies by Turner, et. al. and Richardson, et.al. show that postprandial levels after consuming alcohol with little to no carbohydrate content (e.g. spirits) with a meal were 45-55 mg/dL lower when compared to an equal volume of water served as a control in combination with an identical meal [17,44]. Again, both studies had a small number of participants, 6 and 16, respectively. In addition to drinking in moderation, the ADA suggests that alcohol is consumed with a meal in order to lessen the potential for acute and delayed hypoglycemia [8].

2.5.5 Other factors that influence blood glucose

There are various factors that can affect blood glucose levels that include food, medication, activity, and biology that can be found in the literature and in patient forums. As discussed in section 2.5.1 and 2.5.4, carbohydrates and alcoholic beverages have an effect on glucose levels, but to a varying degree, so does the fat and protein content of foods and caffeine levels of beverages. There are various medications that can cause blood glucose to increase or decrease, with steroids being an example of a medication that can cause glucose levels to spike. Stress, illness, hormones, lack of sleep and scar tissue can also cause glucose levels to rise. The scope of this work is to focus on patient

preferences, and most of the factors listed here are items that patients may have very little control over and are difficult to measure or quantify and therefore were not chosen to be included in the development of the iDECIDE decision aid at this time.

2.5.6 Decision support systems for maintaining glycemic control

Sophisticated decision support tools that are under development are referred to as the artificial pancreas, or closed-loop systems. These systems attempt to almost completely remove the burden of monitoring glucose and delivering insulin by incorporating sensor-augmented insulin pumps with predictive insulin delivery algorithms that account for carbohydrates and learn from historical patient dose-response data [46]. These systems have consistently shown increased percentage of time in target glucose ranges while also averting hypoglycemic events [47–50]. Currently these devices are not ready for commercial use, though there are ongoing initiatives between academia and industry that may aim to bring the technology to the marked in the coming years [48]. While the results from several studies demonstrate that closed-loop devices have the potential to improve glucose control [51–54], few studies have reported specifics on how the proposed algorithms performed when compensating for exercise and alcohol [55–58].

Similarly, existing mobile applications (apps) are sub-optimal for meeting glucose targets. There has been a proliferation of smartphone apps for diabetes care. In 2009 advice from 137 mobile diabetes applications for diabetes were compared against evidence-based guidelines. It was found that there were obvious gaps between the evidence-based recommendations and the functionality of the apps [59]. Another review

found that the majority of the apps available for diabetes offered only one or two functionalities that support self-management, such as documentation, data sharing, analysis, visualization, education, reminders, and therapeutic recommendations [60]. While reviewers found that improved usability scores correlated with that apps that supported fewer functions, patients may result to using multiple apps to gain access to needed functions, thus complicating self-management even further.

GlucoseBuddy, an app that was developed by SkyHealth LLC and released in 2008, had over 100,000 downloads in 2013. GlucoseBuddy allows users to log glucose levels, insulin doses, nutrition, and exercise. Researchers conducted a randomized controlled trial with GlucoseBuddy by recruiting 72 participants with T1D over the course of 6 months. For this study, data was shared with diabetes educators who reviewed the data and sent personalized text messages to participants in the intervention group on a weekly basis. Results showed a significant improvement in glycemic control for participants in the intervention arm of the study [61].

Behavior change is an important part of diabetes self-management, and unfortunately there are few apps that include behavior change techniques, and those that do are not based on validated behavioral theories. Even fewer apps that have been reviewed provide tailored support using data collected from the user to improve adherence to self-management [62]. Additionally, the FDA has determined that it will only regulate apps that qualify as medical devices, leaving patients with little more than app ratings to guide them as they select apps to assist with diabetes self-management. Further complicating the diabetes app market is that there appears to be several insulin

dosing calculators available as apps, a criteria that qualifies them as a medical device, which are not FDA approved [63].

In 2015, 46 insulin dosing calculators were identified that perform simple mathematical calculations using carbohydrate intake and blood glucose [64]. From those, 30% did not document the formulas used, and 67% carried a risk of inappropriate output dose recommendations that violated basic clinical assumptions. In the US there are few FDA-regulated mobile apps that provide bolus calculators, and none of them take into account exercise and alcohol [21]

In order to lessen the burden of manually calculating insulin boluses, bolus calculators have been developed and disseminated to patients. Bolus calculators have been deployed as simple stand-alone sliding scales, but at present bolus calculators are primarily integrated into electronic medical devices [65]. For example, glucose meters and insulin pumps have embedded bolus calculators. It is estimated that one million people use insulin pumps worldwide with Medtronic MiniMed, Inc. reporting 70% of the market share and approximately 400,000 pumps in use in the USA [66,67]. At the outset of this study many of the patients at the Arizona Mayo Clinic used Medtronic insulin pumps, which influenced our choice to focus on Medtronic pumps for the remainder of this study.

2.5.7 Medtronic's decision aid for calculating pre-meal insulin boluses

Current bolus calculators embedded into insulin pumps do not account for exercise or alcohol. They implement variations of Equation 2.1 when computing bolus insulin. Here we describe the algorithm used by the insulin pump manufacturer,

Medtronic, which uses Equation 2.1 as the base equation. In order to determine IOB, the insulin pump requires that a parameter called the active insulin time be set by the user or care provider. The active insulin time is used to back calculate how much insulin may still be left in the patient's bloodstream from previous boluses in order to prevent insulin stacking which can lead to hypoglycemia. Additionally, ICR, CF and low and high target glucose parameters are programmed into the insulin pump bolus calculator, which values are generally determined by the provider.

The Medtronic Bolus Wizard which is embedded into insulin pumps uses 4 variations of Equation 2.1 which are based on current blood glucose levels and how they compare to individualized target blood glucose ranges for the patient [28].

1. If cBG is greater than tBG, IOB is included in the calculation as well as the blood glucose and food correction portions of the equation. If the blood glucose correction minus IOB is a negative number, then only the food correction portion of Equation 2.1 is used in the calculation.
2. If cBG is less than tBG, IOB is not included in the calculation. The blood glucose correction is then added to the food correction.
3. If cBG is at tBG, then only the food correction portion of the equation is used.
4. If no cBG is provided, then only the food correction portion of the equation is used.

These data required for calculating bolus insulin, along with data acquired via glucose meters or continuous glucose monitor systems, changes to pump settings, patient-

reported carbohydrate intake, and other information generated by the insulin pump are recorded in tabular format as depicted in Figure 2.2.

Timestamp	BG	Type	Select	Deliver	Est	High	Low	ICR	ISF	Carbs	BG	IOB
8/8/2016 21:30		Normal	2.3	2.3								
8/9/2016 10:31		Normal	0.7	0.7								
8/9/2016 12:57	106											
8/9/2016 13:04		Normal	1.9	1.9								
8/9/2016 18:54		Normal	0.1	0.1								
8/9/2016 18:54					0	120	85	20	40	0	48	0
8/9/2016 20:07		Normal	1.8	1.8								
8/10/2016 12:00	94											
8/10/2016 13:41		Normal	1.4	1.4								
8/10/2016 21:58	111											
8/11/2016 6:38	78											
8/11/2016 13:06	235											
8/11/2016 13:06		Normal	3.8	3.8								
8/11/2016 18:40	129											
8/11/2016 23:23					0.9	139	120	20	40	28	101	0
8/11/2016 23:23		Normal	0.1	0.1								

Figure 2.2: Screenshot of condensed raw insulin pump data which includes: timestamp, blood glucose reading received from a connected meter (BG), type of bolus delivered (Type), the bolus amount selected by the patient (Select) and actually delivered (Deliver) by the pump, the bolus suggestion (Est), insulin pump settings (High, Low, ICR, ISF), user-reported carbohydrates (Carbs, BG reading used for calculation (BG), the insulin on board (IOB), readings from a continuous glucose meter (not shown), changes made to insulin pump settings (not shown), and other information generated internally by the insulin pump (not shown). In the example above, the bolus calculator made two insulin recommendations, 0 units at 8/9/2016 18:54 and 0.9 units at 8/11/2016 23:23, both of which the user overrode and selected 0.1 units to be delivered. Six additional insulin boluses were delivered by the participant without accessing the insulin pump bolus calculator. Also, the patient checked blood glucose 6 times over the course of three days.

Calculating bolus insulin using Equation 2.1 is a difficult mental task for most people to perform. Bolus calculators have been incorporated into glucose meters and insulin pumps to lessen the cognitive burden of calculating bolus insulin. The use of bolus calculators has been shown to greatly improve patient's accuracy when calculating

an appropriate insulin bolus. Despite the advantages provided by bolus calculators embedded in insulin pumps, these decisional aids do not account for exercise and alcohol, two of many variables (e.g. stress, medications, etc.) that are known to affect glucose levels. During most types of light to moderate exercise blood glucose levels will decrease, while sustained vigorous exercise may actually increase glucose. The acute and delayed effects of alcohol conflict from one study to another. It may be the case that postprandial hypoglycemia may be averted by consuming an alcoholic beverage that contains a high carbohydrate to alcohol ratio (e.g. beer, drinks mixed with regular soda) in conjunction with a meal.

While the artificial pancreas may eventually provide a closed-loop system, this technology has not yet completely addressed the effects of exercise and alcohol and is still not ready for patient use. Smartphone apps that support self-management of diabetes and provide insulin bolus calculations also fail to account for exercise and alcohol and very few have been approved for use by the FDA.

The current state of decisional aids for patients with diabetes leads us to believe that our aim to develop a decision support system deployed as a smartphone app, iDECIDE, that accounts not only for meals and glycemic excursions, but also for exercise and alcohol would be beneficial to improve glucose control.

3 SELF-MANAGEMENT BEHAVIORS IN ADULTS ON INSULIN PUMP THERAPY: WHAT ARE PATIENTS REALLY DOING?

3.1 Introduction

Successful diabetes management requires behavioral changes to improve glycemic control and achieve better health outcomes. While there have been many studies that focus on children, adolescents and emerging adults, little is known about the self-management behaviors of adults on insulin pump therapy. One study that included all ages found that less than one third of the participants had achieved recommended glycemic control (HbA1c < 6.5%) and that those with excellent control were more likely to exercise regularly, self-monitor blood glucose more frequently and have fewer instances of missing an insulin dose [68]. Most studies on adherence have relied upon indirect methods of measurement which introduce error and bias, such as patient self-report via interviews and surveys [69]. Some of the limitations that arise from self-report methodologies can be overcome by using direct methods to assess adherence by using objectively gathered data from diabetes technology [70]. This chapter identifies and quantifies self-management behaviors in adults with type 1 diabetes who employ insulin pump therapy (Aim 2) by using direct and indirect methods and correlates the behaviors with glycemic outcomes based on participant's individual glucose targets.

One month of raw insulin pump data in tabular format was downloaded from 19 participants. For each participant, there were approximately 10,000 rows of data and 30 columns documenting user entry of carbohydrates, function overrides (e.g. adjust basal rates), blood glucose meter readings, continuous glucose monitoring output, calculations

for determining insulin bolus recommendations, and other internal pump messages and functions. Computer programs were written to automatically analyze each row of data in order to quantify the observed frequency of expected behaviors such as insulin bolusing, checking blood glucose and recording carbohydrate intakes, as well as other interaction observed with the insulin pump based on the data collected and stored by the insulin pump. The following behaviors were automatically extracted with computer programs based on a sample of insulin pump data in Figure 2.2: 1) the participant accessed the bolus calculator on two occasions, 2) the participant selected a different amount of insulin bolus to deliver on both occasions, 3) six additional insulin boluses were delivered by the participant without accessing the insulin pump bolus calculator, and 4) the patient checked blood glucose 6 times over the course of three days.

Over 4,000 insulin pump interactions were analyzed from the 19 participants to ascertain behaviors. There was inter-subject variability in adherence to most of the minimally expected behaviors for self-management and a high frequency of behaviors not recommended for self-care. Additionally, there there was little use of advanced insulin pump features despite the participants having an average of 11 years of insulin pump therapy. Adherence to delivering insulin boluses was high and consistent with 96.8% (5.7) daily adherence. Daily documentation of carbohydrates and blood glucose checks had lower rates of adherence and high variability, 76.6% (31.7) and 60.0% (32.5), respectively. Bolusing without accessing the insulin pump bolus calculator, which is in general a not recommended behavior, occurred in 13.0% (16.9) of the delivered boluses while selecting a square waveform, an advanced pump feature, was used in 6.4% (10.8)

of delivered boluses. Higher frequency of adherence to daily behaviors correlated with a higher number of glucose readings at target. We also found that 87% of boluses delivered by patients resulted from accessing the insulin pump bolus calculator which indicates that patients generally use the bolus calculator to deliver insulin boluses. This finding suggests that in many instances patients may benefit from an insulin dosing algorithm that accounts for additional lifestyle preferences, such as exercise and alcohol.

Preliminary results of this work were presented as posters at the 2015 Diabetes Technology Conference and at the American Diabetes Association (ADA) 76th Scientific Session [71,72] (APPENDIX A.2 and A.3). The ADA poster was also selected to be part of a moderated poster discussion on "Insulin-related Issues and Other Topics in Diabetes Care." Chapter sections 3.2 through 3.5 represent the extended version of those posters which has been published in the Journal of Diabetes Science and Technology [73] (Appendix C.1).

3.2 Background

Optimizing glucose control in patients with type 1 diabetes mellitus (T1D) is known to reduce microvascular and macrovascular complications [2]. The intensive insulin therapy needed to accomplish glycemic goals can be delivered either via multiple daily injections or continuous subcutaneous insulin infusion devices, also referred to as insulin pump (IP) therapy. However, intensive insulin therapy alone is not sufficient to achieve desired glycemic goals. Successful diabetes self-management requires behavioral changes in order to achieve glucose targets. The 2016 ADA Standards of Care Guidelines outline the behaviors required for daily self-management, including

recommendations to monitor blood glucose (BG) 6-10 times per day, and dose prandial insulin 3-4 times per day as it relates to carbohydrate intake [8]. Adherence to recommended behaviors is difficult to achieve and maintain for a variety of reasons, with many barriers, such as social, contextual, psychological, educational and economic [74]. Diabetes technology (e.g. insulin pumps and glucose meters) and other consumer health information technologies (e.g. telemedicine and smartphone apps) have been found to to improve diabetes self-management adherence and improve glycemic control [75].

As technology for diabetes has advanced, so have the informatics capabilities of IPs and BG monitors. Devices store objectively measured data that can be downloaded and used to quantify behaviors and outcomes. IPs store data such as the bolus amount suggested by the insulin pump bolus calculator (IPBC), the bolus amount selected by the patient, carbohydrates entered into the IP by the patient, and BG levels from a connected BG monitor and/or a continuous glucose monitoring system (CGMS).

Adherence to self-management behaviors (SMB) such as carbohydrate intake, administering insulin boluses to cover meals, and monitoring of BG have been studied in children, youth and emerging adults (18-26 years old) with various criteria, methods and sources of data, including IPs [76–80]. Although IP therapy has been found to improve glycemic control, suboptimal adherence can result in poor glycemic control [77,81]. There is a lack of studies that describe SMB in adults with T1D. The objective of this study was to use IP data to analyze and characterize common behaviors related to insulin bolus dosing, BG monitoring and carbohydrate intake observed in adults with T1D, and to correlate those behaviors with glycemic outcomes.

3.3 Methods and Materials

3.3.1 Study recruitment

After Institutional Review Board approval, we recruited adults with T1D from an outpatient academic endocrinology practice. We identified potential participants at routine quarterly visits and they were contacted to set up a recruiting appointment. After participant consent we remotely gathered data after 30 days of participation. Therefore, data was collected after the appointment with the provider and well before the next quarterly appointment.

3.3.2 Participant selection

We adopted the following inclusion criteria: patients who had been under the care of the endocrinology team for at least one year, 18-70 years of age, non-pregnant, English speaking, and using the same IP, Medtronic MiniMed, Inc [28]. The exclusion criteria included: fragile health, limited life expectancy, records of mental health problems, advanced vascular disease or micro-vascular complications, known history of severe hypoglycemia or advanced atherosclerosis. Participants were part of a larger study that collected additional data to compare insulin bolus algorithms [82,83].

3.3.3 Data collection and cleaning

Participants' IP data was downloaded in its source format (i.e. spreadsheet). IP data included carbohydrates recorded by the participant, BG levels from CGMS or capillary BG monitor or both, amount of insulin suggested and delivered by the pump, and personalized pump settings and BG targets which may have varied over the course of

a 24-hour period. Computer programs were written to automate the process of quantifying the IP behaviors and glycemic outcomes.

We identified over 4,000 interactions with the IP in this study. Using code, we removed duplicate BG readings that occurred in within 4 minutes of each other since CGMS sent readings every 5 minutes. We included in the analysis values that were entered manually, recorded from IP connected BG meters and CGMS. We did not identify any means to identify BG readings that resulted from user-error, and as such, no BG values recorded with the IP were excluded after the data cleaning process.

3.3.4 Minimally expected self-management behaviors

Following O'Connell, et.al. and Driscoll, et. al. the minimally expected daily SMB for glycemic control were defined as: 1) counting carbohydrates 3 or more times per day (assuming at least 3 meals per day), 2) delivering an insulin bolus 3 or more times per day to correspond to those meals, and 3) checking BG 4 or more times per day (once for each meal and before bedtime) [77,78]. These behaviors were quantified on a daily basis for each participant and two-sided, unequal t-tests were used between those using capillary glucose monitoring and CGMS. Fisher's exact test was used to compare adherent days to non-adherent days when considering BG readings that were within target. These parameters were assessed because they could be directly derived from IP/CGMS data.

The correlation of the above three diabetes SMB was analyzed with BG outcomes. Glycemic control was addressed on a daily basis by categorizing BG as low, at target or high based on each participant's personalized BG targets. The number of BG

readings within the target range for the participant over the course of a 24-hour day were compared to the total number of BG readings. BG readings were obtained from manual entry, synchronized glucose meter or CGMS.

3.3.5 Insulin bolusing behaviors

How often participants selected the same, smaller or larger insulin bolus that was suggested by IPBC was evaluated. Additionally, the number of times the IPBC was accessed was and this value was used to calculate the percentage of IPBC overrides.

Finally, participants may have opted to deliver insulin boluses without consulting the IPBC. They may have changed the waveform (e.g. normal to square), which is considered an advanced IP feature. The delivered boluses for each participant were counted and used to calculate the percentage of delivered boluses that were self-determined (i.e. the participant did not access the IPBC for a suggestion before delivering an insulin bolus) and how often the bolus waveform was changed.

3.4 Results

3.4.1 Participant characteristics

There were 19 participants recruited; 7 employed CGMS and the remainder utilized capillary glucose monitoring (Paradigm System), with 13 participants using one or more BG meters that communicated with the IP. Four IPs were used by the participants: 9 on MiniMed530G-551, 1 on MiniMed530G-751, 5 on ParadigmRevel-523, and 4 on ParadigmRevel-723. The average participant age was 48(15) years and the self-reported duration of T1D and duration of IP therapy was 27(13) and 11(5) years, respectively. Mean HbA1c was 7.3(1.0). There was a higher percentage of recruited

women (63%) and most were white (95%). We analyzed an average of 32(4.8) days of data from each participant and a total of 4,249 interactions with the IPBC. All data are reported as mean and standard deviation (SD).

3.4.2 Daily minimally expected self-management behaviors

Inter-subject variability to the three minimally expected daily behaviors was observed (Table 3.1: Observed frequency of investigator defined minimally expected daily behaviors, differentiating between the group of participants under capillary glucose monitoring and the group using CGMS. Reported as mean (SD), range.). Carbohydrates were entered into the IPBC 3 or more times per day an average of 76.6%(31.7%). Levels of adherence were similar between those on CGMS and capillary glucose monitoring, 84.0%(29.7%) and 72.3%(33.3%), respectively. Five participants showed adherence to this behavior 100% of the time, while one participant showed a maximum of 2 carbohydrate entries per day. Carbohydrates were documented an average of 3.9(1.6) times per day.

Participants delivered insulin boluses an expected 3 or more times per day an average 96.8%(5.7%). There were 11 participants whose observed bolus adherence was 100%; all but one participant achieved 90% or better adherence. On average participants delivered an insulin bolus 7.5(3.6) times per day. Although not statistically significant, participants on CGMS delivered an average of 9.4(4.8) boluses per day while participants using capillary glucose monitoring averaged 6.5(2.3) boluses per day.

Adherence to glucose checks was similar for participants on CGMS when compared to those on capillary glucose monitoring even though providers at the Mayo

clinic advise patients on CGMS to calibrate with a capillary glucose check a minimum of 2 times per day. On average, participants on CGMS checked BG 4.5(1.4) times per day and those on capillary glucose monitoring checked 4.2(2.5) times per day. None of the participants were perfectly adherent to checking or recording BG and only 3 achieved 90% or better adherence.

When all three minimally expected behaviors were considered together participants were simultaneously adherent to all three investigator-defined guidelines on average 52.3%(34.3%) of days. None of the participants were found to be 100% adherent and two individuals never engaged in the three recommendations simultaneously. Adherence of all three behaviors between CGMS and capillary glucose monitoring was similar, 61.5%(32.9%) and 48.4%(35.5%), respectively.

Table 3.1: Observed frequency of investigator defined minimally expected daily behaviors, differentiating between the group of participants under capillary glucose monitoring and the group using CGMS. Reported as mean (SD), range.

BG Behavior	Capillary Glucose Monitoring	CGMS	p-value	Group Total
Documented carbohydrates 3 or more times/day, %	72.3 (33.3) 0.0 – 100	84.0 (29.7) 17.2 – 100	0.44	76.6 (31.7) 0.0 - 100
Administered insulin bolus 3 or more times/day, %	97.4 (5.6) 80.6 – 100	95.6 (6.2) 82.8 - 100	0.53	96.8 (5.7) 80.6 - 100
Documented BG 4 or more times/day, %	55.8 (36.1) 0.0 – 94.4	67.8 (26.4) 37.9 – 96.4	0.45	60.0 (32.5) 0.0 - 96.4
All 3 behaviors/day, %	48.4 (35.5) 0.0 – 88.9	61.5 (32.9) 6.9 – 93.6	0.43	53.2 (34.3) 0.0 - 93.5
Documented carbohydrates/day, #	3.8 (1.5) 1.1 – 6.0	4.2 (1.8) 1.4 – 6.7	0.62	3.9 (1.6) 1.1 – 6.7
Administered insulin bolus/day, #	6.5 (2.3) 3.8 – 11.8	9.4 (4.8) 3.9 – 18.3	0.17	7.5 (3.6) 3.8 – 18.3
Documented BG/day, #	4.2 (2.5) 1.2 – 11.1	4.5 (1.4) 3.2 – 7.2	0.72	4.3 (2.1) 1.2 – 11.1

3.4.3 Relationship between daily minimally expected behaviors and glucose targets

As depicted in Figure 3.1, when participants entered carbohydrates 3 or more times per day they achieved their individualized target BG in 4.6%(4.1%) of the recorded BG values during the 24-hours. Days when that behavior was not observed the target BG was achieved 0.8%(1.7%). When participants were observed bolusing 3 or more times per day it resulted in 5.2%(3.7%) BG readings at target, days when bolusing was less than 3 the target BG was recorded 0.1%(0.3%). On days that participants checked BG 4

or more times per day they achieved target BG 3.5%(3.0%) versus 1.8%(3.3%) on days that expected behavior was not observed. When participants were adherent to all three minimally expected behaviors BG was at target 3.3%(3.0%), and 2.4%(3.2%) on days they failed to meet all three behaviors. Although these findings were not significant (Fisher's exact test), there was a high correlation between the observed frequency of behaviors and the percentage of BG readings that were at target. Although not statistically significant, increasing the number of daily insulin boluses had the largest impact on increasing the number of BG readings at target for the day, r=0.93. Consuming carbohydrates and checking BG had correlation values of r=0.75 and r=0.53, respectively.

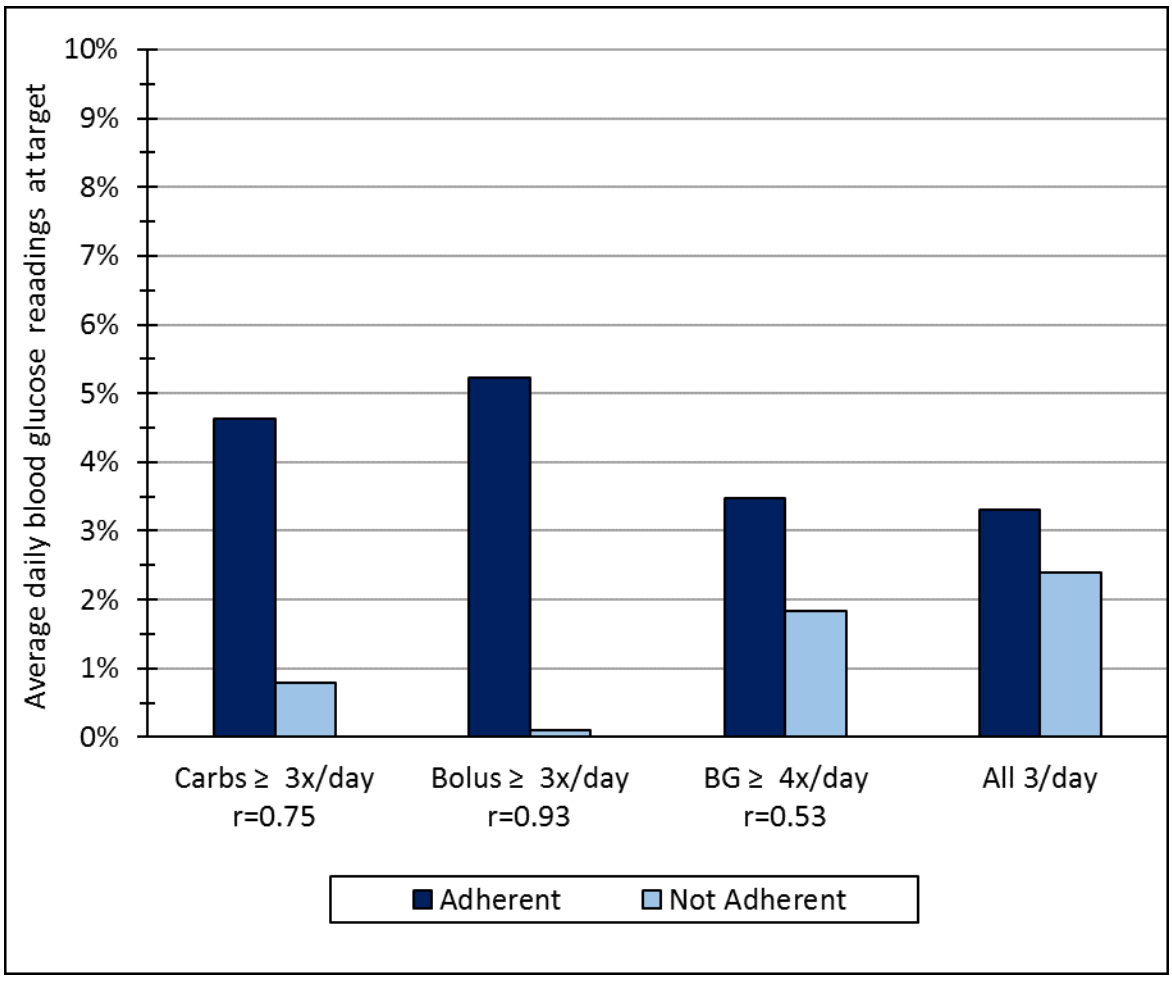


Figure 3.1: Comparison of blood glucose control for observed adherent/non-adherent days based on investigator defined optimal behaviors and percentage of blood glucose readings at target for the day. Along the x-axis are the behaviors of interest, while the y-axis the average of daily blood glucose readings at target on a scale of 0% to 10%.

3.4.4 Daily insulin bolusing behaviors

Table 3.2: Overview of the insulin pump bolus calculator (IPBC), insulin bolus decisions and additional information regarding the optimal behaviors. Data reported as mean or % (SD), range. provides results for additional behaviors that were observed and analyzed. Over the course of the month participants accessed the IPBC on average

198.7(94.3) times and insulin boluses were delivered 220.7(78.7) times during the same time period. Two-thirds, 66.6%(16.1%), of the IPBC recommendations resulted from participants entering carbohydrates. Correction BG readings were provided by participants in 74.8%(24.4%) of the IPBC recommendations. Nine participants frequently entered BG corrections (>90%) while 4 participants entered BG corrections less than 50% of the time.

Participants chose to deliver the same bolus amount as suggested by the IPBC in 85.7%(12.7%) of delivered boluses (Table 3.2: Overview of the insulin pump bolus calculator (IPBC), insulin bolus decisions and additional information regarding the optimal behaviors. Data reported as mean or % (SD), range.). There were 8 participants who very often (>90%) chose the same bolus as the IPBC, while one participant chose a different bolus in 51% of the delivered boluses. Participants were nearly even on their preference for choosing a larger or smaller bolus, 7.4%(6.1%) and 6.9%(9.3%), respectively.

In 6.4%(10.8%) of the delivered boluses participants changed the waveform from normal to dual or square. A majority of the participants (n=14) never or rarely (<5.0%) changed the bolus waveform while 3 participants changed the waveform in over 25% of the boluses they delivered. Participants occasionally chose to deliver an insulin bolus without consulting the IPBC, which constituted 13.0%(16.9%) of the delivered boluses. While 10 participants never or rarely (<5.0%) delivered an insulin bolus without consulting the IPBC, two participants delivered approximately 50% of their insulin boluses without accessing the IPBC.

Table 3.2: Overview of the insulin pump bolus calculator (IPBC), insulin bolus decisions and additional information regarding the optimal behaviors. Data reported as mean or % (SD), range.

Access IPBC	**Value**
IPBC recommendation provided, #	198.7 (94.3), 62 – 449
BG control guidelines	
Carbohydrates entered to IPBC, %	66.6 (16.1), 38.8 – 100
Boluses delivered, #	220.7 (78.7), 109 – 380
BG entered to IPBC, %	74.8 (24.4), 35.8 – 100
Bolus recommendations from IPBC	
Select same bolus suggested by IPBC, %	85.7 (12.7), 49.1 – 100
Select larger bolus than suggested by IPBC, %	7.4 (6.1), 0.0 – 18.5
Select smaller bolus than suggested by IPBC, %	6.9 (9.3), 0.0 – 32.7
Other Bolus Decisions	
Select square or dual bolus waveform, %	6.4 (10.8), 0.0 – 30.4
Bolus without consulting IPBC, %	13.0 (16.9), 0.0 - 52.7

3.4.5 Monthly frequency of expected self-management behaviors

In addition to the daily analysis of participant's behavior (Table 3.1 & Table 3.2), we analyzed for each participant the monthly frequency of five distinct behaviors: 1) disregarding BG readings and only accounting for carbohydrates when using the IPBC, 2) bolusing without consulting the IPBC, 3) changing the bolus waveform to dual/square, 4) choosing insulin boluses different from those suggested by the IPBC, and 5) frequent bolusing: 4 or more boluses in a 5-hour time period or delivering 10 or more boluses during a 24-hour period. As shown in Table 3.3: Categories of insulin compensation techniques observed in study participants, including: 1) disregarding BG readings and

only accounting for carbohydrates when using the IPBC, 2) bolusing without consulting the pump, 3) changing the insulin bolus delivery from waveform to square, 4) choosing insulin boluses different from those suggested by the IPBC, and 5) bolusing 4 or more times in a 5-hour period or delivering 10 or more boluses during a 24-hour period., we categorized each participant as never (0 events), rarely (1-4 events), occasionally (5-14 events), regularly (15-90 events) or excessively (more than 90 events) showing a behavior over the course of one month.

We observed that 15 participants occasionally or regularly chose a different insulin bolus than the one recommended by the IPBC and that 4 participants rarely or never chose a different bolus. All the behaviors reported in Table 3.3 were automatically computed, except for the frequency of blousing which was manually counted on a subset of the participants: 7 on CGMS and 2 on capillary glucose monitoring. Out of the subset of 9 participants, 3 occasionally or regularly bolused frequently while 6 rarely or never bloused frequently.

Using the IPBC to adjust for meal's carbohydrates while omitting a current BG reading was done regularly or excessively by 9 participants, while 9 rarely or never omitted a current BG reading and 1 occasionally did so. Bolusing without consulting the IPBC was done regularly or excessively by 8 participants and 10 rarely or never delivered a bolus without the IPBC and 1 occasionally bolused without the IPBC. There were 13 participants that never or rarely changed the bolus waveform and 6 who regularly or excessively changed the bolus waveform.

There were some associations between insulin pump behaviors and patient profiles that emerged as well. Compensating for carbohydrates without checking BG was negatively correlated with changing the waveform to square while selecting a different bolus was positively correlated with square waveform delivery. There were four participants whose behaviors correlated inversely to the two patterns just mentioned, and these four participants had the highest frequency of delivering square waveform boluses. There were 10 participants that regularly or excessively omitted BG readings when using the insulin pump bolus calculator, and 7 of them never or rarely selected a different insulin bolus than suggested by the pump, while 6 of the remaining 9 participants occasionally or regularly selected a different bolus. This pattern may arise from situations where participants are unaware of glucose trends or are unable to check glucose levels, and as such are less likely to override the IPBC when only compensating for carbohydrates.

Table 3.3: Categories of insulin compensation techniques observed in study participants, including: 1) disregarding BG readings and only accounting for carbohydrates when using the IPBC, 2) bolusing without consulting the pump, 3) changing the insulin bolus delivery from waveform to square, 4) choosing insulin boluses different from those suggested by the IPBC, and 5) bolusing 4 or more times in a 5-hour period or delivering 10 or more boluses during a 24-hour period.

Behavior	**Never** (0 events)	**Rarely** (1-4 events)	**Occasionally** (5-14 events)	**Regularly** (15-90 events)	**Excessively** (90+ events)
Compute carbs only (n=19)	7	2	1	5	4
Bolus without consulting pump (n=19)	7	3	1	7	1
Change waveform to dual/square (n=19)	10	3	0	5	1
Clinically different bolus selected (n=19)	3	1	7	8	0
Frequent boluses (n=9)	4	2	2	1	0

3.5 Discussion

Diabetes behavior studies have mainly relied upon self-reported data gathered from interviews, surveys and questionnaires [76,80,84]. These methods have been used to gather qualitative data which contributes to the understanding of behavioral diabetes such as insights about the beliefs, motivations, perceptions and expectations of the patient which can be used to inform changes to therapy regimens that can improve adherence [85,86]. There are limitations to self-reported data such as recall bias (i.e. inaccurately remember and report behaviors) and social desirability (i.e. over-report favorable

behavior and under-report poor behavior). White coat adherence may be a source of bias when measurement instruments are delivered during patient-provider encounters since patients may improve their SMB in the days or weeks leading up to the appointment [87,88]. In our case data was collected after the appointment with the provider and months before the next appointment.

Although we were able to assess the adherence to diabetes management recommendations and other SMB by using device recorded data, this study was limited by a small sample size which lacked the power to detect differences between groups. The demographics of this cohort may not be representative of the general T1D population based on race and HbA1c. Another limitation of this study is that participants may have used one or more glucose meters that did not communicate with the IP and subsequently the use of those devices would not have been captured by the IP.

Consistent with other studies, we found that there was variability of observed behaviors across participants and that there was a direct correlation between daily adherence to expected SMB and better glycemic control [76–80]. Although this cohort had an average of 11 years' experience with IP therapy, advanced features, such as changing the bolus waveform to dual or square, were used infrequently.

The ADA guidelines suggest that treatment regimens may be intensified if patients are adherent to their current regimen, or in the case of poor adherence the routine should be simplified in order to improve adherence [8]. Clinicians relying only on self-reported assessments may overestimate patients' adherence since it has been shown that patients who struggle with adherence are less likely to honestly report their deficiencies

in SMB [84,89]. While clinicians mainly rely on quantified data coming from diabetes technology, this type of data has limitations, too. Actual behaviors may be different from what was documented in the IP. For instance, a participant had a meal and delivered a bolus without entering carbohydrates and without requesting advice from the IPBC. This may partially explain why the behavior with the highest frequency was delivering insulin boluses.

In this study we found that increasing the frequency of insulin boluses, calculating carbohydrate consumption and checking BG had a positive impact on glycemic control with the delivery of insulin boluses having the greatest impact. Providing real-time monitoring via the IP, or other appropriate device (e.g. smartphone app with wireless connection to IP) on these minimally expected behaviors could empower patients and improve daily diabetes self-management and glycemic control.

For providers, presenting information gathered by IPs in ways that are clinically relevant and actionable could be empowering. Availability of precise and complete BG data that is presented in a structured manner enables providers to more efficiently and accurately identify glucose patterns which can lead to more accurate therapeutic decisions [90–92]. Take for instance Table 3.3: Categories of insulin compensation techniques observed in study participants, including: 1) disregarding BG readings and only accounting for carbohydrates when using the IPBC, 2) bolusing without consulting the pump, 3) changing the insulin bolus delivery from waveform to square, 4) choosing insulin boluses different from those suggested by the IPBC, and 5) bolusing 4 or more times in a 5-hour period or delivering 10 or more boluses during a 24-hour period., where

we classified the frequency of five observed behaviors by monthly frequency (never, rarely, occasionally, regularly and excessively), instead of daily means and SDs (Table 3.2). This way to visualize the data could help the clinician to better identify patients that behaved in a certain way more often or less often than the average patient. For instance, if during the last month the patient never changed the bolus waveform, the clinician could spend time during the next clinical encounter reviewing how to change the bolus delivery in the IP and discussing potential meal types that could benefit from a square insulin delivery to improve glycemic control. For the example of the patient who frequently boluses (15-90 monthly events when the patient delivers 10 insulin boluses per day or more than 5 boluses within 4 hours), the clinician can review the patient's endocrine settings to identify if the basal rate needs to be changed to reduce frequency of insulin bolusing. Even with the small number of participants we were able to identify associations between certain behaviors. Identifying patient profiles based on similar behaviors could also be helpful in the design and implementation of interventions aimed at improving adherence. It remains as an open question to understand which are the best ways to present patients' diabetes SMB to providers to facilitate their decision process.

3.6 Conclusion

This study quantified observed SMB of adults on IP therapy by analyzing objectively recorded data from IPs. A limitation of our research is that we did not collect information on the reasons behind observed participants' behaviors. Nevertheless, the results from this quantitative study show that the majority of the adult patients on insulin pump therapy in this study regularly seek guidance from the bolus calculator imbedded in

the insulin pump to dose preprandial insulin boluses as well as boluses to correct for out-target glucose. This study establishes that for meals and glucose excursions patients have adopted SMBs that incorporate technologies that provide decisional support as they self-monitor glucose levels.

In Chapter 2 we reviewed the Medtronic MiniMed, Inc. [28] bolus calculator and its intended use as specified by the manufacturer [28]. We also met with a diabetes education nurse to understand how patients with diabetes are trained to use the IPBC. This helped us to understand in theory how the IPBC has been designed to be incorporated in the self-management of diabetes. In this study we were able to observe patients in real-life situations which helped us to understand how they actually integrate the IPBC into daily self-management routines. The insight we gained from this study has proved to be very helpful as we have progressed with the design and development of the iDECIDE decision aid and incorporating it into the iDECIDE smartphone app.

In Chapter 2 we also identified that current diabetes technologies do not incorporate exercise or alcohol, two lifestyle preferences known to affect glucose levels, into algorithms that suggest insulin bolus amounts. In the following chapter we conducted a study on how patients compensate for exercise and alcohol to further assess the need for decisional support tools that account for exercise and alcohol.

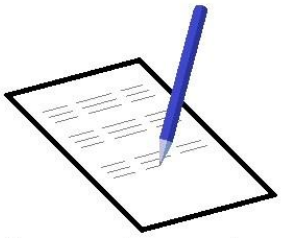
4 CHARACTERIZATION OF EXERCISE AND ALCOHOL SELF-MANAGEMENT BEHAVIORS OF TYPE 1 DIABETES PATIENTS ON INSULIN PUMP THERAPY

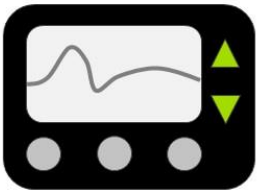
4.1 Introduction

There is a lack of systematic ways to analyze how diabetes patient use their insulin pumps to self-manage blood glucose to compensate for alcohol ingestion and exercise. This chapter uses qualitative and quantitative methods to better understand how patients on insulin pump therapy compensate for exercise and alcohol to maintain glycemic control (Aim 2).

We recruited adults with type 1 diabetes (T1D) on insulin pump therapy to analyze "real life" insulin dosing decisions occurring in conjunction with alcohol intake and exercise. Participants were asked to maintain their daily routines, including those related to exercising and consuming alcohol. Participants kept a 30-day journal on the exercise they performed and the alcohol consumed which were later manually coded into tabular format. Thirty days of corresponding insulin pump data were downloaded. Computer programs were written to automatically collate insulin pump and journal data. Each row in the journal data that contained an exercise or alcohol event was analyzed for its temporal relationships to participants' actual insulin dosing behaviors as recorded by the insulin pump. For example, the computer programs would scan for an exercise or alcohol event from the journal data and then identify if any compensation techniques (e.g. consume carbohydrates, check BG) occurred immediately before, during or after the exercise event. In the collated data in Figure 4.1 there are two exercise events, the first

one was accompanied by blood glucose check, carbohydrates and an insulin bolus 21 minutes after completion. The participant also consumed carbohydrates and delivered an insulin bolus 22 minutes before consuming alcohol but did not check blood glucose levels.





Time	Event	Intensity	Duration	Drink	Volume
3/30 07:00	Exercise	Vigorous	30 min.		
3/30 12:30	Alcohol			Light Beer	12 oz.
3/31 06:30	Exercise	Light	25 min.		

Time	Bolus (U)	Carbs (g)	BG (mg/dL)
3/30 07:51	1.2	10	118
3/30 12:08	3.5	45	--
3/30 18:11	2.7	30	172

Time	Event	Intensity	Duration	Drink	Volume	Bolus	Carbs	BG (mg/dL)
3/30 07:00	Exercise	Vigorous	30 min.					
3/30 07:51	Pump					1.2	10	118
3/30 12:08	Pump					3.5	45	--
3/30 12:30	Alcohol			Light Beer	12 oz.			
3/30 18:11	Pump					2.7	30	172
3/31 06:30	Exercise	Light	25 min.					

Figure 4.1: Paper logs were manually coded into tabular data and then were automatically merged with raw data from the insulin pump. Each row of collated data was analyzed for temporal relationships between insulin pump behaviors and exercise and alcohol.

Nineteen patients were recruited and over 4,000 interactions with the insulin pump were analyzed. The analysis exposed variability in how subjects perceived the

effects of exercise and alcohol on their blood glucose, inconsistencies between self-reported and observed behaviors, and higher rates of blood glucose control behaviors for exercise vs. alcohol. These findings further validated the need to propose an insulin dosing algorithm that accounts for exercise and alcohol (Aim 3).

The results from this research were first presented as a poster at the Diabetes Technology Meeting 2015 and then as a poster at the ADA 76th Scientific Session 2016 [71,72] (APPENDIX A.2 and A.3). Chapter sections 4.2 through 4.5 comprises the extended version of those posters which was published in the Journal of Diabetes Science and Technology [93] (APPENDIX C.2).

4.2 Background

While evidence shows that alcohol and exercise affect the absorption of insulin and increase the risk of hypoglycemia, there is a lack of evidence-based decision tools to allow for translation of this information into practice [11,13,15,16]. Patients with T1D must manage their disease by injecting insulin deliverable through syringes, insulin pens, or insulin pumps. Pre-meal insulin dosage compliance and accuracy is a key factor in achieving target postprandial glucose levels. Insulin pumps, being used in 2013 by over 350,000 people in the US [94], incorporate proprietary mathematical algorithms called bolus calculators or bolus wizards to determine individualized pre-meal dosing [29,95,96]. The benefits achieved through the use of insulin pumps and continuous glucose monitors (CGM) are not necessarily a direct result of wearing the devices but rather due to behavioral and management changes enabled by the information provided by the devices to the users [95]. While bolus calculators and CGMs can lead to better

glucose control [7,10], bolus calculators currently cannot account for the lifestyle complexities of alcohol ingestion and planned exercise [12–14,17,97,98].

Among adult T1D patients, little is known about patient self-management behaviors in the setting of alcohol intake and exercise. A review of the literature demonstrated a lack of studies analyzing adult T1D patients' self-reported behaviors against their actual behaviors documented from data collected by an insulin pump. Better understanding of these behaviors could help in the design of educational programs, particularly as it relates to intensive insulin therapy, and aid in designing better dosing algorithms that account for behaviors related to alcohol consumption and exercise patterns. The aim of this study was to analyze adult T1D patients self-reported vs. actual self-management behaviors occurring in conjunction with alcohol intake and exercise.

4.3 Methods and Materials

4.3.1 Subject Recruitment

After Institutional Review Board approvals 19 adult T1D patients were recruited from an academic outpatient endocrinology clinic. Participants were between the ages of 18-70, non-pregnant, English speaking, who had been using an insulin pump from a single vendor for at least one year. Patients in fragile health, limited life expectancy, a history of mental health problems, advanced vascular disease or micro vascular complications and known history of severe hypoglycemia were excluded. Study personnel identified potential subjects at the time of their scheduled outpatient visit. Subjects were handed a flyer that provided details on the study.

4.3.2 Data collection

The study team conducted structured interviews to collect participants' self-reported perceptions of how alcohol and exercise affected blood glucose levels and the sources of information used to learn about these interactions. Additionally, subjects were asked if they accounted for alcohol and exercise in their insulin dosing decisions, and what type of techniques they used to compensate for these behaviors (e.g. carbohydrate consumption, reduction in insulin bolus or basal rate, or some combination of these methods).

Participants were asked to maintain their daily routine and to keep a journal on the time, duration and intensity of exercise performed (e.g. at 9:00 a.m. performed 20 minutes of high intensity exercise) and the time, type and amount of alcohol consumed (e.g. at 10:20 p.m. drank a can of light beer) for 4 consecutive weeks. Patient's recorded how they compensated for alcohol and exercise on the logs. Participants were called once during the study to assess progress and answer questions. At the end of the data collection period, patients mailed or faxed in their completed alcohol and exercise logs.

The study team also obtained the data contained within the participants' insulin pump during the same 4-week period. The patients uploaded the insulin pump data through a website provided by the insulin pump's manufacturer, which was remotely accessed by study personnel. Once the data was downloaded the patients were encouraged to change their passwords. Alternatively, patients could meet in person with a member of the study team who could download the data from the patient's insulin pump.

4.3.3 Data analysis

Subjects' perceptions of the effect of alcohol and exercise on glucose levels and their sources of information regarding alcohol and exercise were tabulated. Data from the paper-based diaries were electronically coded and analyzed to quantify for each study participant number of drinks and frequency of exercise. To report patients' observed behaviors for exercise and alcohol we reviewed data downloaded from the insulin pumps and from the participants' paper-based diaries to quantify how often patients used techniques to compensate for alcohol ingestion and exercise activity, such as adjusting insulin (basal rate or bolus) or taking snack within 30 minutes before exercising. Computer algorithms were written to associate self-reported days and times of alcohol consumption and exercise to the corresponding data collected by the insulin pumps. Using the aggregated data, the frequency of compensation techniques related to carbohydrate consumption, insulin boluses delivered, and blood glucose monitoring occurring in close temporal proximity to exercise or alcohol consumption was computed for each study participant. Close temporal proximity was defined as ±30 minutes of alcohol consumption or exercises.

4.4 Results

4.4.1 Demographics

Nineteen subjects with T1D were recruited. Mean (SD) age was 48 (15) years, 12 were women, and 18 were of white race. Mean (SD) hemoglobin A1c was 7.3 (1.0)%, self-reported duration of diabetes was 27 (13) years, and duration of insulin pump therapy was 11 (5) years. Seven participants wore a CGMS, and the remaining used capillary

glucose monitoring. There were 4,249 interactions between the study participants with the insulin pump bolus calculator analyzed. There were 347 exercise events recorded by 17 participants and 155 alcohol events recorded by 11 participants.

4.4.2 Perceived interactions and sources of alcohol and exercise information

When subjects were asked about how alcohol or exercise impacted their glucose control, there were no consistent responses observed (Table 4.1). There were 7 participants who all stated that exercise lowers blood sugar, another 7 whose responses varied on how glucose reacted to exercise, and another 5 without responses. With respect to alcohol (Table 4.1), 8 participants stated that their reactions to alcohol depended on factors like the number of drinks (e.g. only compensating when consuming 2 or more drinks) or type of drinks (e.g. differentiating between drinks with high or low alcohol concentration), 1 who stated there was no effect on glucose, 2 who did not know, and 8 who did not respond.

Participants also reported deriving information on how exercise and alcohol affected their blood glucose from a number of different sources (Table 4.2). Most participants indicated they learned about the interactions from trial and error and had developed their own heuristics. Few participants reported having received information or education from providers on approaches to compensate for alcohol or exercise when self-managing blood glucose. Two participants indicated that they would like to receive more information on the way alcohol affects blood glucose.

Table 4.1: Subject perceptions on how exercise and alcohol affect blood glucose.

Activity	No. of subjects	Perception	Sample comments
Exercise	7	It lowers blood glucose	"In the past, drinking causes low blood glucose overnight"
	7	Various effects, based on type of activity, intensity and time of day	"Interval training elevates or lowers blood glucose, backpacking raises it" "The effect depends on the time of day and the type of exercise" "Exercise may not drop blood glucose" "Morning exercise raises the blood glucose, but evening exercise lowers it"
	5	No reported data	
Alcohol	8	Various effects, based on number of drinks and drink type	"Alcohol raises blood glucose initially and lower it hours later" "Beer raises blood sugar" "I feel I have to take insulin if I have beer, but no insulin if I have hard alcohol" "Almost always raises it" "If I have more than a few drinks the blood glucose lowers, if I have hard alcohol it raises and then lowers"
	1	No effect or minimal effect	"I don't see much effect"
	2	Lack of knowledge	"I don't know; I need more information"
	8	No reported data or N/A	"I don't drink"

Table 4.2: Subject self-reported sources of education on how exercise and alcohol affect their blood glucose.

Activity	No. of subjects	Source of education
Exercise	19	Trial and error
	2	Literature/online reading
	2	Provider education
	1	Other diabetes patients
Alcohol	12	Trial and error
	3	Literature/online reading
	1	Provider education
	5	Other diabetes patients
	4	N/A

4.4.3 Overall self-management behaviors

Current American Diabetes Association (ADA) Standards of Care Guidelines suggest that patients should consider checking blood glucose prior to exercise and recommend that in order to avoid hypoglycemia the insulin dose and/or carbohydrate intake may need to be altered [8]. Many health care organizations suggest that alcohol should be consumed with a meal containing carbohydrates in order to avoid hypoglycemia [98–100]. Data entered into the subjects' insulin pumps indicated self-management techniques did not match current recommendations (Figure 4.1). When comparing self-management techniques for exercise versus alcohol, participants consumed carbohydrates (40.9% vs. 20.6%), delivered an insulin bolus (38.3% vs. 26.8%), or checked their blood glucose (60.7% vs. 27.3%) more consistently with exercised than when consuming alcohol.

Similar to [76], study participants' adherence to ADA recommendations for alcohol consumption and exercise were quantified [8]. According to the guidelines "adults with diabetes should be advised to perform at least 150 min/ week of moderate-intensity aerobic physical activity (50–70% of maximum heart rate), spread over at least 3 days/week with no more than 2 consecutive days without exercise". Weekly adherence to this guideline by study participants was 38.4% (45.4), with 5/17 subjects reporting 100% adherence and 10/17 subjects at 0%. The ADA also recommends "adults with diabetes who drink alcohol should do so in moderation (no more than one drink per day for adult women and no more than two drinks per day for adult men)". Adherence to the ADA guidelines for daily alcohol moderation was 94.6% (9.2) within the range of 70 to 100.

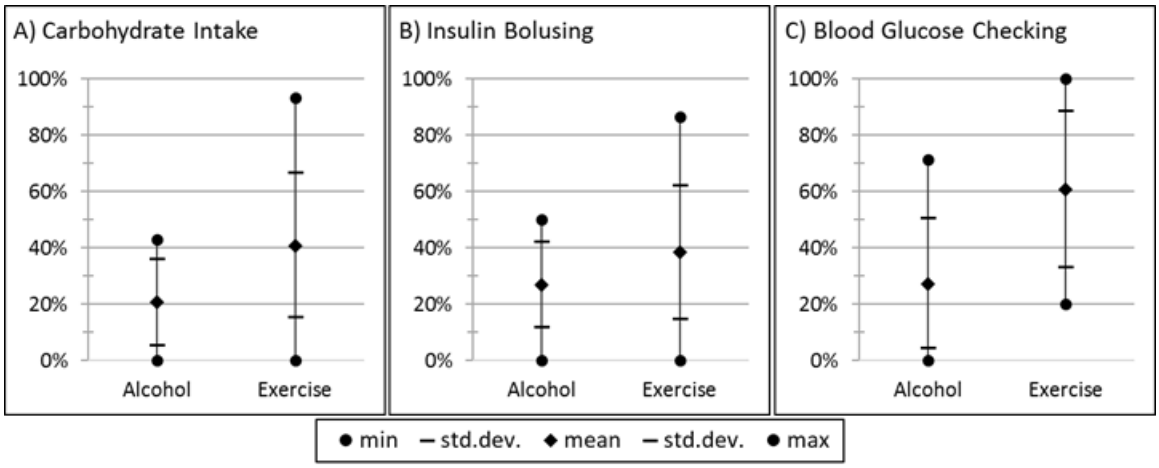


Figure 4.2: A) Carbohydrate intake, B) Insulin bolusing and C) Blood glucose checking within ±30 minutes of exercise or alcohol consumption. For instance, as depicted in A) in temporal proximity of alcohol events subjects consumed carbs with 20.6% mean, 15.3% standard deviation, and 0-42.9% range. In contrast, in proximity to exercise events subjects consumed carbs with 40.9% mean, 25.5% standard deviation and 0-93.3% range.

4.4.4 Observed versus actual behaviors associated with exercise and alcohol

Next, we contrasted subjects reported self-management techniques against observed behaviors for exercise and alcohol, as derived from analysis of corresponding data contained with the subjects' insulin pumps. Self-described compensatory self-management techniques to compensate for exercise and alcohol consumption were categorized as: no compensation, adjusting insulin (reducing basal rates or boluses), ingesting snacks, or removing the pump. When examining behaviors related to exercise, discordance was seen between what subjects claimed they did versus actual behavior. For instance, 16 subjects reported they would adjust insulin pump settings when exercising, while only 7 were observed to have done so (Table 4.3). Another 2 indicated they would take a snack, but 5 were noted to employ this technique. While 2 study participants reported always adjusting basal insulin, no patients were observed always adjusting their basal settings. Although 2 patients reported sometimes removing the pump during exercise, the pump disconnection was not explicitly recorded in the insulin pump data we had access to, hence we were not able to quantify this behavior.

Similar discrepancies were noted between what subjects said they would do and what they actually did when reviewing self-management behaviors related to alcohol ingestion (Table 4.3). For example, 5 subjects indicated they would not compensate for alcohol use, while 8 were actually observed not making any adjustments. There were 10 subjects who indicated they would adjust insulin when drinking alcohol, but only 3 were noted to have done so.

Table 4.3: Patient self-reported compensation techniques and observed behaviros for exercise and alcohol.

Activity	Compensation technique	Comments	No. of subjects reported using the technique	No. of subjects who used the technique
Exercise	No compensation		1	1
	Adjust insulin (basal rate or bolus) sometimes or always	"When I perform strenuous exercise I reduce basal rate" "When I play hockey I take a bolus of 1 ½ unit, then I remove the pump" "When involved in anaerobic exercise I take insulin, if it is aerobic exercise I don't take insulin"	16	7
	Remove pump	"Sometimes I remove my pump"	2	0
	When needed, take snack before exercising	"If my blood sugar is less than 200 in the evening I eat a snack or I reduce the basal rate to half and I get to 100."	2	5
	No data		2	9
Alcohol	No compensation		5	8
	Adjust insulin by compute drinks' carbs, sometimes or always	"I was told by my endocrinologist to not compute drinks' carbs when I take 1 or 2, otherwise yes" "I feel I have to take insulin when I drink beer but no insulin when I drink hard alcohol"	10	3
	No data or NA	"I don't drink"	4	8

4.5 Discussion

Qualitative studies of children, adolescent, and adult diabetes patients have been performed with the purpose of understanding behavioral diabetes care [76,77,80,85,101]. While in general qualitative studies are limited by small sample sizes and do not generate statistically significant data, their findings are crucial to give a glimpse into patients' beliefs, attitudes, behaviors, culture and lifestyle. With diabetes in particular, understanding patients' behaviors is very important to discover the reasons behind non-adherence to treatment or poor glycemic control, and to identify the best ways to deliver effective interventions.

With respect to self-care, qualitative studies have shown that many patients lack understanding of how medications, food, and exercise affect blood glucose control and what kind of information needs to be taken into account (carbohydrate content of food, activity level, etc.) to self-manage diabetes effectively [102,103]. In terms of physical activity, the qualitative study by Hendricks et al. interviewed forty nine emerging adults (18 to 26 years old) to understand their exercise habits and to determine their compliance with the ADA recommendations on physical activity [76]. The ADA recommends at least 30 minutes of daily physical activity for youth. In Hendricks, et. al. study 41% of participants engaged in exercise at least once daily; 55% of those individuals who engaged in daily exercise demonstrated a mean duration of 30 minutes or more. Mean exercise duration was 29.56 minutes/day and ranged from 0 to 157 minutes.

To eliminate inaccuracies from self-reported data and to obtain statistically significant results by increasing the sample sizes, quantitative studies are taking full

advantage of the data generated by diabetes technology as was conducted here. Blood glucose monitors, continuous glucose monitors and insulin pumps can objectively store data that reflects what patients actually do, as opposed to what patients say they are doing (self-reported data). Driscoll and Young-Hyman provide a detailed review of the use of such technology in assessing adherence to diabetes self-management behaviors [70]. Their 2014 review focused on patients' adherence to the ADA Clinical Practice Recommendations with an emphasis on studies that assessed patient adherence to glucose monitoring, insulin administration, medical nutrition therapy, and physical activity [104]. The review by Driscoll and Young-Hyman did not discuss alcohol consumption. In terms of physical activity, their review highlighted the lack of studies that quantify physical activity and suggest the future use of accelerometers to objectively measure physical activity.

The goal of this study was to address the lack of qualitative and quantitative studies to understand adult T1D patients' self-management practices occurring in conjunction with alcohol intake and exercise. Results indicated that subjects did not have a consistent understanding of how exercise and alcohol affected their glucose control, nor did they report a common set of standards on how they compensated for the impact of these common lifestyle choices in their diabetes management. Additionally, there was no one means by which they obtained information on these important topics. Documented adjustments in carbohydrate intake, insulin doses, and glucose monitoring occurred at frequencies lower than what might be expected. In the case of alcohol consumption, very few instances of changes in self-management behavior were noted.

The results demonstrate the need for a revision of current educational strategies to help patients understand proper alcohol and exercise compensation techniques and to encourage consistent behaviors. A number of approaches could be utilized, such as the use of social media, or incorporating more consistent or complete training during diabetes self-management education sessions. Another approach could be the development of software applications that assist patients in making decisions about how to change carbohydrate intake or adjust insulin doses in the event of an exercise or alcohol event.

Further research will be needed to better understand and explain the findings observed here and their practical implications. This study revealed that many patients described using a behavioral technique that was inconsistent with their actual behaviors. While it is clear that subjects were often acting in a manner different than that reported, it is unclear if these study subjects were conscious of these inconsistencies. Future work could aim to better understand real life insulin pump behaviors and look for explanations for observed behaviors from study participants by re-contacting and interviewing them using sets of detailed scenario-based questions that replicate the most frequently observed behaviors. It would also be interesting to review patient data with the subjects to see if they were aware of their inconsistencies. Similar detailed scenario-based questions that could help to understand reasons for patients' common self-management behaviors could be posted to diabetes patients online communities, like Glu (https://myglu.org) or PatientsLikeMe (https://www.patientslikeme.com), that are designed to accelerate research and amplify the collective voice of thousands of diabetes patients.

An important limitation of our study was the use of paper-based records for collecting participant's self-reported data on exercise, alcohol and carbohydrate intake. It is possible that subjects were not recording all their exercise or alcohol events. There are methods available to improve upon the accuracy of the data collected that are currently being employed in a follow-up study currently underway. For instance, to achieve higher accuracy in the reported data on exercise wristband heart rate accelerometers are being provided to subjects that measure the intensity and duration of exercise. In this follow-up study, participants are being asked to use a smartphone app to self-report data on perceptions on how alcohol/exercise affect insulin absorption and sources of education, and food and alcohol consumed and exercise performed. The authors expect to take advantage of the ubiquity of smartphones to obtain more precise records on food and alcohol consumed and exercise performed. Another limitation is the small sample size, although each subject did generate multiple behaviors that could be analyzed.

4.6 Conclusion

The reported analysis of real life diabetes self-management decisions provided insight on behaviors occurring in conjunction with alcohol intake and exercise among patients using insulin pump therapy. The results of this study revealed the need for improved individualized educational techniques and decision support systems to assist patients with incorporating exercise and alcohol into daily life and self-management of their blood glucose. The lessons learned from this study reinforces the need for a decision support tool, like iDECIDE, that accounts not only for meals, but also exercise and alcohol when making insulin bolus suggestions.

5 EVIDENCE-BASED INSULIN BOLUS DOSING ALGORITHM: IDECIDE

5.1 Introduction

In Chapter 2 we reviewed the state of the art on clinical evidence on lifestyle factors that affect diabetes patients' blood glucose control, and decision support tools available to help patients self-manage blood glucose control (Aim 1). Our review indicates that while clinical evidence shows that carbohydrates, alcohol and exercise affect blood glucose control, current diabetes technology only account for carbohydrates when recommending insulin dosing. Chapter 3 helped us to better understand how patients with diabetes use insulin pumps to daily manage their blood glucose and how they compensate for lifestyle choices when they are away from their endocrinologist (Aim 2). The results presented in Chapter 4 showed that subjects did not have a consistent understanding of how exercise and alcohol affected their glucose control, nor did they report a common set of standards on how they compensated for the impact of these common lifestyle choices in their diabetes management (Aim 2). These findings further validated the need to propose an insulin dosing bolus decision aid that accounts for exercise and alcohol. Here we propose iDECIDE, an evidence-based insulin dosing decision aid (Aim 3).

5.2 Background

Current decision aids available to diabetes patients, such as bolus calculators embedded into insulin pumps, consider blood glucose, active insulin, and carbohydrate loads when making insulin recommendations. Exercise and alcohol are two lifestyle preferences known to have an effect on blood glucose. Reference Chapter 2.4.1-2.4.4 for

additional information regarding the effects of carbohydrates, insulin, exercise and alcohol on blood glucose. Reference Chapter 2.4.5-2.4.6 for an expanded background on the state of the art decision support systems for diabetes management.

The objective was to adapt the standard insulin bolus equation (Equation 2.1) to account for exercise and alcohol in order to make recommendations that improve glucose control which are based on evidence identified in the literature review conducted in Chapter 2 (Aim 1).

5.3 Methods and Materials

Evidence regarding the effects of exercise and alcohol were identified in a literature search, see Chapter 2.3 for literature review methods. The results of the literature review with regards to exercise and alcohol were briefly presented in Chapter 2.4.3-2.4.4 (Aim 1). The findings from the literature review were used to expand the standard insulin bolus equation (Equation 2.1) in order to account for exercise and alcohol.

5.4 Results

We propose a new insulin dosing equation (Equation 5.1) that builds upon the standard insulin blousing equation (Equation 2.1). As we noted previously, insulin pump calculators do not consider *exercise* when calculating insulin dosage, neither do they factor in the effects of carbohydrates in alcoholic beverages (*alcohol carbs*). The proposed algorithm incorporates these two additional factors to suggest the dosage of rapid acting insulin or the consumption of carbohydrates. In the following subsections, we describe the components of the iDECIDE insulin dosing bolus calculator.

Equation 5.1: Proposed insulin dosing equation to account for exercise and alcohol carbs**:**

$$U = \left(\frac{carbs + alcohol\ carbs}{ICR} + \frac{cBG - tBG}{CF} - IOB\right) - exercise$$

$$If\ U \leq 0\ then\ carbs = exercise$$

5.4.1 Accounting for carbohydrates in meals

A preprandial insulin bolus is delivered in order to account for the carbohydrate load in meals. The amount of carbohydrates that 1 unit of insulin will cover is the insulin to carbohydrate ratio (ICR). The amount of carbohydrates to be consumed is divided by the ICR in order to determine the amount of insulin bolus to deliver, represented by *U*, which represents the units of insulin.

5.4.2 Accounting of out-of-range blood glucose

When the target blood glucose range is set (*tBG*), the insulin sensitivity factor (ISF), or correction factor (*CF*), is used to determine the amount of insulin to compensate for a current blood glucose (*cBG*) which may be out-of-range. The *CF* is the ratio of how much 1 unit of fast-acting insulin will lower blood glucose over the course of 2-4 hours during a fasting of pre-meal state. When a range of target blood glucose is provided, iDECIDE will correct to the nearest target value when the current blood glucose is out or range.

5.4.3 Accounting for insulin on board

Insulin on board (*IOB*) is calculated to determine the amount of insulin still available in the blood stream to present "insulin stacking" which can lead to hypoglycemia. We adapted the insulin concentration as reported by Lindholm, et. al. as

free serum insulin [105]. Table 5.1 shows the functions that were extrapolated from the Lindholm study and Figure 5.1 depicts the resulting linear function. The calculation of *IOB* considers the area under the linear function by integration which results in 212.52 mU/L of free serum insulin. The calculation for *IOB* is aggregate, so for example if 2.5 hours had elapsed from the injection of 3 units of insulin the area under this portion of curve would be 157.24 mU/L, which is (157.24/212.52) = 74% of the area, or 74% of the insulin would be absorbed. The IOB would be (3 * 0.74) = 0.78 units of insulin.

Table 5.1: Time based calculations for insulin on board, where x is the time in hours following the delivery of an insulin bolus and y is the insulin amount in units.

x	y
x = 0.00 to x <= 0.33	181.82 x
x > 0.33 to x <= 0.49	38.0 + 67.0 x
x > 0.49 to x <= 0.65	60.5 + 21.5 x
x > 0.65 to x <= 2.50	88.5 – 21.5 x
x > 2.50 to x <= 4.00	65.0 – 12.0 x
x > 4.00 to x <= 6.00	50.5 – 8.42 x

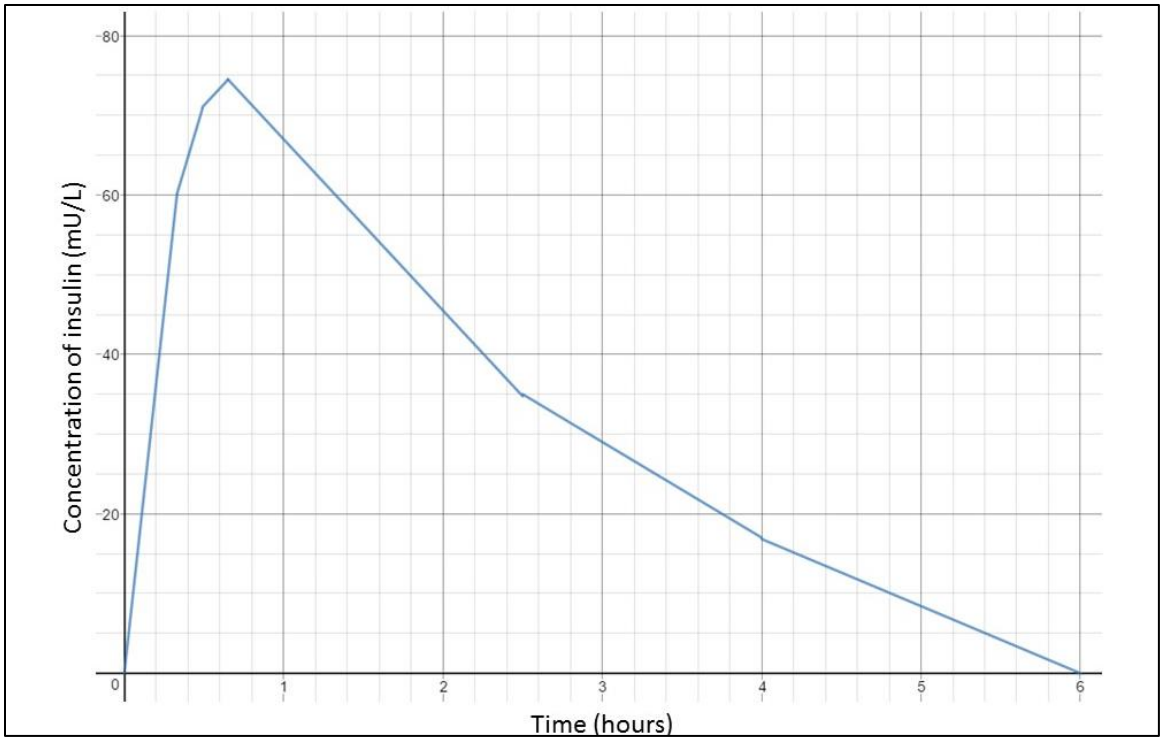


Figure 5.1: Linear function that results from the function shown in Table 5.1, which were extrapolated from Lindholm, et.al. [105].

5.4.4 Accounting for carbohydrates in alcoholic beverages

Studies done by Koivisto, et.al. and Gin, et.al. show that alcohol does not lead to hypoglycemia when the alcoholic beverage served was red wine, a beverage that contains carbohydrates [43,45]. Richardson, et.al. and Turner et.al. served alcoholic beverages with little to no additional carbohydrates and found that blood glucose levels were an average 50 mg/dL lower than when identical meals were served with water [17,44]. This leads us to consider that the carbohydrates associated with the alcoholic beverage may play a role in blood glucose levels and we chose to account for them when calculating insulin boluses.

We reviewed the alcoholic and carbohydrate content of the standard drink size of various beverages and grouped the drinks into the following five categories as depicted in Figure 5.2: Five classes of alcoholic beverages based on the carbohydrate and alcoholic content of one standard serving size. 1) spirits, 2) red wine, 3) light beer, white wine or cocktails, 4) beer or fortified wine, and 5) hard cider or mixed drinks. These categories are used to determine the amount of carbohydrates associated with alcoholic beverages which allows the carbohydrates to be accounted for when calculating an insulin bolus which is reflected in Equation 5.1 (*alcohol carbs*).

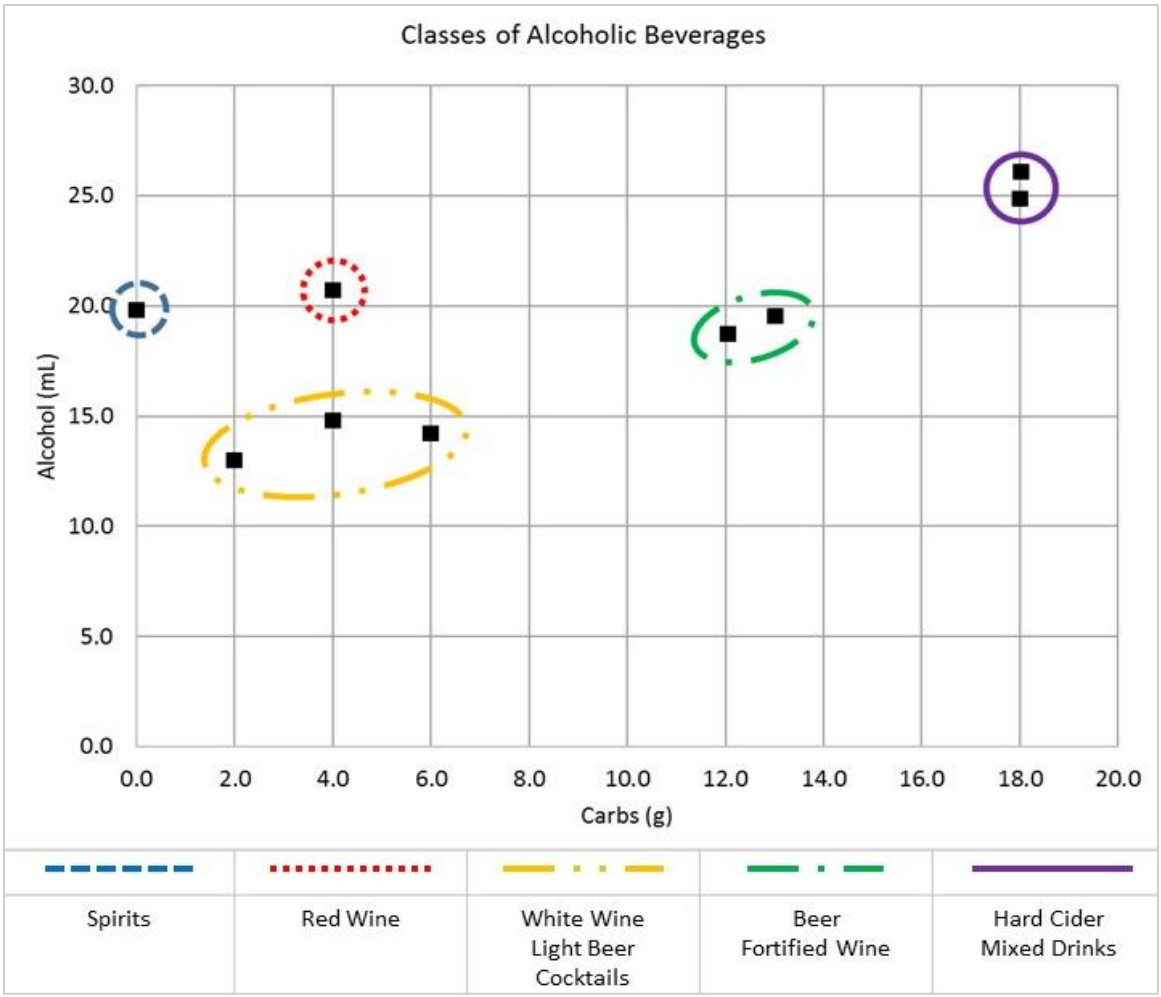


Figure 5.2: Five classes of alcoholic beverages based on the carbohydrate and alcoholic content of one standard serving size.

5.4.5 Accounting for exercise

In the case of *exercise*, the algorithm can suggest an insulin bolus or to consume carbohydrates. After carbohydrates (carbs/*ICR*), including those from alcohol (*alcohol carbs/ICR*), out-of-target blood glucose (*cBG – tBG/CF*) and *IOB* are considered in Equation 5.1, the combination of intensity and duration provides a reduction of the insulin bolus, see Table 5.2 [30]. If the calculation results in a positive amount of insulin

then insulin is suggested, if the calculation results in no insulin or a negative amount of insulin then the body weight of the individual is considered along with the intensity and duration of the exercise to suggest consuming a snack with carbohydrates. See Table 5.3 for the carbohydrate replacement values for every 30 minute increment of exercise [30]. In order to use the carbohydrate replacement lookup table, we specified the weight ranges that map to the weight categories, see Table 5.4

Table 5.2: Insulin reduction based on exercise duration and intensity.

Exercise Intensity	Short Duration (20-40 min)	Moderate Duration (40-60 min)	Long Duration (>60 min)
Light	-10%	-20%	-30%
Moderate	-25%	-33%	-50%
Vigorous	-33%	-50%	-67%

Table 5.3: Carbohydrate suggestion in grams for every 30 minutes of exercise, based on body weight and exercise intensity.

Exercise Intensity	23 kg	45 kg	68 kg	91 kg	114 kg
Light	3g	5g	8g	10g	12g
Moderate	5g	8g	10g	12g	15g
Vigorous	8g	12g	18g	24g	30g

Table 5.4: Weight ranges for using Table 5.3.

Weight Category	Weight Ranges
23 kg	Weight <= 34 kg
45 kg	34 kg < Weight <= 56 kg
68 kg	56 kg < Weight <= 79 kg
91 kg	79 kg < Weight <= 102 kg
114 kg	Weight > 102 kg

5.5 Discussion

We proposed an insulin dosing bolus calculator, iDECIDE, that not only accounts for standard variables, such as carbohydrates from meals and current blood glucose, but also considers exercise and alcohol, two factors that influence glycemic outcomes (Aim 3). One of the limitations of the proposed algorithm is that in its current form it only accounts for the acute effects of exercise and alcohol, although both are known to also have delayed effects on glucose levels [11,44]. One of the advantages of the iDECIDE algorithm is that it is based on clinical evidence that can easily be accessed by clinicians and patients, unlike closed-loop algorithms that use proprietary formulas and techniques such as machine learning that hide the rationality behind proposed recommendations.

Also, recommendations from iDECIDE can be broken down by each component of the equation to provide the reasoning for the insulin of carbohydrate suggestion. As more studies come forward, the iDECIDE decision aid can be adjusted to account for the latest evidence available.

6 A NOVEL METHODOLOGY TO COMPARE INSULIN DOSING ALGORITHMS IN REAL-LIFE SETTINGS

6.1 Introduction

In Chapter 5 we proposed the iDECIDE evidence-based decision aid (Aim 3) to recommend an insulin bolus dosage or carbohydrate intake, by taking into account relevant input on planned carbohydrate consumption from meals and alcohol, and intensity and duration of exercise. Once the decision aid was developed it became necessary to assess its effectiveness to achieve blood glucose control, prior to its implementation as part of a smartphone application and dissemination to patients and providers for clinical use (Aim 4).

Typically, clinical trials are used to determine the safety and efficacy of an intervention. Clinical trials are prospective studies that require a significant amount of resources and expose patients to risks. We found that there was a lack of low-cost and risk-free methods to retrospectively assess the performance of insulin bolus algorithms in preparation for future clinical trials. Therefore, in this chapter we introduce novel methods to retrospectively: 1) compare the appropriateness of insulin bolus suggestions from bolus calculator that was prospectively applied in a real-life setting against a retrospective recommendation from a proposed bolus calculator, and 2) determine the appropriateness of a proposed insulin bolus calculator in cases where there are no recommendations from the conventional approach to compare against.

Later, in Chapter 7, we applied the proposed methods to assess the effectiveness of iDECIDE's recommendations and share lessons learned from collecting, aggregating

and analyzing real-life data generated by insulin pumps and self-reported patient behaviors.

Preliminary results from this research were presented as posters at the Diabetes Science and Technology Meeting 2015 and the American Diabetes Association 76th Scientific Session 2016 [83,106] (APPENDIX A.3 and A.5). An extended version of those posters has been published in the Journal of Diabetes Science and Technology [107] (APPENDIX C.3). Chapter sections 6.2 through 6.3 comprise the portions of the published manuscript that introduce the novel method. The remaining portions of the published manuscript are presented in Chapter 7.

6.2 Background

Models exist to study insulin delivery algorithms in controlled, simulated settings. Before undergoing clinical trials, a common practice to facilitate the design, development and testing of diabetes technology is to use *in-silico* methods [108–113]. Recently, Wong et al. proposed a method to retrospectively compare insulin bolus (IB) algorithms using Intensive Care Unit (ICU) data [114]. They concluded that *in-silico* comparisons appear to be an efficient nonclinical method for allowing rapid and inexpensive identification of computer-based protocols that justify expensive and burdensome clinical trials.

Although algorithms exist to study IB algorithms in controlled environments, there is a lack of methods capable of analyzing glucose data simultaneously with patient behaviors and the goals was to develop an analytic method to retrospectively compare prandial IB recommendations.

6.3 Methods and Materials

6.3.1 Retrospective comparison of two insulin bolus algorithms

To evaluate the performance of the PDA against conventional approaches to prandial insulin dosing, the authors adapted methodology from Wong et. al. [114]. For this study, the conventional approaches to insulin dosing were defined as either use of the IPBC or participant's self-determined doses. The PDA's recommendations were compared against those made by the participant's IPBC, or against the participant when they either overrode or neglected to get advice from their IPBC (Figure 6.1)

The "appropriateness" of an IB was defined as one that brings the postprandial glucose to the desired target [114]. The method assumes that a conventional insulin dosing calculator, BCa (i.e. IPBC or the participant), has made an IB recommendation. The point in time when BCa made the IB suggestion and when the insulin was delivered is referred to as the initial time, t_i. The method assumes that a proposed insulin dosing calculator, BCp (e.g. PDA), is retrospectively executed at the same data point, t_i, to compare at time t_{i+1} the effect on BG of the insulin suggestion from BCp against the actual suggestion that was made by BCa. We considered that one calculator "outperformed" another calculator if there was a major performance enhancement over the competitor. For instance, in the case of a low postprandial BG we consider that a lower insulin dose recommendation outperformed higher insulin dose advice, potentially avoiding a hypoglycemic event.

Applying this methodology requires that each preprandial BG at t_i can be paired with a corresponding postprandial BG at t_{i+1}. For meal events and BG corrections, we

defined t_{i+1} to be the first BG reading obtained 3 hours $\pm$15 minutes, after t_i. This time frame was chosen considering that the majority of the carbohydrate load and the rapid acting insulin analog bolus would have been absorbed and BG levels would have stabilized [105]. The BG readings at t_{i+1} were broken into three categories, based on pre-determined individual target BG levels obtained from the insulin pump settings of each participant. The analysis determines which algorithm provided at time t_i an IB recommendation that would have placed the participant closer to their target BG based on the category of the actual BG reading at t_{i+1}. In the case of a target postprandial BG reading, we considered that a smaller insulin recommendation outperforms a larger recommendation because it could have avoided a hypoglycemic event.

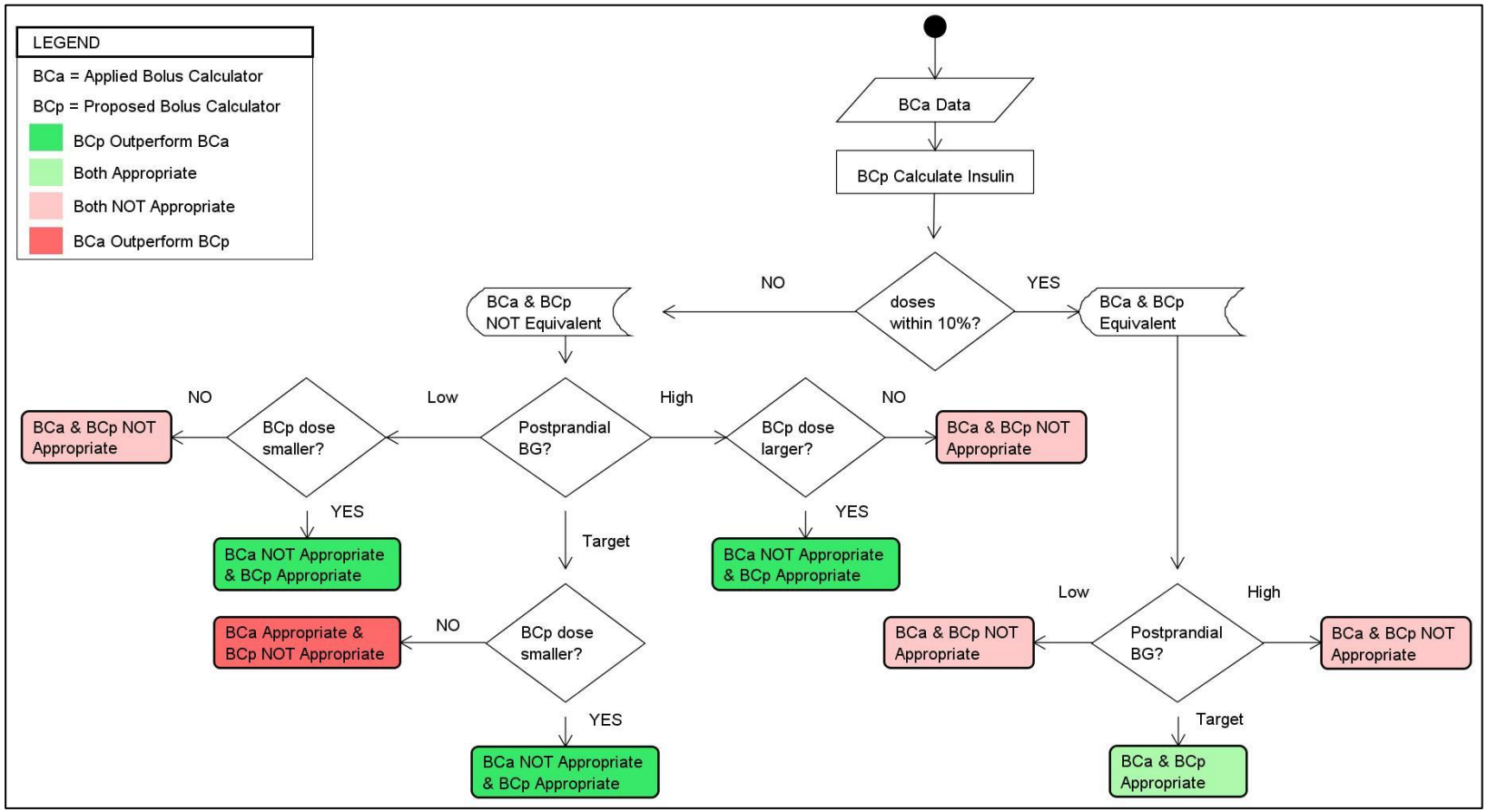

LEGEND
BCa = Applied Bolus Calculator
BCp = Proposed Bolus Calculator
BCp Outperform BCa
Both Appropriate
Both NOT Appropriate
BCa Outperform BCp
BCa Data
BCp Calculate Insulin
doses within 10%?
NO
YES
BCa & BCp NOT Equivalent
BCa & BCp Equivalent
Postprandial BG?
Low
High
BCp dose smaller?
NO
YES
BCa & BCp NOT Appropriate
BCa NOT Appropriate & BCp Appropriate
BCp dose larger?
NO
YES
BCa & BCp NOT Appropriate
BCa NOT Appropriate & BCp Appropriate
Target
BCp dose smaller?
NO
YES
BCa Appropriate & BCp NOT Appropriate
BCa NOT Appropriate & BCp Appropriate
Postprandial BG?
Low
High
BCa & BCp NOT Appropriate
BCa & BCp NOT Appropriate
Target
BCa & BCp Appropriate

Figure 6.1: Method used to retrospectively compare recommendations from two insulin bolus dosing algorithms, BCa and BCp. If the recommendations from *BCa* and *BCp* were within 10% of each other they were considered to be equivalent. If the BG at t_{i+1} was low, then the smaller of the two recommendations from *BCa* and *BCp* was considered appropriate; if they were equivalent then neither was considered appropriate. If the BG at t_{i+1} was at target, then the smaller of the two recommendations from *BCa* and *BCp* was defined as appropriate, preferring recommendations that could avoid hypoglycemic events; if they were equivalent then both were considered appropriate. If the BG at t_{i+1} was above target, then the larger of the two recommendations from *BCa* and *BCp* was deemed appropriate; if they were equivalent then neither was considered appropriate. We considered that one algorithm outperformed the other if there was a major performance enhancement over competitor algorithm. In the case of on target postprandial BG, we consider that a lower insulin dose recommendation outperformed higher insulin dosing advice, potentially avoiding a hypoglycemic event.

The method outlined in Figure 6.1 was used to compare the appropriateness of two calculators, *BCa* and *BCp*, and assumes that *BCa* (IPBC) has made IB recommendations that were delivered to the patient. A variation of that method is needed to assess the appropriateness of recommendations from *BCp* (PDA) when there is no available data from *BCa* (ie, no recommendation from the IPBC).

6.3.2 Assessing the appropriateness of an insulin bolus algorithm for alcohol and exercise

Conventional IPBCs do not provide IB recommendations for alcohol. For these cases the method explained in Figure 6.2 was adopted. The postprandial time frame of interest, t_{i+1}, was defined as the first BG reading obtained within 3 hours $\pm$15 minutes. This time-frame neglects to consider any delayed effects from alcohol induced hypoglycemia and primarily focuses on the carbohydrates associated with alcoholic beverages.

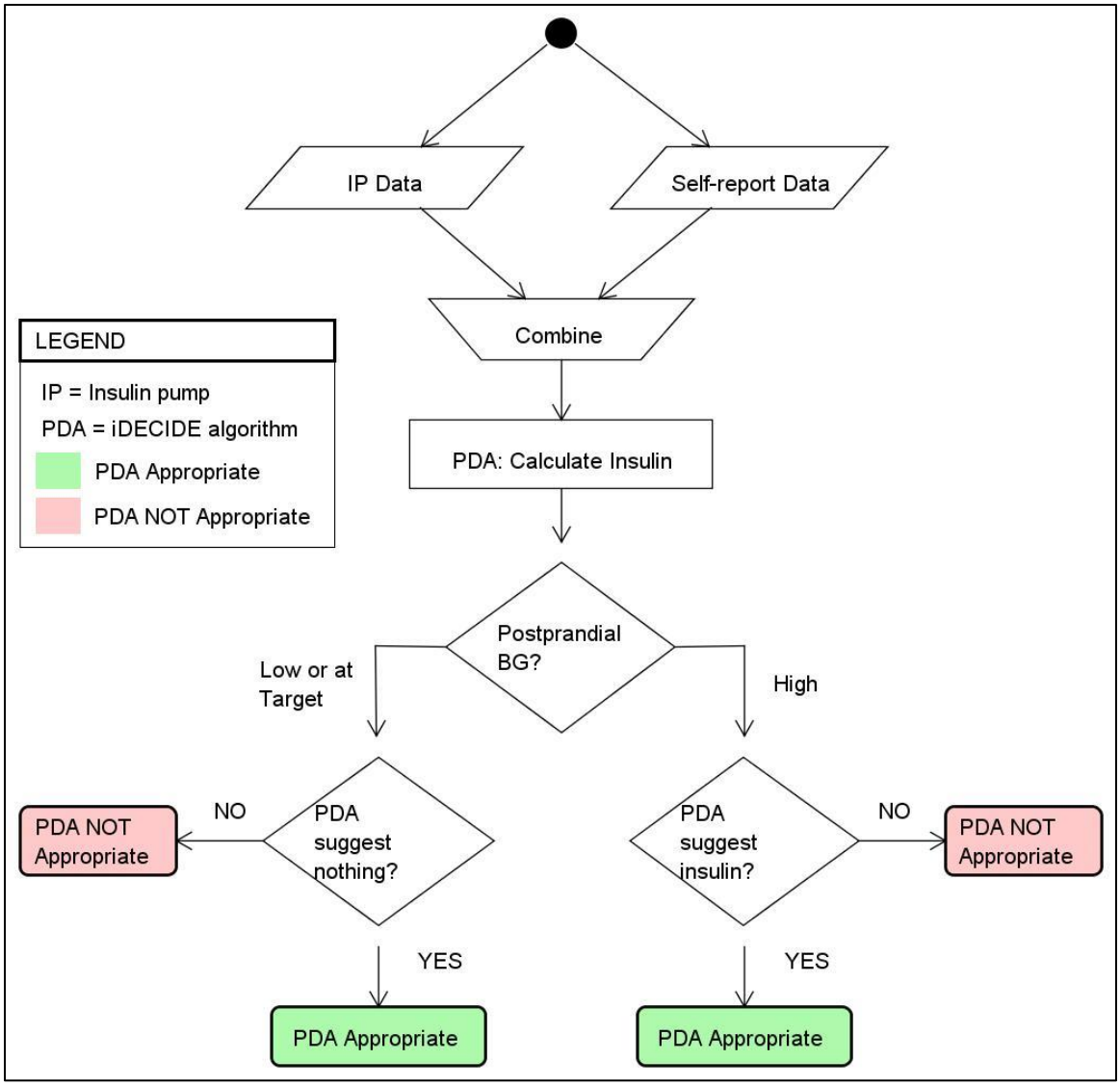


Figure 6.2: Method used for assessing the appropriateness of the recommendations from the proposed decision aid (PDA), when patients choose to consume alcohol, for which the IPBC does not provide insulin dosing recommendations. If the BG at t_{i+1} is low or at target and the PDA did not recommend insulin the recommendation from the PDA was appropriate; if the PDA recommended insulin the recommendation was not considered appropriate. If the BG at t_{i+1} is high and the PDA recommended insulin the recommendation from the PDA was appropriate; if the PDA did not recommend insulin the recommendation was not considered appropriate. Given that our PDA is not compared against another calculator, outperformance is not defined.

As with alcohol ingestion, when participants exercised there were no recommendations made by the IPBC. For those cases, we used the method in Figure 6.3. We modified the window of t_{i+1} to be the first BG reading within 15 minutes of finishing exercise as recorded by the participant to detect any immediate effects of exercise-induced hypoglycemia. For example, if the participant finished exercising at 8:30 AM, we used the first available BG between 8:30 and 8:45 AM. In the case of exercise, the PDA's recommendations could be a carbohydrate snack in addition to an IB dose. For exercise scenarios, the appropriateness of the IB and/or carbohydrate was defined as in Figure 6.3

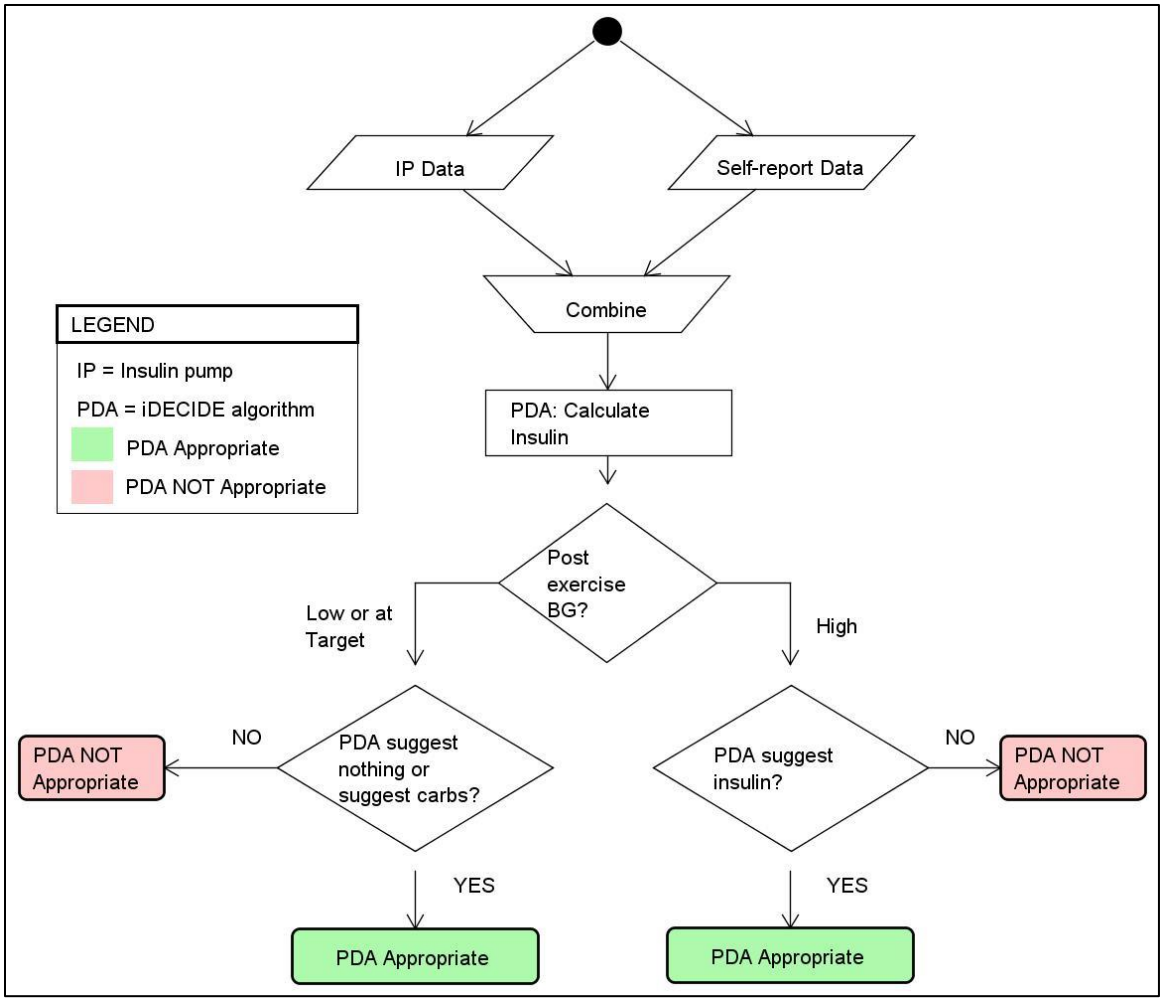


Figure 6.3: Method used for assessing the appropriateness of the recommendations from the proposed decision aid (PDA) when patients choose to exercise, for which the insulin pump bolus calculator does not provide insulin dosing or carbohydrate intake recommendations. If the BG at t_{i+1} was low or at target and the PDA suggested nothing or suggested consuming carbohydrates the recommendation from the PDA was considered appropriate; if the PDA recommended insulin, then the recommendation was deemed not appropriate. If the BG at t_{i+1} was high and the PDA suggested insulin the recommendation from the PDA was considered appropriate; if the PDA suggested no insulin or recommended consuming carbohydrates, then the recommendation was not considered appropriate. Given that the PDA is not compared against another calculator, outperformance is not defined.

6.4 Conclusion

Here we have proposed novel methods for assessing the performance of insulin bolus calculators. This method is low-cost and low-risk as it is designed to use data collected from prospective studies to retrospectively compare a proposed bolus calculator against a conventional approach for prandial insulin dosing (i.e. gold standard). In the next chapter, we will apply these techniques to assess the performance of the iDECIDE algorithm, presented in Chapter 5, against the Medtronic MiniMed, Inc. insulin pump bolus calculator [28] (Aim 4).

7 RETROSPECTIVE ANALYSIS OF THE IDECIDE DECISION AID VS. CONVENTIONAL APPROACHES TO PRANDIAL INSULIN DOSING

7.1 Introduction

In Chapter 6 we proposed novel methods to retrospectively compare insulin bolus recommendations (Aim 4). In this chapter, we apply the methods to: 1) test the performance of the iDECIDE decision aid, explained in Chapter 5, against the Medtronic MiniMed, Inc. [28] IPBC described in Chapter 2, and 2) evaluate the performance of iDECIDE's recommendations in events when the patient exercises or drinks alcohol and no recommendations are provided by the Medtronic IPBC. The results from applying the proposed methods will help to validate the hypothesis that postprandial blood glucose levels can be improved by providing insulin bolus (IB) or carbohydrate recommendations that account for meal and alcohol carbohydrates, exercise and glycemic excursions.

In this study, 15 patients with T1D using insulin pumps were recruited. Informatics capabilities inherent in their insulin pump devices were used to gather glucose and insulin bolus data. Self-reported data on alcohol and exercise, along with the pump data, were collected for 30 days, see Tables 7.1, 7.2 and 7.3 for the tabular format, respectively. The methods described in Chapter 6 were used to compare the IPBC against iDECIDE, a decision aid that accounts for carbohydrates, alcohol and exercise to make recommendations.

Table 7.1: Sample of self-reported alcohol consumption in tabular format. Participants reported the time, drink type and volume. Carbohydrates that were included in the insulin bolus calculation were also reported.

Timestamp	Drink Category	Carbs	Volume (mL)
03/30/2016 08:26:00 PM	Beer	5	237
03/31/2016 07:50:00 PM	Wine	0	100
04/01/2016 09:00:00 PM	Wine	0	148

Table 7.2: Sample of self-reported exercise in tabular format. Participants reported the start time, duration and intensity of the exercise.

Timestamp	Intensity	Duration
03/30/2016 06:58:00 AM	Moderate	65
03/31/2016 08:32:00 AM	Light	255
04/01/2016 07:30:00 AM	Vigorous	50

Table 7.3: A sample of insulin pump data paired with a continuous glucose meter. Two instances of accessing the insulin pump bolus calculator are shown, and the carbohydrates consumed are included in these data.

Timestamp	BG (mg/dL)	Bolus Type	Selected (U)	Delivered (U)	Estimate (U)	High (mg/dL)	Low (mg/dL)	ICR	CF	Carbs	BG	IOB	CGMS
04/03/16 19:38	87												
04/03/16 19:40					4	120	85	20	95	50	87	0	
04/03/16 19:40		Normal	2.5	2.5									
04/03/16 19:50													85
04/03/16 19:55													81
04/03/16 20:00													87
04/03/16 20:05													93
04/03/16 20:15													99
04/03/16 20:20													105
04/03/16 20:25													116
04/03/16 20:35													126
04/03/16 20:41	135												
04/03/16 20:45					0.7	120	85	20	95	40	135	1.5	
04/03/16 20:45		Normal	0.5	0.5									
04/03/16 22:35													165
04/03/16 22:40													161
04/03/16 22:45													154

When comparing iDECIDE against the IPBC, equivalent insulin recommendations were made in 63% cases and iDECIDE outperformed in 23% while the IPBC outperformed in 14%. When comparing iDECIDE against participants' self-determined boluses (bolus amounts delivered by participants without consulting the IPBC or overriding recommendations form the IPBC), iDECIDE made equivalent recommendations in 36% of the events and outperformed in 37% and the participants outperformed in 27%. iDECIDE made appropriate recommendations in 64% of the alcohol events and 75% of the exercise events.

Preliminary results from this research were presented as posters at the Diabetes Science and Technology Meeting 2015 and the American Diabetes Association 76th Scientific Session 2016 [83,106] (APPENDIX A.4 and A.5). An extended version of those posters has been published in the Journal of Diabetes Science and Technology [107] (APPENDIX C.3). Chapter sections 7.2 through 7.4 comprise the portions of the published manuscript that deal with subject recruitment, data collection and results from applying the novel methodology. The portions of the published manuscript, i.e. introduction of the novel methodology to compare insulin dosing algorithms, was presented in Chapter 6.

7.2 Background

Current standards of care for patients with type 1 diabetes (T1D) advocate for tight control of blood glucose (BG) [8]. One treatment challenge for patients with T1D is optimization of postprandial glucose levels [115–117]. To help patients achieve improved glucose regulation, continuous subcutaneous insulin infusion devices (CSII, aka "insulin

pumps") sometimes coupled with continuous glucose monitoring systems (CGMs), have been developed. Although devices can assist patients in making insulin dosing decisions through the use of bolus calculators, it is unknown how accurate the bolus recommendations are in real-life scenarios when complex lifestyle choices, such as exercise and alcohol intake, have to be considered in decision making. Recent data suggests that patients are often confused and inconsistent when trying to factor in these behaviors when deciding insulin doses [73,93].

The aim was to apply the proposed method (Chapter 6) in a real-life setting to test the performance of the iDECIDE evidence-based IB algorithm against the bolus calculator of an insulin pump, and share lessons learned from collecting, aggregating and analyzing real-life data generated by insulin pumps and self-reported patient behaviors.

7.3 Methods and Materials

7.3.1 Description of the iDECIDE Evidence-based based Insulin Bolusing Dosing Decision Aid

iDECIDE, the PDA evaluated here, is an evidence-based decision aid to recommend IB doses, carbohydrate intake, or both, by taking into account carbohydrates and alcohol consumed, and/or exercise plans [22]. The PDA was deployed as a smartphone app to help patients with T1D incorporate varied lifestyle choices simultaneously into decisions about prandial insulin dosing. The PDA is based on the formula proposed by Colin [29] to include alcohol [17,44], exercise [11,12,15,30] and the absorption rate of rapid-acting insulin [105], The PDA corrects to the nearest target glucose setting when the blood glucose is out of range, but would not account for the

CGMS trendline. Exercise is accounted for based on body weight and duration and intensity of exercise, while the alcoholic beverage type and volume consumed are necessary to adjust for alcoholic beverages.

When the user launches the PDA application the first time he is prompted to set up a diabetes profile: weight, insulin-to-carbohydrate ratios, target BG levels, correction factors and active insulin time [118]. Although participants did not set up their user profile for the study, those that did not use paper logs interacted with the self-reporting module to log (1) exercise, describing duration and intensity, (2) food intake, specifying food type, serving size and carbohydrate content, and (3) alcohol intake, indicating number of drinks, size, and type of drink (Figure 7.4). In addition, when self-reporting plans, the user is expected to enter the BG reading. The PDA subsequently recommends an IB or carbohydrate intake by incorporating current evidence on the way food and alcohol carbohydrates and exercise influence BG, but these recommendations were assessed retrospectively and were not provided to the participants.

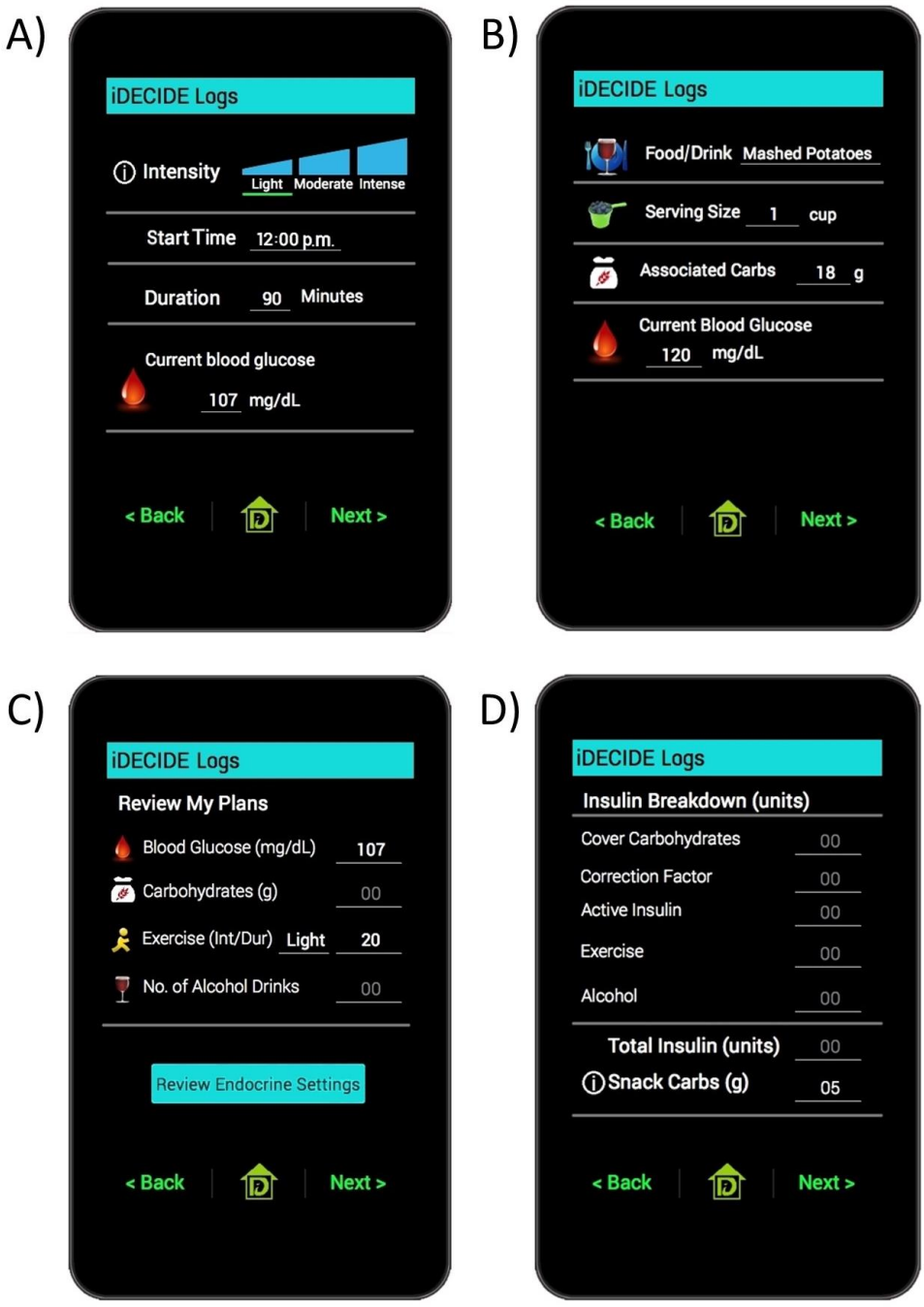


Figure 7.1: Screenshots of the iDECIDE mobile application: A) Self-reported exercise plans; B) Self-reported plans for food and alcohol consumption; C) Summary of relevant preprandial information; D) Advice to take 5 grams of snack carbohydrates to avoid exercise-induced hypoglycemia.

7.3.2 Participant Recruitment

Following Institutional Review Board approval (APPENDIX E

First round of recruitment of Mayo patients with Type 1 diabetes: Mayo Clinic IRB Approval #14-004649, APPENDIX F

Second round of recruitment of Mayo patients with type 1 diabetes: Mayo Clinic IRB Approval #15-006155), 31 study participants were recruited from an outpatient academic endocrinology practice. Patients with T1D 18 years or older who had been under the care of the endocrinology team while on CSII therapy using a Medtronic MiniMed, Inc. (Minneapolis, MN) [28] insulin pump for at least one year were eligible to participate.

7.3.3 Data Collection

Participants were asked to continue their usual fitness and nutrition routine. For 30 days, participants recorded their exercise activity and alcohol consumption via paper logs or the self-reporting module of the PDA, according to subject's preferences. Exercise was recorded by start time, duration and intensity, and categorized as light, moderate or vigorous. Alcohol was recorded by tracking drink time, type, volume, and number (e.g. 6PM, 1 pint of beer, no carbohydrates entered). Carbohydrate content was entered in the insulin pump. After 30 days, logs were manually encoded into tables or downloaded from a secure cloud-based server.

Self-reported data on exercise and alcohol was used as input for the PDA. For exercise, the PDA recommends an IB or carbohydrate intake by considering body weight

and intensity and duration of exercise [11,12,15,30]. For alcohol, the PDA accounts for the carbohydrates of the alcoholic drinks based on type, volume and count.

CSII data from the corresponding 30-day timeframe was downloaded in tabular format. CSII device data included carbohydrates recorded by the participant, BG levels either from a continuous glucose monitoring system (CGMS) or capillary BG monitor or both, amount of insulin delivered, pump settings, and the IB suggested by the insulin pump bolus calculator (IPBC).

7.3.4 Data analysis

Computer programs were written to automate the process of collating and analyzing the data generated by the insulin pumps with the self-reported patient behaviors, see Figure 4.1. Assessing the performance of the PDA at t_{i+1} against the IPBC was automated as was the comparison of the PDA against participants' self-dosing choices when the IPBC was not used as anticipated. The computer programs were able to identify and extract all of the information needed for the PDA to make a recommendation at time *t*, which included storing previously delivered boluses in memory in order to calculate IOB. The computer programs then scanned ahead in order to identify the postprandial glucose at time t_{i+1} and categorized the outcome according to participant glucose targets (below, at, or above target). Example 1: depicted in Figure 7.1. B) is the consumption of a meal at 19:40 (time = *t*) of 50 grams of carbs accompanied by a blood glucose check. The participant delivered the same amount of insulin as recommended by the pump. The PDA would have used the information in that row to make an insulin bolus recommendation. The outcome of the insulin pump recommendation was

identified at 22:40 (time = t_{i+1}) where the CGMS recorded 161 mg/dL, which was considered above target due to the target blood glucose range of 85-120 mg/dL. Example 2: a meal containing 40 g of carbs was consumed at 20:45 which was also accompanied by a blood glucose check. In this case the participant chose to override the recommendation made by the insulin pump bolus calculator. The PDA would have made an insulin recommendation at this point, which included a calculation of IOB from the previous insulin bolus. In this case the PDA would have been compared against the insulin delivered by the participant and not the recommendation from the insulin pump. If available, the computer program would have scanned ahead to obtain the postprandial glucose in order to determine which bolus amount outperformed.

7.4 Results

7.4.1 Participant characteristics and data

There were 31 participants recruited for the study, with 4 withdrawals. Of the remaining 27 participants, a subset of 15 participants (Table 7.1) had pre-prandial glucose readings paired with t_{i+1} BG readings, with 13 of them on CGMS (9 on Minimed 530G-551, 3 on Minimed 530G-751, and 1 on Paradigm Revel-723).

A total of 2,104 events had postprandial glucose readings that allowed for a comparison between the IPBC and the PDA, and there were 419 events where the PDA was compared against cases where the participants did not use their IPBC, they overrode the IPBC recommendations, or they did not provide a prandial BG. There were 235 exercise and 105 alcohol events that had sufficient data for analysis. Most (56%) exercise

events were of moderate intensity. There were few (14%) alcohol events where participants accounted for the carbohydrates associated with the beverage.

IPBCs allow different settings (BG target, insulin-to-carbohydrate ratio, and correction factor) throughout the day and the PDA accounted for these different settings for each participant at each time of day. While participants used different Medtronic insulin pumps, all use the same formula for computing IB recommendations, and an adaptation of [119] for computing active insulin. The Medtronic 530G includes a threshold suspend feature, that is designed to automatically stop insulin delivery when the CGMS value falls below a patient-specific pre-set threshold. There were 5 insulin suspension events that occurred in close temporal proximity to events of interest; such low frequency did not warrant removing data from the analysis.

Table 7.4: Demographics of 15 subjects with Type 1 diabetes. Data reported as mean (SD) or %.

Characteristic	Value
Age (years)	48.7 (13.9)
% Women	73.3
% White	93.3
Hemoglobin A1C	7.5 (1.2)
Diabetes duration (years)	26.9 (11.8)
Duration on insulin pump (years)	11.5 (5.3)
Daytime Low/High Target BG	89.9 (8.6) / 112.3 (10.8)
# Analyzable exercise events/day	1.1 (0.34)
# Analyzable alcohol events/day	0.2 (0.18)

7.4.2 Comparison of iDECIDE against the insulin pump bolus calculator or participant

We used the algorithm described in Figure 6.1 to compare the appropriateness of the PDA's recommendations against events when the patient followed the IPBC recommendations for BG correction doses and/or carbohydrate loads that included a prandial and postprandial BG.

The first assessment was was how the PDA (i.e. iDECIDE) compared against the IPBC (Table 7.2). The IPBC brought the participants to target glucose levels in 13% (278/2104) events, below target in 10% (207/2104) and above target in 77% (1619/2104). When considering very low and very high postprandial BG, the BG was below 70 mg/dl in 3% (55/2104) and over 180 mg/dl in 35% (737/2104). When considering instances where glucose was below target, iDECIDE would have recommended an appropriately smaller dose in 14% (28/207), but a larger dose in 13% (27/207) and an equivalent IB in 73% (152/207). For glucose levels at target, iDECIDE would have suggested an equivalent IB in 58% (162/278) compared to the subject's IPBC, but a higher dose in 20% (56/278) and lower in 22% (60/278). In events where post-prandial glucose was higher than target, iDECIDE would have suggested a higher dose in 25% (406/1619), a lower dose in 13% (212/1619), and an equivalent dose in 62% (1001/1619). Overall, iDECIDE would have recommended an equivalent dose compared to the IPBC in 63% (1315/2104) of IB decisions.

We used the algorithm in Figure 6.1 to compare the appropriateness of the PDA against decisions made by the participant (Table 7.2). The participants self-dosing led to above target postprandial glucose in 76% (319/419), below target in 13% (54/419) while

participants only achieved target glucose levels in 11% (46/419). There were 3% (14/419) of the events with a postprandial BG below 70 mg/dl and 37% (154/419) over 180 mg/dl. When considering instances where glucose was below target, iDECIDE would have recommended an appropriately smaller dose in 43% (23/54), a larger dose in 19% (10/54), and an equivalent IB dose in 38% (21/54). For glucose levels at target, iDECIDE would have suggested an equivalent IB amount in 9% (4/46) compared to the subject's own decision, but a higher dose 39% (18/46) and lower in 52% (24/46). In situations where post-prandial glucose was greater than target, iDECIDE would have suggested a higher dose in 34% (107/319), a lower dose in 27% (86/319), and an equivalent dose in 39% (126/319). Overall, iDECIDE would have recommended an equivalent IB in only 36% (151/419) of instances compared to when the participant made their own decisions.

Table 7.5: Results from retrospective comparison of the appropriateness of the recommendations from iDECIDE's algorithm against the insulin pump bolus calculator (IPBC), and from iDECIDE's algorithm against the participant's self-dosing choices.[1]

Event type	Postprandial BG (mg/dl)	iDECIDE insulin recommendations			Total
		Larger Dose	Smaller Dose	Equivalent Dose	
IPBC	Low (< target)	27 ‡	28 †	152 §	207
	Target (participant target)	56 ‡	60 †	162 ¶	278
	High (> target)	406 †	212 ‡	1,001 §	1,619
	TOTAL	489	300	1,315	2,104
Participant	Low (< target)	10 ‡	23 †	21 §	54
	Target (participant target)	18 ‡	24 †	4 ¶	46
	High (> target)	107 †	86 ‡	126 §	319
	TOTAL	135	133	151	419

[1] † iDECIDE recommendation was appropriate and insulin pump bolus calculator (IPBC) (or participant) was not appropriate, iDECIDE outperformed the bolus calculator (or patient). When iDECIDE recommends a lower insulin dose recommendation than the bolus calculator (or participant) and the postprandial BG is on target, iDECIDE could potentially avoid a hypoglycemic event and therefore outperformed the bolus calculator (or participant).
‡ Bolus calculator (or participant) was appropriate and iDECIDE recommendation was not appropriate, Bolus calculator (or participant) outperformed iDECIDE.
§ Events where iDECIDE and bolus calculator (or participant) recommendations were not appropriate.
¶ Events where iDECIDE and bolus calculator (or participant) recommendations were appropriate.

7.4.3 Assessment of the appropriateness of iDECIDE's recommendations for exercise and alcohol

In cases of exercise and alcohol the pump does not suggest insulin. In these cases, the PDA is only assessed based on the BG outcomes since it could not be compared against the IPBC. We used the algorithm described in Figure 6.2 to assess the appropriateness the PDA's recommendations when alcohol consumption was recorded. As reported earlier, patients self-reported accounting for the carbohydrate content of the beverage in 15 of the 105 events. As indicated in Table 7.3, in 64% (67/105) of overall alcohol events the PDA would have provided appropriate advice. The PDA performed well when the postprandial BG was high with 78% (64/82) appropriate IB recommendations, but had poor performance when the postprandial BG was at target with only 5% (1/19) recommendations deemed appropriate.

Table 7.6: Results from assessing the appropriateness of the recommendations regarding insulin dosing for alcohol consumption from the iDECIDE algorithm.

Postprandial BG	iDECIDE recommendations		Total
	Appropriate	Not Appropriate	
Low (< target)	2	2	4
Target (participant target)	1	18	19
High (> target)	64	18	82
TOTAL	67	38	105

We used the algorithm described in Figure 6.3 to assess the appropriateness of the PDA's recommendation before exercise (Table 7.7: Results from assessing the

appropriateness of the recommendations regarding insulin dosing and carbohydrate ingestion for exercise from the iDECIDE algorithm.4). The PDA appropriately suggested insulin or to ingest carbohydrates in 75% (176/235). Similar to the alcohol results, the PDA performed well when post exercise BG was high 87% (154/178), but only made appropriate suggestions in 37% (10/27) and 40% (12/30) when the post exercise BG was low or target, respectively. There were 26 exercise events that had a duration of 90 minutes or longer and the PDA made appropriate recommendation in only 27%.

Table 7.7: Results from assessing the appropriateness of the recommendations regarding insulin dosing and carbohydrate ingestion for exercise from the iDECIDE algorithm.

Post exercise BG	iDECIDE insulin dose and carbohydrate recommendations		Total
	Appropriate	Not Appropriate	
Low (< target)	10	17	27
Target (participant target)	12	18	30
High (> target)	154	24	178
TOTAL	176	59	235

7.5 Discussion

Although advances in *in-silico* model technology have allowed for incorporation of new features into existing technologies to improve BG control, these often do not account for variables that affect BG (e.g. exercise, stress, sleep and illness). Decision aids that assist patients with T1D to make better prandial insulin dosing decisions are

needed, particularly when patients must account for multiple simultaneous lifestyle variables that may impact BG levels.

One of the main differences between this study and others that retrospectively evaluated the performance of prandial insulin dosing algorithms is the source of the clinical data. For instance, previous studies have compared the effectiveness of insulin dosing algorithms in controlled environments such as in the ICU [114,120], where glucose control is closely monitored and tracked and lifestyle behaviors are not a factor. In contrast, this study focused on free-living outpatients who made their own choices about insulin therapy, and where individual lifestyle choices have the potential to impact treatment decisions and outcomes.

One of the analytic challenges we encountered when developing, testing, and comparing the effectiveness of insulin dosing algorithms is the complex nature of data generated from free-living participants. In our study, many of the self-management and daily living activities recorded by the participants occurred in tight temporal succession and could not be assessed as isolated events. This required development of a new analytic approach to evaluating the data. An unexpected positive outcome of this study was gaining a better understanding of patients' self-management behaviors as they interact with insulin pumps [73,93].

The methodology outlined here permitted an assessment of how our PDA would perform when used in different scenarios. When compared to the IPBC embedded in the subject's insulin pump, iDECIDE in general was non-inferior, recommending IB doses equivalent to the IPBC standard in 63% of decisions overall and nearly equivalent

number of smaller doses when glucose levels were below or at target. There were some instances, 23% (494/2104), where iDECIDE was superior to the IPBC, such as when it would have recommended larger doses in cases when glucose levels were above target. Initial analysis of iDECIDE in cases where the doses were too large or small, provided insights which were used to improve performance with continuing analysis necessary for further refinement of the recommendations [83,106]. For instance, we used an initial setting of 3 hours of active insulin time to calculate IOB. To improve performance, this was later adjusted to 4 hours which reduced the number of inappropriate recommendations that could have led to hypoglycemia. In the future, iDECIDE should be adapted to the insulin action time specified for each patient.

Employing the analytic paradigms developed here, we also assessed the performance of iDECIDE when there was a lack of recommendations from the IPBC with exercise and alcohol events. In these analyses the postprandial glucose was used as the outcome measure. For cases involving alcohol consumption, iDECIDE may have offered an advantage with deciding a compensatory insulin bolus. iDECIDE could have improved post-exercise BG when the duration was 90 minutes or less and the iDECIDE should be restricted to such events until further study.

There are limitations to the study. This study incorporated self-reported data for exercise, meal and alcohol behaviors. It is possible participants did not record all these events, or may have recorded them inaccurately. Also, participants' insulin pump settings were not adjusted for the study. Inappropriate insulin pump settings, such as basal rates, could have influenced the results. Sample sizes for alcohol and exercise events were

small with respect to the larger comparisons involving the IPBC. The study also did not consider late-onset hypoglycemia that can arise from engaging in exercise, and possibly when consuming alcohol. To automate the analysis, we opted against determining an appropriate post-exercise timeframe on a case by case basis and instead focused on the immediate effects of exercise by employing a standard 15-minute post-exercise time-frame. Considering BG levels outside of the time-frames used for analysis in this study is another important factor to consider in the future when assessing and calibrating IB calculators.

In addition, the analysis was done retrospectively. A prospective analysis, where iDECIDE makes suggestions in real time, would help further delineate its capabilities, improve performance and assess user acceptance. A recent analysis suggests that mobile apps can offer advantages in diabetes management, but more rigorous studies are needed [121]. Finally, the analytic algorithms tested here were for a very specialized group of patients (T1D on insulin pumps) and we did not conduct an analysis of the outcomes in relation to A1c scores. Testing these methodologies in a wider selection and more diverse population of patients (e.g. T1D patients on multiple daily insulin injections or patients with type 2 diabetes) would be needed to test the generalizability of the approach.

7.6 Conclusion

We introduced an analytic method to use prospective real-life data to retrospectively compare insulin dosing recommendations (Chapter 6). This novel methodology was used to assess the recommendations of iDECIDE, an evidence-based decision aid (Aim 4). The analysis done with the novel methods validates the hypothesis

that postprandial glucose levels of adult patients with T1D can be improved by providing insulin bolus or carbohydrate recommendations that account for meal's carbohydrates, glycemic excursion, alcohol consumption and planned exercise. The results presented in this study support the case for accounting for planned exercise, while accounting for carbohydrates from alcohol is not definitive at this point.

8 DESIGN AND DEPLOYMENT OF THE IDECIDE DECISION AID AS A SMARTPHONE APPLICATION

8.1 Introduction

Exercise and alcohol have an effect on blood glucose, but as discussed in Chapter 2, there are currently no decision aids that account for those two variables when suggesting insulin boluses (Aim 1), despite patients' daily needs for adjusting for exercise and alcohol to improve glycemic control (Chapters 3 and 4) (Aim 2). Results from a completed retrospective analysis performed using proposed novel methodological approaches demonstrated that the iDECIDE insulin dosing algorithm could lead to improved glycemic control when compared against a proprietary insulin pump bolus calculator (Chapters 6 and 7) (Aim 4).

In this chapter, we discuss completed and future work to deploy the proposed iDECIDE insulin dosing algorithm as an iOS smartphone application (app) (Aim 5).

8.2 Background

Mobile technology, such as smartphone apps, show promising results in their ability to improve health outcomes due to their low-cost and high penetration of smartphone ownership [122]. But researchers have yet to confirm the effectiveness of app-based interventions in improving glycemic control in patients with T1D, which is likely due to the lack of high quality controlled trials [121,123].

Although there are over 1,000 diabetes apps available for download, unfortunately very few undergo usability testing and most are not evidence-based [124,125]. Currently, clinicians and patients rely on app ratings and reviews from other users when selecting a

diabetes app. While good ratings may be indicative of the usability of the app, it is not possible to translate app ratings into improved health outcomes for the users [60].

In a systematic review of diabetes mobile apps, researchers found that a large number of the apps were merely digital versions of logbooks and many only provided one functionality out of many of the desirable tasks for self-management that are feasible to be implemented with mobile technology [126]. Other limitations of the reviewed apps were data entry issues and integration with electronic health records. Another systematic review of diabetes apps found that the majority of the apps were similar to each other and that they typically only offered one or two functions [60]. The authors from this review indicated that providing multiple functionalities would be beneficial to producing an app for diabetes self-management and that patients and clinicians should be part of the app development process.

According to Goyal, et.al. [127], diabetes apps should provide the following functionalities: monitor BG and objectively track medications, nutrition, exercise and body weight. A recent study was only able to identify 9 apps out of 965 that were free and available for download from Apple [128], Google (Android) [129], or Microsoft (Windows) [130] app stores that provided the four functionalities [131]. These results indicate that there is a gap between evidence-based research and the apps available in the marketplace.

There are very few apps that provide decisional support, for example, providing recommendations for bolus insulin. Two such apps are “Diabeo” [132] and “”ABC4D” [133–135]. Diabeo uses carbohydrate loads, blood glucose and planned exercise to make

insulin recommendations. Additionally, Diabeo uses an algorithm to automatically adjust ICR and basal rates when postprandial glucose levels do not fall within a predetermined target range. A 6-month clinical trial demonstrated the app's ability to improve HbA1c scores in patients with T1D [132]. The ABC4D app uses case-based reasoning to make insulin recommendations for meals. Meal instances and glycemic outcomes for an individual are described by a set of 10 parameters which are stored and later referenced by ABC4D in order to make insulin recommendations by matching the current meal to a similar one stored in memory. A 6-week study showed that out of the 10 possible parameters for the bolus calculator, participants used exercise and alcohol the most [135]. The safety, but not efficacy, of the app was demonstrated by a decrease in the number of hypoglycemic events during the study period [134].

Although there are similarities between the bolus calculator capabilities of Diabeo, ABC4D and iDECIDE, iDECIDE is different in that it not only makes insulin recommendations, but also recommends carbohydrates. The recommendations from iDECIDE are transparent and can be broken down and understood by patients and clinicians. Insulin recommendations from Diabeo and ABC4D use artificial intelligence methods when making insulin recommendations, which can make it difficult for patients and clinicians interpret the reasoning behind the recommendations. Also, the iDECIDE app includes other functionalities beyond providing insulin and carbohydrate recommendations. iDECIDE provides several features for self-tracking meals and assistance with carbohydrate counting, such as suggested carbohydrate content of alcoholic beverages, barcode and text search access to food databases, a user-specified

favorite foods list, and documenting meals with a photograph. iDECIDE also provides links to educational material, allows users to set their iDECIDE calculation parameters (e.g. ICR, CF and target BG), and integrates with Apple's HealthKit [136]. These functionalities are presented in more detail in this chapter.

The objective was to design and deploy the iDECIDE decision aid as an app that incorporates the evidence-based bolusing algorithm in order to improve glucose control.

8.3 Methods and Materials

Prototypes of the iDECIDE app were developed with Proto.io [137], Justinmind [138], Android Studio [139] and PhoneGap [140]. For the development of the iDECIDE app as a clinical decision support system (CDSS) we adopted the conceptual model proposed by Greenes in [141], where the iDECIDE app is composed of a knowledge base, an information model, an execution engine and results (output generation) (Figure 8.1). As suggested by Greenes, the modular deployment of the iDECIDE application has the potential to facilitate future updates and maintenance of the CDSS. In the next subsections, we explain the iDECIDE's implementation modules in more details.

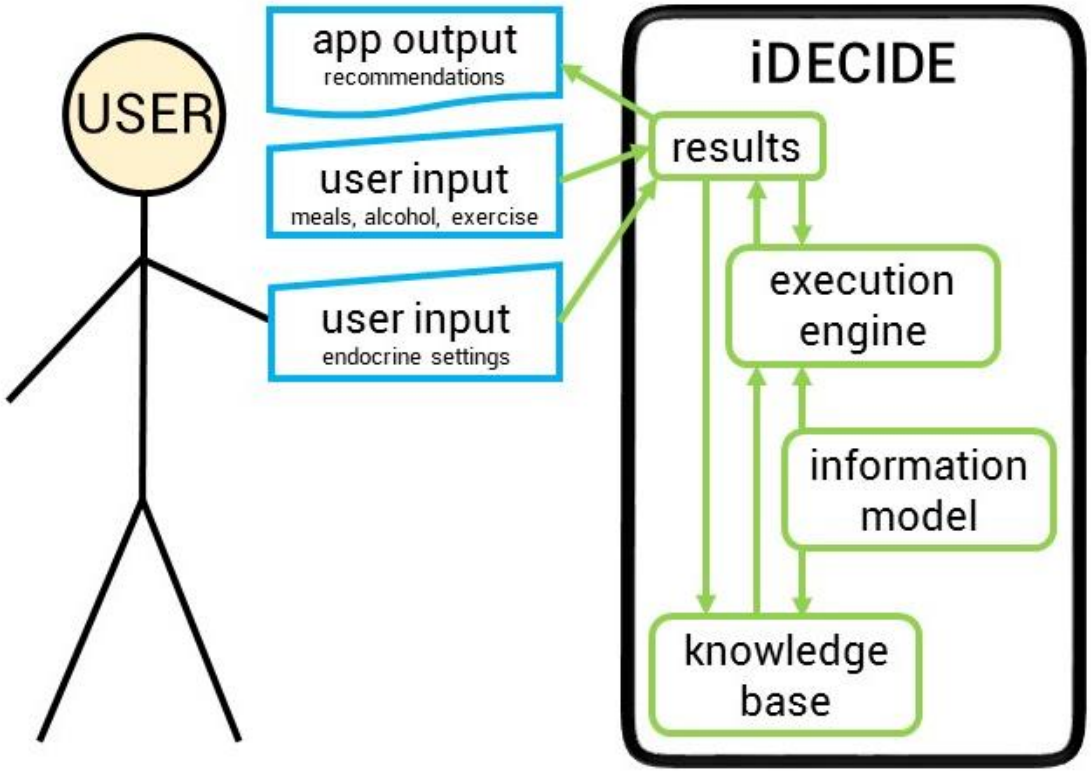


Figure 8.1: The user of the iDECIDE app input information about his endocrine settings and plans for meals, alcohol and/or exercise which are saved to the knowledge base through the results module. The information model specifies the data format for the knowledge *base*. The *execution engine* reasons over the data stored in the *knowledge base* to make recommendations for insulin and/or carbohydrates to maintain glycemic control. The recommendations are output to the user on a smartphone via the *results* module.

8.3.1 User

The intended users of the iDECIDE app are adults with type 1 diabetes who self-manage glycemic control with intensive insulin therapy which can be delivered via one of two treatment options: multiple daily injections (MDI) or continuous subcutaneous insulin injections (CSII). The user interacts with iDECIDE by self-reporting endocrine

settings and lifestyle preferences that have an effect on blood glucose levels. The user then receives recommendations from iDECIDE to maintain glycemic control.

8.3.2 Information Model

iDECIDE's information model was specified as a Unified Modeling Language (UML) class model, see Figure 8.2. The information model supports the three functions of iDECIDE:

1. store user endocrine settings,
2. track daily meals, alcohol and planned exercise,
3. apply the evidence-based iDECIDE algorithm to recommend pre-meal bolus and/or carbohydrate intake based on current blood glucose, alcohol and food intake, exercise plans and endocrine settings.

8.3.2.1 Setup user's endocrine settings

Upon launching the iDECIDE app for the first time the *Diabetes Patients* is prompted to self-report their diabetes profile settings: *Target Glucose,* correction factor (*CF*), insulin to carbohydrate ratio (*ICR)* and body *weight*. *Target Glucose*, *CF* and *ICR* are *Endocrine Test Findings*; the values for these settings are advised and guided by the patient's endocrinologist. For example, *ICR* could be set to 10 mg/dL for the a full 24-hours, see Figure 8.3. iDECIDE supports the storage of multiple values for each of the three endocrine settings over a 24-hour period, for example, *ICR* could be set at 10 mg/dL from midnight to 4:00 p.m. and a value of 15 mg/dL could cover the remainder of the day from 4:00 p.m. to midnight. *Target Glucose, CR and ICR,* along with *weight*, are *Observable Entities* that belong to the *Diabetes Patient.*

8.3.2.2 Self-tracking meals, alcohol, and exercise

iDECIDE can be used to record *Plans* made related to carbohydrates from meals (*Carbs Plan*), alcoholic intake (*Alcohol Plan),* exercise (*Exercise Plan*) and delivered insulin (*Insulin Plan*). *Alcohol Plans* also have *Carbs Plans* based on the type and amount of alcohol consumed. An example of a combination of a *Carbs Plan* along with an *Alcohol Plan* could be to consume 2 slices of pizza that contains 35 grams of carbs (Figure 8.3.B) while also having a 12-ounce beer that consists of 8 grams of carbs (Figure 8.3.C). A potential *Exercise Plan* could be to engage in 30 minutes of light activity at noon (Figure 8.3.E). An example of a more complex *Exercise Plan* would be to warm up with 10 minutes of moderate activity at 7:00 a.m., followed by 20 minutes of intense activity at 7:10 a.m. An example of an *Insulin Plan* is to bolus 3 units of insulin at 6:30 p.m.

8.3.2.3 Apply evidence-based algorithm

iDECIDE uses an *Evidence*-based algorithm to generate insulin bolus (*Insulin Plan*) or carbohydrate intake (*Carbs Plan*) *Recommendations* based on endocrine settings (*Observable Entities)* and *Plans* for carbohydrates (*Carbs Plan*), alcohol (*Alcohol Plan*) and exercise (*Exercise Plan*). The dosing algorithm also considers previous *Insulin Plans* that the user delivered *(commits)* in order to determine how much insulin is on board (*IOB Evidence*) (Table 5.1). While the user is self-tracking carbohydrates, alcohol and exercise, they are also prompted to provide a current blood glucose reading (*Current BG*). In the case when the meal that consisted of 2 slices of pizza (*Carbs Plan)* and a beer (*Alcohol Plan)* the current blood glucose (*Current* BG) was 135 mg/dL, iDECIDE

recommends the diabetes patient to deliver 4.8 units of insulin (*Insulin Plan*) (Figure 8.3.D). In the exercise example (*Exercise Plan)* of 30 minutes of light activity at noon with a current blood glucose of 107 mg/dL, iDECIDE *recommends* the diabetes patient consume a snack of 5 grams of carbohydrates (*Carbs Plan*) (Figure8.3.F).

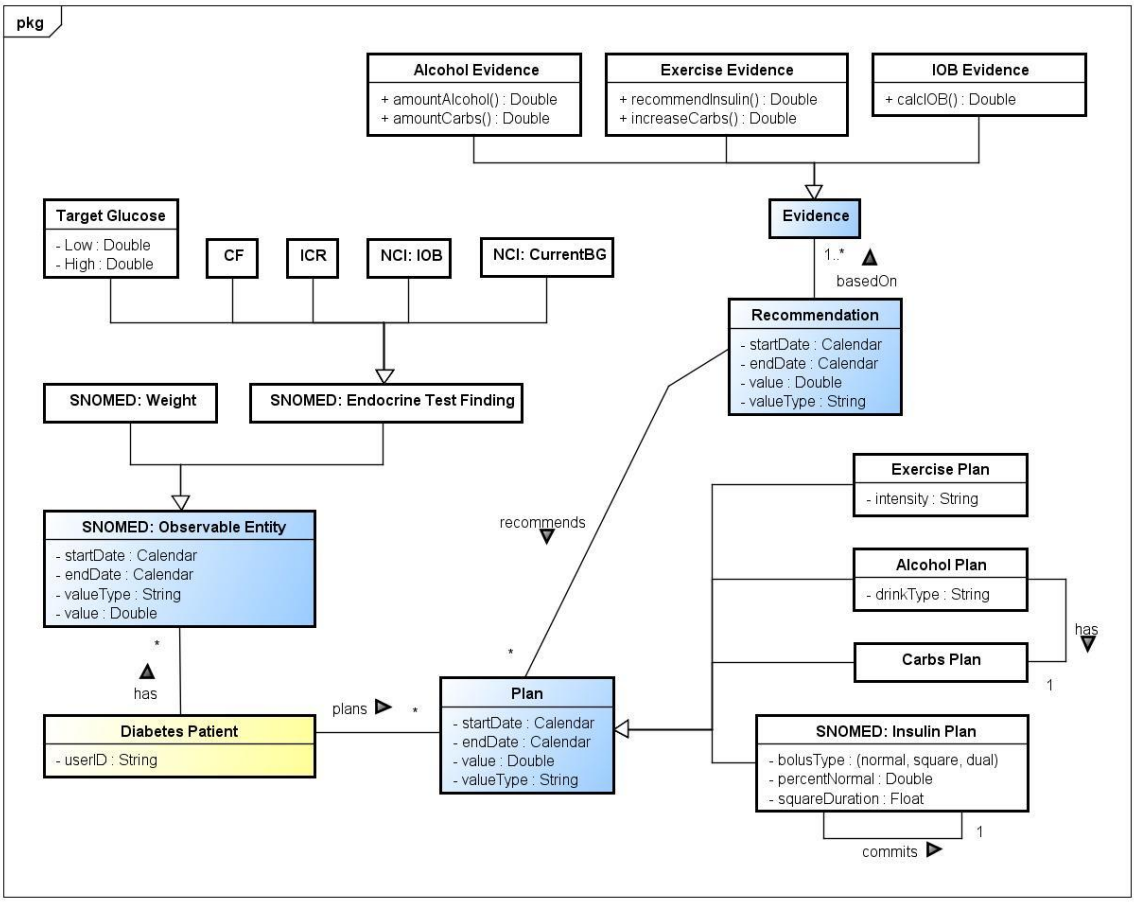


Figure 8.2: UML class diagram depicting the information model of the iDECIDE app. The classes and relationships support the three functionalities of the app: 1) store endocrine settings; 2) self-track meals, alcohol and exercise; 3) apply relevant evidence to recommend insulin bolus or carbohydrates based on current blood glucose, carbohydrates, alcohol, planned exercise and endocrine settings.

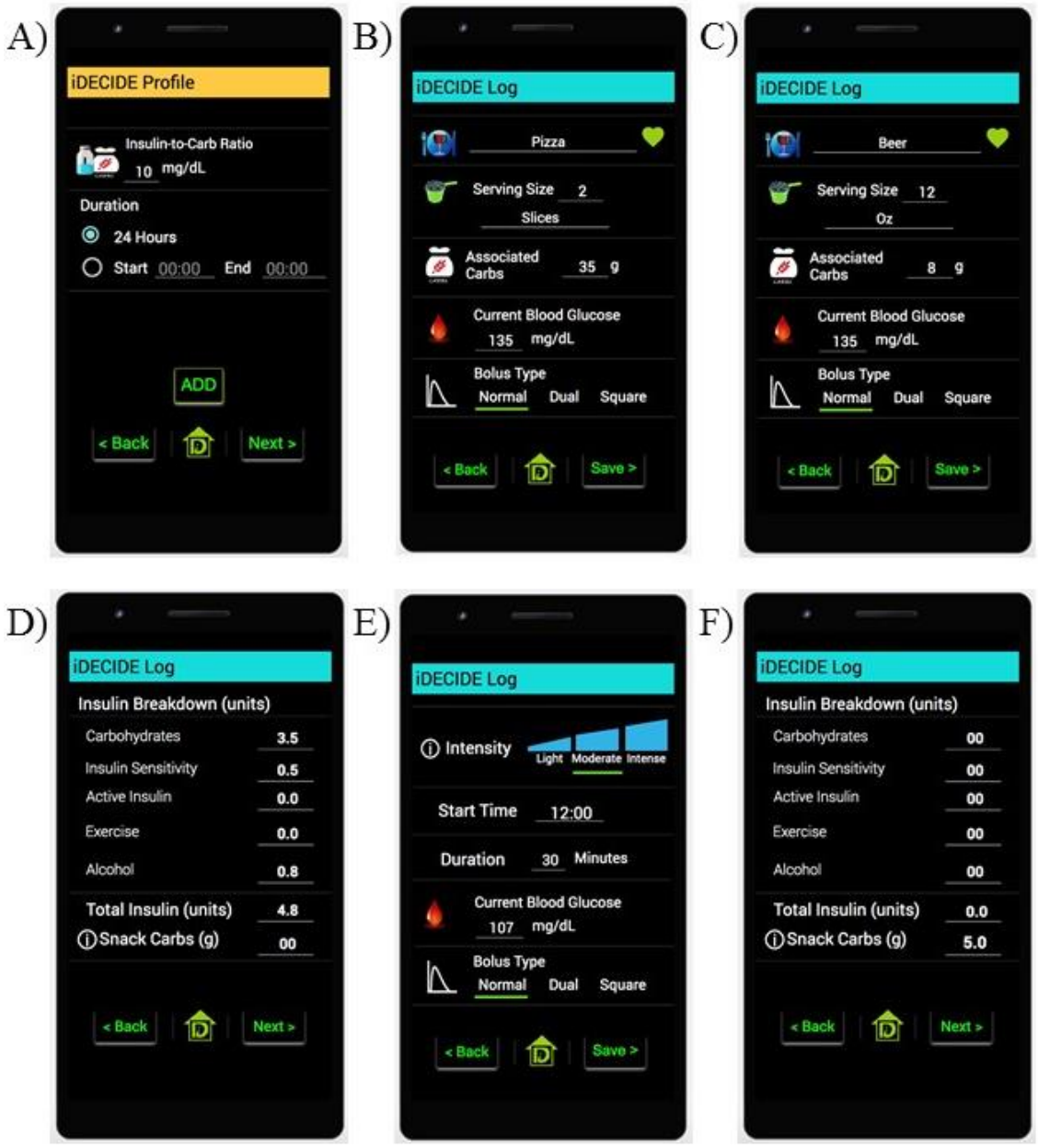


Figure 8.3: Screenshots of the iDECIDE app; A) setting the endocrine setting: insulin to carbohydrate ratio (ICR); B) self-tracking a meal with carbohydrates; C) self-tracking an alcoholic beverage; D) iDECIDE's insulin recommendation to cover carbs associated with a meal, alcohol and out-of-range blood glucose; E) self-tracking exercise; F) iDECIDE's carbohydrate recommendation to compensate for exercise.

The *Alcohol Evidence* breaks alcoholic beverages into five classes based on the carbohydrate and alcohol content of one standard serving size (Figure 5.2), which values are used to adjust the amount of insulin recommended. *Exercise Evidence* has two components: reduce the insulin bolus and/or suggest taking a carbohydrate snack. The reduction of insulin considers the duration and intensity of the exercise (Table 5.2) while suggesting carbohydrates takes into account body weight and exercise duration (Tables 5.3 and 5.4). A complete description of the evidence-based insulin dosing equation is found in Chapter 5.

8.3.3 Knowledge Base

As discussed in Chapter 5, relevant evidence is incorporated into the insulin dosing algorithm in order to provide recommendations for insulin or carbohydrates. The static portion of the knowledge base includes: user's self-reported endocrine settings (*Target Glucose, CF, ICR)*, the categorizing of alcoholic beverages and the effect on glycemic control (*Alcohol)*, the effects of exercise on blood glucose *(Exercise)*, as well as the evidence for calculating *IOB*. Dynamic portions on the knowledge base incorporate real-time data entry when the user engages in self-tracking of meals *(Carbs Plan)*, alcohol *(Alcohol Plan)*, exercise *(Exercise Plan)* and current blood glucose *(Current BG)*.

8.3.4 Execution Engine

The execution engine is comprised of the proposed evidence-based insulin bolusing algorithm (Chapter 5). The engine has access to the evidence (*Alcohol, Exercise, IOB*) which is encoded in a static format to the knowledge base. The execution engine also accesses additional information that is user-generated which also populates

the knowledge base (*Findings*). Real-time user input regarding current plans (*Carbs, Alcohol* and/or *Exercise Plans)* and the *CurrentBG* are required for the insulin bolus decision aid to make recommendations. In short, the engine reasons over the patient's stored endocrine settings and the current *Plans* to make suggestions for an *Insulin Plan* and/or a *Carbs Plan* while incorporating the appropriate *Evidence* based on the context of the situation.

8.3.5 Input, Output and Results

The results are related to how the CDSS presents output and elicits input from the user. Interfaces have been designed that support the functionalities of iDECIDE, see Figure 8.3. The interfaces and functionalities have been improved after two rounds of usability testing.

8.4 Results

In this section, we describe two usability studies of the iDECIDE app. The author, Danielle Groat, conducted the first usability study under the direction of Dr. David Kaufman and Dr. Vimla Patel while enrolled in the course "BMI 591: Human Computer Interactions and Human Factors in Biomedicine." The second usability was carried out by Hiral Soni, a graduate student in the Department of Biomedical Informatics. The first usability study served as a template for the follow-up study by influencing the content and flow of the tasks and questionnaires.

8.4.1 Usability Testing, First Round

For the first usability test we secured approval from the Arizona State University (ASU) IRB to recruit five Arizona State University (ASU) students, faculty or staff aged

at least 18 years. The iDECIDE app was installed as a native app to a ZTE N9130 smartphone running the Android operating system (OS) 4.4.4 Kit Kat. Participants were given a brief introduction to diabetes with a fictitious diabetes patient profile. The Android smartphone with the iDECIDE app launched was then presented to the participant. Participants were then given brief instructions to help them navigate the Android phone and then they were given instructions to think aloud as they interacted with the app. Participants were given 5-minutes to explore the app and then a total of 7 tasks were given one at a time. The usability testing was recorded using Morae® [142] and real-time screenshots of the smartphone screen were simultaneously captured using Droid@Screen [143]. Upon completion of the tasks the participants were then given a usability survey which was a modified version of the System Usability Scale (SUS) as it was published by the Healthcare Information and Management Systems Society (HIMSS) [144]. The audio-video recordings were analyzed and annotated with Morae software. Participant errors and comments were noted and grouped into themes. Time to complete tasks were measured.

Five graduate students from ASU were recruited. Three were female, two were male. The average years of experience using a smartphone was 5.5 years.

Table 8.1 shows the results of the average time it took to complete the tasks and the average number of errors associated with each task. The exploratory task yielded the highest amount of errors while tasks 6 and 7 resulted in no errors from the participants. This suggests that users were able to learn the system over time. The average subjective usability rating from the System Usability Scale (SUS) questionnaire was 76.4, higher

than the average score of 68 for the SUS [145]. As the audio-video recordings were analyzed there were 7 usability issues, or themes, that emerged.

Table 8.2 provides a brief description of each issue, the frequency of the issue across all the participants and the number of participants that were affected by the issue. The cursor issue with numeric data entry (Issue #2) had the highest number of errors. This was due to bug in the prototype that defaulted the cursor position to the right side of numeric data entry fields instead of the left side.

Table 8.1: Quantitative results of usability evaluations. All values are reported as means and standard deviation (SD).

Task	Time in minutes (SD)	Number of Errors (SD)
Exploratory	5.87 (1.80)	5.8 (4.32)
1	0.71 (0.30)	1.0 (1.00)
2	1.28 (0.46)	1.8 (0.84)
3	1.95 (0.74)	2.0 (0.71)
4	2.24 (0.76)	3.4 (1.52)
5	0.95 (0.18)	0.2 (0.45)
6	0.96 (0.58)	0.0 (0.00)
7	1.20 (0.50)	0.0 (0.00)

Table 8.2: Usability issues and their frequency.

#. Brief Description	Frequency	# Participants Affected
1. Screen contents overwhelming	3	2
2. Numeric data entry, cursor position	33	5
3. Error in icon selection	12	5
4. Unwanted functionality	7	3
5. Desired functionality missing	7	3
6. Slider obstructs visibility	1	1
7. Scroll gesture interferes with time picker	2	2
Total	65	5

8.4.2 Usability Testing, Second Round

For the second round of usability testing, received IRB approval from the Mayo Clinic (APPENDIX F

Second round of recruitment of Mayo patients with type 1 diabetes: Mayo Clinic IRB Approval #15-006155). We recruited Mayo Clinic patients with type 1 diabetes. A prototype version of the iDECIDE app was built using Justinmind [138]. The usability study with the first participant was done by launching the iDECIDE prototype on an Android smartphone. Unfortunately, this environment produced a considerable amount of lag and all subsequent studies with the remaining 5 participants were conducted with simulated smartphone screens on a laptop computer. All the participants completed a total of 8 tasks, which included 5 minutes of exploration, 6 tasks specific to a fictitious diabetic character and 1 task to set up a personal fitness goal. The tasks included: setting the user's profile, including endocrine settings, and setting up meal/alcohol/exercise plans

and goals. Morae® software was used to record interactive behaviors and their voiced thoughts during the testing.

Table 8.3 shows the results of the average time it took to complete the tasks and the average number of errors associated with each task. The number of errors remained fairly low across all the tasks with most problems occurring during first four tasks and patients gradually adapting to the app after 5 minutes of exploration. This may indicate that overall the app was easy to learn.

A total of 13 issues were detected, see Table 8.4 for a brief description and frequency of errors. Four of the issues did not require immediate changes. We made necessary changes to address the 9 remaining issues. For example, users found some icons confusing, therefore, we proposed new icons for carbohydrates, insulin to carb ratio, and insulin sensitivity. Most importantly, participants were unclear about differences between goals and plans, hence we replaced the notion of plans for logs. The average SUS rating was 79.9, an above average SUS rating. The interfaces depicted in Figure 8.3 were modified based on the results of the two usability tests.

Table 8.3: Quantitative results of usability evaluations. All values are reported as means and standard deviation (SD).

Task	Time in minutes (SD)	Number of Errors (SD)
1	1.17 (0.58)	0.0 (0.0)
2	4.67 (1.34)	2.0 (1.4)
3	1.34 (0.58)	0.8 (0.4)
4	0.36 (0.10)	0.0 (0.0)
5	1.35 (0.74)	0.3 (0.5)
6	2.56 (0.53)	1.3 (0.5)
7	1.05 (0.65)	0.5 (0.5)

Table 8.4: Usability issues and their frequency.

#. Brief Description	Frequency during Exploratory task	Frequency during Tasks 1-7	# Participants Affected
1. Confusion with the "+" button	1	1	1
2. Confusion with endocrine settings	3	2	3
3. Repeat button selection	0	5	5
4. Confusion with adding drinks	0	1	1
5. Time slider	1	3	3
6. Skipped task	0	4	3
7. Felt lack of direction form app	0	1	1
8. Confusion between goals and plans	0	3	3
9. Carbs icon meaning unclear	2	0	2
10. Screen content overwhelming	1	2	3
11. Lack of "no" for an option	1	0	1
12. iDECIDE bottom bar	0	1	1
13. Confusion with plans icons	0	1	1
Total	9	24	6

8.4.3 iDECIDE decision aid deployed for the Apple iOS iPhone

At the conclusion of the 30-day study from the second calibration of the iDECIDE app (APPENDIX F: Mayo Clinic IRB #15-006155), participants were given a usability survey on the self-reporting module of the iDECIDE app (APPENDIX F.3). Nine of the participants responded to the web-based usability survey. A Likert rating score from 1 to 5 was used to rate various aspects of the app with 5 being a positive rating. The average rating across all questions was 3.8. In the comments area, most of the responses were positive with some mention as to the areas that needed improvement.

The main themes that resulted from the comments was that participants desired more functionalities for logging meals and exercise and more flexible searching abilities for accessing food content.

Here we present the interfaces and functionalities that were built for the Apple iOS version of the iDECIDE decision aid (Figure 8.4). Most notably different is the color palate has been changed from a dark theme to a light theme. Also, some of the widgets have been modified to align with the Apple's developer's guidelines and the built with the iOS platform interface kit. As you can see in Figures 8.4.A and 8.4.B, there are additional functionalities for tracking meals and carbohydrates. Using the Nutritionix food database [146], users can search for grocery foods with a barcode scanner while restaurant menu items and common foods are identified with a text search. Nutritionix also provides access to the United States Department of Agriculture food composition databases [147]. The nutritional content of over 570,00 grocery items, 116,00 restaurant items and 24,700 common foods has been verified before their addition to the Nutritionix database.

Additionally, users can now store a list of favorite food items that can be easily retrieved when reporting food intake to auto populate meal entry. Photos of the meal can also be recorded with the food data entry (Figure 8.4.C). In addition to providing an insulin (or snack in the case of exercise) recommendation, the user can also report any overrides made to the recommendation (Figure 8.4.D). The interfaces for tracking exercise are relatively unchanged, Figures 8.4.E and 8.4.F. The entry of endocrine settings has changed to allow up to three values over a 24-hour period, Figure 8.4.G.

HealthKit has been integrated into the app to allow read and write capabilities for blood glucose, carbohydrates, and body weight, Figure 8.4.H.

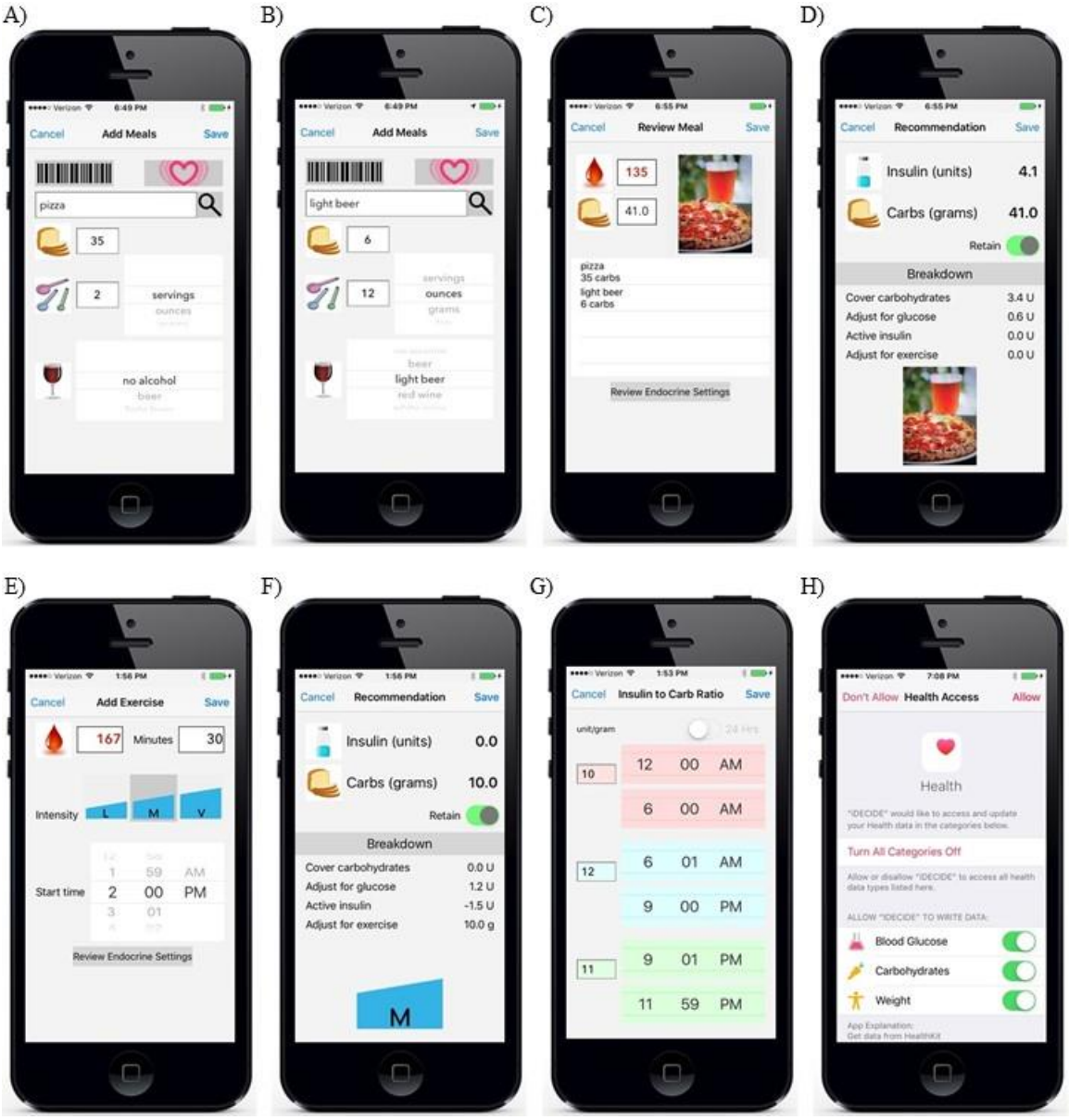


Figure 8.4: iDECIDE interfaces for the iOS platform: logging meal with A) pizza, B) light beer, C) blood glucose and photo, D) insulin recommendation for meal, E) logging exercise, F) carbohydrate recommendation for exercise, G) setting insulin to carbohydrate ratio values for 24-hours, H) enabling read and write functionalities with HealthKit.

8.5 Discussion

As mentioned earlier, the previous versions of the app were built with various prototyping software with the Android platform in mind. The self-tracking module used by study participants was built as a multi-platform app with PhoneGap, again with the Android design guide contributing to the look and feel of the interfaces. The final installment of iDECIDE is deployed on Apple's iOS platform. Apple has been chosen as the target platform for two main reasons. According to the latest document from the FDA concerning mobile medical applications [148], iDECIDE falls under the regulatory requirements as a Class II medical device. Although mobile medical applications can be deployed on any number of operating systems, currently the majority of applications that have been approved by the FDA have been for the iOS platform [149,150]. Most importantly, the demographics of diabetes patients at the Mayo clinic suggest that a greater number of them use Apple iPhones as opposed to other smartphones available on the market. This is an important consideration as future research with the iDECIDE app will likely be conducted in collaboration with the Mayo Clinic and its patient population.

One of the frameworks that has recently been released by Apple for iOS is HealthKit [136]. Mayo Clinic, HealthKit and Epic [151], an electronic health record vendor, have partnered to improve the ability of patients to share their health-related data with their providers via the MyChart patient portal from Epic. At this point in time Mayo Clinic is preparing to transition to the Epic EHR, and when the transition is complete, the framework for patients to share data with providers in a timely fashion will be in place. Other health care institutions that are already using Epic have proven the feasibility of

patients with T1D using the Dexcom G5 Mobile CGMS with an insulin pump and the Dexcom iPhone companion app to be apple to wirelessly transfer their data in nearly real-time to their providers through the Epic and MyChart platform interfacing with Apple's HealthKit [152,153]

In order for iDECIDE to make insulin recommendations a current glucose reading is necessary. With the introduction of HealthKit, several diabetes technology device manufacturers have released companion apps that allow glucose meters and CGMS to automatically share their data with HealthKit. The HealthKit framework stores all health-related data locally on the phone and allows all data, with permission from the user, to share data points with other apps installed on the phone. iDECIDE takes advantage of the HealthKit framework and when granted permission by the user, iDECIDE can read and write glucose data points to and from the framework on the phone. Not only are the glucose readings integrated to HealthKit, but nutrition content and body weight are other data points that iDECIDE contributes to the HealthKit data ecosystem.

8.6 Conclusion

The iDECIDE evidence-based algorithm for making insulin and carbohydrate recommendations has been deployed as an app for the iOS platform. As a smartphone app, iDECIDE can easily be disseminated at a low cost to patients. The iDECIDE app as it is currently implemented is ready for prospective testing. There also lies the potential for patient-generated data from the iDECIDE app to be connected to the Epic EHR, which can grant physicians more timely access to patient data.

9 CONCLUSION

Type 1 diabetes is a complicated disease that requires patients to interact with various technologies in order to self-manage blood glucose and avoid complications that arise from glycemic excursions [2]. Patients are more likely to adhere to treatments when they incorporate personal lifestyle choices [20,26]. Two lifestyle choices that influence glucose control are exercise and alcohol consumption [11,13,15,17,43,45]. Current diabetes technologies do not account for exercise and alcohol when making insulin bolus suggestions [29]. The hypothesis is postprandial blood glucose levels of adult patients with T1D can be improved by providing insulin bolus or carbohydrate recommendations that account for meal and alcohol carbohydrates, glycemic excursion, and planned exercise.

The solution proposed is iDECIDE, an evidence-based decision support tool that suggests insulin or carbohydrates to improve glucose control and it is deployed as a smartphone application. This research demonstrates that the iDECIDE decision aid is not inferior to the Medtronic MiniMed, Inc. [28] IPBC, providing equivalent recommendation in 63% and outperformance in 23% of cases. iDECIDE's alcohol recommendations may have provided an advantage in 64% of cases, while recommendations for exercise with a duration less than 90 minutes could have improved post-exercise BG in 81% of cases.

One of the limitations to this research stems from the demographics of the participants. All participants were recruited from the endocrinology department at the Arizona Mayo Clinic. The population was well controlled with a mean HbA1c score of

7.5%. A smaller, but overlapping population, was given portions of the short test of functional health literacy in adults (S-TOFHLA) and all participants received a perfect score. Also, almost all patients approached for participation owned smartphones, and of those that did participate nearly all owned an Apple smartphone. Due to the homogeneity of the atypical population, the results may not be generalizable. The iDECIDE decision aid was extended to include exercise and alcohol in order to incorporate lifestyle preferences, and other factors that influence glucose levels were not included, such as stress, medications and hormones.

The results of iDECIDE's performance in the case of alcohol consumption were not conclusive, which was in part due to a small sample size. Others have assessed alcohol behaviors in emerging adults with T1D via questionnaires and surveys [154,155], but to our knowledge, ours was the first attempt to gather and analyze alcohol behaviors from free-living patients self-tracking with a smartphone app.

This research has implications for various stakeholders. For example, the literature review and the study of self-management behaviors (Aims 1 & 2) can inform diabetes technology researchers as they develop and design future diabetes technology and devices. The results from the study of self-management behaviors (Aim 2), indicate that self-reported behaviors do not always translate into actual behaviors recorded by self-tracking and/or diabetes technology. The analytical techniques we used to assess patients' behaviors and compensation techniques can guide the development of bed-side tools for clinicians that could support shared-decision making and treatments. Also ongoing is the analysis of the qualitative data regarding self-reported compensation

techniques for exercise and alcohol as well as the perceptions on the effects of exercise and alcohol on BG control [156].

The novel methods developed to compare and assess iDECIDE's recommendations (Aim 4) can be applied more broadly in order to identify, calibrate and assess other bolus calculators before undergoing costly clinical trials. It also opens the possibility of using non-traditional sources of data for conducting research. The OpenAPS (Open Artificial Pancreas System) data repository [157], under the umbrella of the Open Humans project [158], has provided a means where individuals with T1D can upload and donate their data. Traditional researchers can propose research studies and the OpenAPS community determines which projects will be granted access to the donated data. Future work with real-life data from a broader population, like that of OpenAPS, could improve the generalizability of the results from assessing bolus calculators with the proposed methods.

When the iDECIDE decision aid is deployed as a smartphone app for the Apple iOS platform (Aim 5) it benefits patients and clinicians. There is the potential for clinicians to have more timely access to patient data, such as and receiving alerts when pre-determined thresholds for blood glucose are crossed. This functionality for clinicians requires the integration of Apple's HealthKit with Epic's patient portal, MyChart, which has been accomplished by other healthcare institutions that already use the Epic EHR [152,153]. Patients can conveniently download the app to their smartphone and receive decision support that integrates with other HealthKit enabled apps and devices. Currently

the iDECIDE app is going through the necessary requirements to receive FDA approval and there are plans to pursue a prospective randomized clinical trial.

This research is an example of using novel informatics data collected by existing diabetes technologies and self-reported by patients to understand the burden of the disease and influence the design of a solution. Multiple sources of heterogenous and disparate data were gathered, collated and analyzed. Data sources included a self-report via interview and/or survey, real-time self-record via paper logs/smartphone app, and data generated by medical devices, e.g. insulin pump and glucose monitors/meters. There were no existing methods to retrospectively assess iDECIDE's recommendations and hence part of this research incorporated the development of a novel methodology that uses patient-generated data to retrospectively compare bolus calculators.

The proposed novel decision aid and comparison methodology present practical solutions that can be applied to broader range of problems, such as T2D and other chronic diseases, and to other lines of research, such as collaboration with patient-controlled diabetes data repositories, including additional factors that affect glucose levels, and further identifying patient profiles to inform the development of personalized therapies to improve adherence. The identification of correlating behaviors with respect to insulin pump usage and compensation for exercise and alcohol could lead to the creation of patient profiles that would allow clinicians to personalize treatments regimens that target increased adherence and result in improved glycemic control. Furthermore, iDECIDE could be extended to include other factors that affect glucose control (e.g. stress, hormones, and medications), and user-reported or device-recorded data could be used to

retrospectively calibrate and assess the performance of the new parameters included in the decision aid using the methods described in Chapters 6 & 7.

There are many other chronic diseases (e.g. congestive heart failure, asthma, hypertension), whose treatment therapies require patients to engage in self-care at home, that could benefit from the methodologies presented in this dissertation. Reviews of mobile technology based interventions for chronic diseases management report positive effects, including improved provider and patient adherence to practice guidelines as well as health outcomes [122,159]. Many of the studies included in these reviews did not collate data from heterogenous sources and few had a decision support system in place. Most of the studies relied heavily on providers to access, gather, and analyze the data in order to personalize treatment therapies on the fly and initiate phone calls or text messaging to relay treatment changes. These resource intensive mobile-based interventions could benefit from several aspects of the work presented related to iDECIDE. The methods used to understand and define user needs (Chapters 2,3 and 4) could be used to develop a decision aid aimed at assisting providers by extending the framework depicted in Figure 8.2 to account for scenarios where providers adjust aspects of the treatment plan, e.g. changing ICR or CF settings. The provider-specific decision aid could be assessed by adapting the performance assessment methods presented in Chapters 6 and 7 using real-life patient and provider generated data.

Future work with iDECIDE could migrate to patients with T1D who do not use insulin pumps or to type 2 diabetes (T2D). Similar to T1D, suboptimal adherence to self-management guidelines for T2D results in poor glycemic, blood pressure and lipid

control, which can lead to increased morbidity and mortality rates [160]. All patients with T1D require insulin therapy and it is necessary for about half of patients with T2D to achieve glycemic control [161]. Glucose control within the United States is poor with about 50% of patients with T2D that achieve target HbA1c scores [162]. Currently much of the data generated by patients with T2D is recorded with paper logs. The efficacy of changes to treatments are more difficult to assess with fewer objectively gathered data points, and iDECIDE could prove useful in providing a better snapshot of of patients' self-care at home. Clinicians and patients would then be able to make better informed decisions regarding adjustments to treatments and therapies to improve adherence and outcomes.

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APPENDIX A

PRESENTED POSTERS

A.1 iDECIDE: A Mobile Application for Pre-Meal Insulin Dosing Using an Evidence Based Equation to Account for Patient Preferences

Authors: Akram Farhadi, MS, Buffy Lloyd, B.S, Danielle Groat, B.S., Jelena Mirkovic, Ph.D., Curtiss B. Cook, MD, Adela Grando, Ph.D.

Presented at: American Medical Informatics Association 2014 and Mayo Academic Excellence Day 2014

iDECIDE: A Mobile Application for Pre-Meal Insulin Dosing Using an Evidence Based Equation to Account for Patient Preferences

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Abstract

Type 1 diabetes (T1D) requires the patient to conduct frequent self-monitoring of blood glucose and dosing of insulin. Evidence has shown that patients are more compliant with their diabetes management when they incorporate personal preferences[1]. We have developed a mobile application prototype, iDECIDE, to further personalize pre-meal insulin dosing by incorporating current evidence related to two variables that influence prandial glucose level: alcohol and exercise.

Introduction

Insulin pumps are medical devices that deliver continuous insulin. Current insulin pumps do not incorporate the latest medical evidence to further personalize *pre-meal insulin dosing* based on individual's *preferences* for *exercise* and *alcohol* intake[2, 3]. Evidence shows that these personal preferences have a short-term impact on *glucose measurements*, which in turn affects insulin dosing. The proposed solution is to incorporate these parameters into the current equation that calculate and *recommend insulin dosing* to help achieve *target glucose*. In contrast, there are numerous mobile applications for diabetes management that allow users to track carbohydrate intake, exercise, medications and insulin dosage. iDECIDE differs from these current mobile applications in that it is evidence based, a criterion largely missing in current mobile applications.

Methods

First, we conducted a literature review to gather the latest guidelines and evidence on insulin dosing for T1D patients to expand the current insulin dosing equation to include exercise and alcohol intake. Second, we created three prototypical T1D patient case scenarios with different pre-meal preferences. The scenarios were based on the American Diabetes Association guidelines and the opinion of domain experts. Third, we use the Ontology Web Language (OWL) to model the domain knowledge (Fig. 1 depicts main OWL classes and relationships).

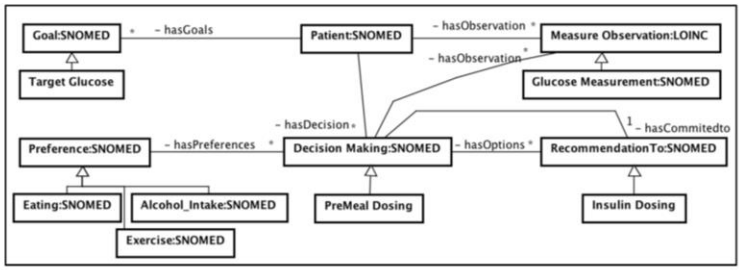

Figure 1: Knowledge Representation

Finally, we deployed a mobile application prototype (Fig. 2) that uses the new dosing equation to suggest insulin amounts based on patient's glucose reading and pre-meal preferences for carbs, alcohol and exercise.

Future work

We have submitted an IRB for approval to conduct a preliminary retrospective calibration of iDECIDE evidence-based formula. We will collect data from 20 diabetes patients on alcohol and exercise preferences, and data generated from their insulin pumps. We will compare insulin recommendations from iDECIDE against insulin pumps, as recorded by study participants. Future work will also incorporate patient SMART goals (Specific, Measurable, Attainable, Realistic and Timely) related to fitness and nutrition to further help patients achieve a healthy lifestyle.

Figure 2: iDECIDE Mobile Application

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A.2 Understanding Self-Management Behaviors to Improve Insulin Dosing

Authors: Danielle Groat, M.S; Hiral Soni, B.E.; Bithika Thompson, M.D.; Mary E. Boyle, CNP, MSN, RN, Marilyn Bailey MS, RN, Curtiss B. Cook, M.D.; Adela Grando, Ph.D.

Presented at: American Diabetes Association 76th Scientific Session 2016 and selected for a moderated poster session discussion.

Little is known about how patients with type 1 diabetes (T1D) incorporate exercise or alcohol when making decisions about insulin dosing. We recruited 19 patients with T1D to determine: 1) perceptions of how alcohol/exercise affect blood glucose (BG), 2) how they learned about alcohol/exercise, and 3) what compensation techniques were used to account for alcohol/exercise. Subjects manually recorded exercise and alcohol events for 30 days. Corresponding data from subjects' insulin pump was downloaded and combined with log data. We analyzed 4249 insulin pump interactions, 347 exercise events and 155 alcohol events. When subjects were asked how they learned about how alcohol/exercise affects BG, trial and error was cited most often (12/19 for alcohol, 18/19 for exercise). Self-reported perceptions of influence of alcohol/exercise on BG levels matched with self-reported compensation techniques in 43% and 50% of the cases, respectively. Reported techniques and observed behaviors for alcohol/exercise compensation matched 33% and 50%, respectively. Four patterns of insulin pump interactions were automatically quantified from 4249 events from 19 subjects: 1003 events of patients computing carbohydrates only, 494 events of standard boluses, 262 events of bolus waveform adjustments, and 306 events overriding the pump's bolus advice. Three behaviors were quantified manually in a subset of 9 patients: 9 patients not tracking carbohydrates, 6 patients disconnecting from the pump for prolonged times, and 5 patients bolusing too frequently. This study highlights the need for better educational strategies and/or decision support aids to improve diabetes self-management strategies that include incorporation of alcohol/exercise.

A.3 Characterizing Self-Management Behaviors of Type 1 Diabetes Patients on Insulin Pump Therapy

Authors: Danielle Groat, B.S; Hiral Soni, B.E.; Bithika Thompson, M.D.; Curtiss B. Cook, M.D.; Adela Grando, Ph.D.

Presented at: Diabetes Technology Meeting 2015

Objective:

Very little is known about patient insulin dosing behaviors in relationship to alcohol and exercise. Identifying patterns of behavior could assist clinicians in developing decision aids in support of improving glycemic control. The purpose of this study was to analyze patient insulin dosing decisions occurring in conjunction with alcohol intake and exercise.

Methods:

We recruited 9 subjects with type 1 diabetes on insulin pumps, seven of whom used continuous glucose monitoring systems (CGMS). Participants were interviewed regarding their perception of how exercise and alcohol affect glucose control. They were asked to keep a 30-day journal on the duration and intensity of exercise performed and the type and amount of alcohol consumed. After 30 days, stored glucose, carbohydrate, and insulin data was downloaded. Participants' reported behaviors with insulin dosing in the setting of alcohol and exercise were compared to data stored on their pump/CGMS devices.

Result:

Over 1,000 subject interactions with the bolus wizard were analyzed. There were 186 events associated with exercise and 81 related to alcohol. How subjects compensated for alcohol and exercise varied among subjects. Subjects varied between sometimes or never entering alcohol associated carbohydrates into the bolus wizard. Some subjects accounted for exercise when making decisions regarding insulin boluses, while others did not, and within subject inconsistency was also noted. We observed that subjects' actual behaviors regularly diverged from their reported alcohol and exercise compensation techniques.

Conclusion:

Alcohol and exercise can affect glycemic control. However, how patients dosed their prandial insulin in response to alcohol and exercise behaviors was inconsistent. Further study is needed to understand these inconsistencies and to develop improved strategies to help patients make better treatment decisions.

A.4 Introducing a Method to Retrospectively Compare Insulin Dosing Recommendations

Authors: Danielle Groat, B.S; Hiral Soni, B.E.; Bithika Thompson, M.D.; Curtiss B. Cook, M.D.; Adela Grando, Ph.D.

Presented at: Diabetes Technology Meeting 2015

Objective:

Introduce a method to compare the performance of insulin dosing algorithms. Exemplify the method by comparing in terms of postprandial control the evidence-based iDECIDE algorithm accounting for carbohydrates, alcohol and exercise, against insulin bolus recommendations made by the proprietary algorithm of the type 1 diabetes (T1D) patients' devices.

Method:

We recruited 9 T1D patients on insulin pump therapy. Patients kept a 30-day journal to track exercise performed and alcohol consumed. Glucose, carbohydrate, insulin dosing, exercise and alcohol data were downloaded and entered into the iDECIDE algorithm. The prandial insulin dose recommended by iDECIDE was compared to that made by the insulin pump. We considered that a recommendation was more favorable if it was more likely to cause blood glucose to be within the patient's target range 3 hours after dosing. Two doses were equivalent if they were equal or had a variation of less than 10%.

Result:

We analyzed over 1,000 patient events. Equivalent prandial insulin doses were suggested in 61% of the interactions. In 23% cases iDECIDE outperformed the insulin pumps, while the pumps outperformed 16% of the time. In the cases where iDECIDE outperformed, hypoglycemia could have been avoided in 26% of events. In over 50% of the reported exercise events iDECIDE would have appropriately dosed insulin or suggested a proper amount of carbohydrates to consume before exercising.

Conclusion:

By using a detailed method to compare algorithms instead of the standard technique of computing number of hypoglycemic cases avoided, we hope to better calibrate the iDECIDE algorithm and to learn from differences between patients' actual reactions versus expected reactions to exercise and alcohol as reported by evidence resulting from controlled studies.

A.5 Retrospective Evaluation of an Evidence-based Equation for Insulin Dosing Accounting for Exercise and Alcohol

Authors: Danielle Groat, MS, Maria Adela Grando, PhD, Garrick Wallstrom, PhD, Bithika Thompson, MD, Mary E. Boyle, CNP, MSN, RN, Marilyn Bailey MS, RN, Curtiss B. Cook, MD

Presented at: American Diabetes Association 76th Scientific Session 2016

iDECIDE (iD) is an evidence-based decision aid that accounts for exercise, alcohol and carbohydrate (CHO) loads in order to recommend rapid-acting insulin boluses to improve postprandial blood glucose (pBG) control. We recruited 9 subjects with type 1 diabetes on insulin pump therapy to retrospectively evaluate the prandial insulin dose recommendations of iD against those from the insulin pump's bolus wizard and against subject's self-dosing choices. Subjects reported exercise performed and alcohol consumed for 30 days, and pump data from the corresponding timeframe was downloaded. A prandial insulin dose recommendation outperformed if it could lead to a closer-to-target 3-hour pBG level. Two doses were considered equivalent if there was a difference of less than 10%. In 713/1033 (69%) recorded pump events iD suggested an equivalent prandial dose as the pump. In 17% of events iD outperformed the pump while the pump outperformed iD in 13% cases. In 117/198 (59%) cases iD and the subjects had equivalent boluses. iD outperformed the subjects in 36% of the cases while the subjects outperformed iD in 2% of the cases. In 99/101 (98%) exercise events iD appropriately advised on insulin and CHO. In 30/48 (63%) alcohol events iD appropriately advised on insulin. We conclude that the iD algorithm may provide enhanced decision making with regards to prandial insulin dosing compared to conventional methods, particularly when incorporating complex life-style choices (exercise, alcohol) into the application. The complicated nature of real-life data required new approaches to data collation and analysis for measuring bolus calculator performance.

APPENDIX B

CONFERENCE PAPERS

B.1 A Mobile Application for Insulin Dosing Using an Evidence Based Equation to Account for Patient Preferences

Authors: Buffy Lloyd, B.S, Danielle Groat, B.S., Curtiss B. Cook, MD, David Kaufman, Ph.D., Adela Grando, Ph.D.

Presented at: MEDINFO Conference 2015

Abstract

Diabetes is a complex disease affecting 29.1 million (9.3%) of US citizens[1]. Diabetes is a chronic illness that needs continual medical care and ongoing patient self-management, education, and support[2]. There is no cure for diabetes, requiring patients to conduct frequent self-monitoring of blood glucose and dosing of insulin in many cases. Evidence has shown that patients are more adherent to their diabetes management plan when they incorporate personal lifestyle choices[3]. To address the challenge of empowering patients to better manage their diabetes, we have developed a novel mobile application prototype, iDECIDE, that refines rapid-acting insulin dose calculations by incorporating two important patient variables in addition to carbohydrates consumed that are not currently a part of standard insulin dose calculation algorithms: exercise and alcohol intake[4], [5]. A retrospective analysis for the calibration and evaluation of iDECIDE is underway by comparing recommendations made by the application against insulin dosing recommendations made by insulin pumps.

Keywords:

Diabetes mellitus, insulin dosing, clinical decision support systems, mobile application, disease self-management

Introduction

Patient-centered care is defined as health care that respects patients' wants, needs and preferences, and supports patient desires to make decisions and participate in their own care[6]. Too often patients must adapt to pre-existing protocols and guidelines, rather than receiving services designed to focus on their individual needs and preferences[6]. Patient-centered decision support that translates evidence-based care into health care practice in ways that account for individual preferences and goals is needed.

Many patients with chronic conditions such as diabetes can benefit greatly from self-management[7]. Self-monitoring of blood glucose can be empowering for patients with diabetes, but tracking such data can be overwhelming[8]. Additionally, even patients well trained in diabetes self-management often fail to meet personal glycemic goals. Despite ongoing research to identify patient preferences, track treatments, and integrate patient data to provide personalized options, significant advances in the design and deployment of patient-centered decision aids are still to be made[9], [10].

Type 1 diabetes (T1D) is a chronic disease in which a person's pancreas does not produce insulin, a hormone required to regulate carbohydrate and fat metabolism in the body. Type 2 diabetes (T2D) results from a relative insulin deficit and can be due to a diminished insulin effect or insufficient production to maintain normal blood glucose levels. T2D patients may need insulin injections, oral medications, non-insulin injectable medications, or various combinations of these to control hyperglycemia. Patients with T1D must manage their disease by using insulin injections deliverable through syringes, insulin pens, or insulin pumps. Contemporary insulin pumps utilize a rapid acting insulin analog and deliver continuous basal insulin. Additionally, insulin pumps have bolus calculators that calculate the units of insulin needed based on settings, food intake and active insulin time. Such bolus calculators, which are designed to cover mealtime glucose excursions, do not take into account patient preferences such as alcohol intake and exercise. Evidence shows that these personal preferences can have a significant short-term impact on glucose levels, which in turn affects insulin dosing[4], [5]. Our hypothesis is that by incorporating current evidence regarding the impact of exercise and alcohol intake on insulin dosage, we can further improve postprandial glucose levels for adult individuals with diabetes, thereby empowering them to make informed, evidence-based self-management decisions. We have designed and seek to evaluate a novel, evidence-based decision support tool, iDECIDE, which customizes and refines rapid-acting insulin dosing calculations by incorporating individual preferences for exercise and alcohol. The target population of iDECIDE are adult diabetes patients with T1D or T2D.

Why employ iDECIDE when there are hundreds of mobile applications that allow users to track carbohydrate intake, exercise, medication and insulin dosage? Most of the available mobile applications are not evidence-based[11], while iDECIDE is based on the most current medical evidence.

Methods

A literature search that included diabetes pathophysiology, treatment and management options was conducted. We identified insulin dosage calculations based on glycemic levels, carbohydrate intake, exercise, and alcohol consumption.

Next, we reviewed the literature on smartphone apps for diabetes self-management and apps for healthy eating, physical activity, and personal health and wellness [11], [12]. Based on the review there is a proliferation of apps that are not evidence-based or do not align with well-established behavior change theories.

Following our literature review, we met with an endocrinologist and diabetes care team to further understand diabetes and to discuss current clinical challenges that patients with diabetes encounter. We participated in a guided simulation training session with a diabetes nurse educator at the Mayo Clinic Arizona Simulation Center that included hands-on experience with insulin pumps and continuous glucose monitors. The training excluded review of existing smartphone apps for diabetes management, fitness or nutrition. Based on the trainings we created three prototypical patient cases to reflect the daily regimens and personal preferences encountered on a daily basis by diabetes patients. We learned that diabetes is not a "one size fits all"

disease and that personal management requires special consideration for each patient.

We also reviewed existing insulin pump technologies commercially available in the US. State of the art insulin pumps compute mealtime insulin doses based on proprietary formulas that are approved by regulatory entities like the US Federal Food and Drug Administration (FDA). While alcohol intake and exercise can have an impact on blood glucose levels, no insulin pump takes into consideration alcohol and exercise to compute the insulin needed to correct for a meal. While insulin pumps provide bolus wizards to compute pre-meal insulin boluses, diabetes patients can manually compute pre-meal insulin bolus using an equation from Colin et al. (*Equation 1*) which takes into consideration important factors, except alcohol and exercise, for choosing the correct insulin dose[13].

***Equation 1* for Standard Insulin Dosing**

$$U = \frac{carbs}{ICR} + \frac{cBG - tBG}{CF} - IOB$$

In *Equation 1*, the variable *U* represents units of insulin. The first fraction in the equation, "*carbs/ICR*", calculates the relationship between the grams of carbohydrates (*carbs*) intended to be consumed covered by one (1) unit of insulin (*ICR*). *ICR* is calculated as 450/TDD, where Total Daily Dose of insulin (TDD) = body weight (lbs) x 0.23. The second fraction in the equation calculates the difference between the actual blood glucose level (*cBG*) and the target blood glucose level (*tBG*) and divides this difference by the Correction Factor (*CF*). The correction factor, also called insulin sensitivity factor (ISF) is defined as how much one (1) unit of rapid acting insulin lowers an individual's blood glucose over the course of 2-4 hours during a fasting or pre-meal state. These correction doses can account for approximately 9% of the TDD by compensating for the deficits in basal rates or carbohydrate boluses. *CF* is calculated as (1700mg/dl) / TDD. The final segment of the equation subtracts the Insulin On Board (*IOB*) i.e. the theoretical amount of insulin remaining in the body after the last bolus dose.

The ADA states that regular physical activity is important for maintaining health and fitness for those diagnosed with diabetes. People with diabetes are advised to participate in at least 150 minutes of moderate-intensity physical activity per week. Regular exercise has been shown to improve blood glucose control, reduce cardiovascular risk factors, contribute to weight loss and improve well-being[14]. Evidence suggests that most forms of low-to-moderate intensity physical activity result in an increase of insulin sensitivity, which produces a drop in blood glucose levels. When glucose levels drop to abnormally low levels it is called hypoglycemia. Hypoglycemia can be averted by reducing the bolus insulin, increasing food intake, or a combination of both [5]. The evidence recommends ingestion of carbohydrates (e.g. snacks) before exercising to avoid hypoglycemic events.

Alcoholic beverages present an even more complex insulin dosing challenge. Depending on the specific content of the drink, alcoholic beverages can be a carbohydrate source and/or result in delayed hypoglycemia. It is difficult for patients to factor alcoholic drinks into their insulin dosing calculations. Also, they frequently are not aware that more than 2 alcoholic drinks can increase the probability of hypoglycemia a few hours after alcohol consumption[15].

We therefore propose a new insulin dosing equation (patent pending) that accounts for the intensity and duration of physical exercise as well as the alcohol load and related carbohydrates from alcoholic beverages. We have added to the standard equation *(Equation 1)* parameters to account for patient preferences for exercise and alcohol consumption. As we noted previously, insulin pump calcuators do not consider exercise when calculating insulin dosage, neither do they factor in the effects of alcohol on insulin sensitivity. iDECIDE incorporates these factors to suggest the dosage of rapid acting insulin and sets an alarm to recommend glucose level monitoring in certain circumstances related to alcohol consumption.

Results

Several prototyping platforms such as WireframeSketcher, POP and Proto.io™ were compared. Proto.io™ emerged as the best choice due to its drag-and-drop intuitive interface for building interfaces. Figure 1 depicts screenshots of the resulting iDECIDE prototype built with Proto.io™.

To exemplify the use of iDECIDE, Figure 1 demonstrates a T2D patient using the app to decide if insulin should be taken before starting a 30 minute, medium-intensity bike ride. Based on the exercise plan and his current blood glucose level of 150 mg/dl, (cBG=150) iDECIDE recommends no insulin and suggests consuption of an additional 10 g of carbohydrates before starting the exercise to achieve a target glucose level of 130 mg/dl (tBG=130) and to avoid hypoglycemia. iDECIDE is using the ICR=10 and CF=20, based on input from the patient's endocrinologist. The IOB=0.75 because the previous insulin dose was 1.25 units from 2 hours prior[16]. To account for exercise (Ex), 0.25 is subtracted off given the short duration (30 minutes) to be completed[17]. The suggested carbohydrates (10 g) were derived from the evidence regarding the patients weight of 150 pounds and the choice of performing 30 minutes of moderate exercise[5].

Figure 2 exemplifies another use case scneario showing how iDECIDE can set up an alarm if the patient chooses to consume more than 2 alcoholic drinks. The alarm is to remind the patient to monitor blood glucose levels to help avoid hypoglycemic events.

Both Figures 1 and 2 assume that the user enters information immediately before eating, drinking or exercise in order to compute the insulin bolus. It is not uncommon for diabetes patients to input data after they eat or drink to account for last-minute changes.

We incorporated feedback on this mobile application and on the iDECIDE evidenced-based insulin dosing equation from domain experts in clinical decision support systems and usability, as well as fellow biomedical informatics graduate students. The iDECIDE prototype displayed in Figures 1 and 2 resulted from these recommendations. Then, we deployed the resulting improved interfaces and functionalities as an Android app and we performed a usability study. We secured IRB approval from Arizona State University to recruit 5 students to participate in the study. Participants were given 7 tasks to complete after a 5 minute period of self-guided exploration of the tool. Afterwards they were given a usability survey to complete. A total of 7 usability issues were identified. The exploratory task resulted in the most issues, 5.8, with the final two tasks resulting in no reportable issues. This may suggest that users were able to learn to use the system over time.

The class diagram in Figure 3 shows the main classes (domain concepts) and relationships used for designing iDECIDE. When possible, the domain knowledge of iDECIDE was mapped into terminologies and thesaurus like the Current Procedural Terminology (CPT), the SNOMED Clinical Terms, the National Cancer Institute thesaurus (NCI) and RXNORM. For instance, the concept *currentBG* was mapped to the NCI with the code C0392201.The *Diabetes Patient* using *iDECIDE* takes daily multiple measurements of blood glucose *(currentBG),* which is a type of *Endocrine Finding*. We are also modeling that, for example, a patient can use iDECIDE to set up clinical goals (*hasDesiredState*) related to *Target Glucose, Target Carbs, Target Exercise,* and *Target Alcohol*. For instance, one

Figure 1 - Screenshots of the iDECIDE: a) the patient inputs 150 mg/dl as current blood glucose and that no carbs will be consumed, b) he also inputs that he will be performing 30 minutes of medium intensity exercise; then c) iDECIDE summarizes the input data, the parameters set up by the patient's endocrinologist (e.g. target glucose), and the computed active insulin or IOB; finally d) iDECIDE generates recommendations (take 0 U of insulin and consume a snack with 10 grams of carbohydrates) and a breakdown of how the suggested insulin dosage was computed (0 U= 0 U to cover carbs + 1 U for correction factor -0.75 U of active insulin – 0.25 U for planned exercise).

Figure 2 - Screenshots of the iDECIDE prototype: a) the patient inputs 138 mg/dl as current blood glucose and that 51 grams of carbs will be consumed, b) he also inputs that he will be drinking 3 alcoholic drinks, to what iDECIDE reacts by setting an alarm to remind checking blood glucose levels to avoid hypoglycemia; then c) iDECIDE summarizes the input data, the parameters set up by the patient's endocrinologist, the computed IOB and indicates that it has setup un alarm; finally d) iDECIDE generates recommendations (take 4.5 U of insulin and check the blood glucose levels in 2 hours when the alarm rings) and a breakdown of how the suggested insulin dosage was computed.

goal could be to have no more than 2 alcoholic drinks per day during weekends. Every time the patient interacts with iDECIDE he is requested to input his daily preferences (*hasPreferences)* on *Carbs Plan, Alcohol Plan, Exercise Plan* and *Insulin Plan*. For example, the patient plans to have 3 alcoholic drinks and a dinner, which account for 51 grams of carbs. Based on the input, iDECIDE triggers recommendation messages to remind the patient that his goal was to consume less than 3 drinks, and can also remind the patient the ADA guidelines on alcohol consumption. The patient can decide to follow iDECIDE's recommendations (*makesRecommendations*) or can decide to stick to the original plan, committing to a plan (*hasCommitedTo*). Patients with chronic illnesses, such as diabetes, frequently encounter *Obstacles* when trying to achieve goals or follow treatment recommendations; they are more likely to be successful if back up plans are identified in advance (*hasBackUpState*) and suggested to the patient when obstacles are encountered.

Also, we are incorporating patient Specific, Measurable, Attainable, Realistic and Timely (SMART) goals related to diabetes management, fitness and nutrition to attempt to further *empower patients* to achieve a healthier lifestyle. For instance, "walk more" is too general as a goal. Instead, "I will walk three times a week for 20 minutes" can be measured, is action oriented, can be chosen based on clinician assessment of the patient's clinical state and self-motivation to change behavior, and has a time frame. Patients can understand SMART goals, and the achievement of SMART goals can be assessed and tracked by decision support systems. Therefore, we are currently working on decision mechanisms to provide suggestions to help patients achieve their chosen goals. For instance, in the example case-scenario described above, the patient has a fitness SMART goal of daily lunchtime exercise for 30 minutes at medium intensity. An obstacle arises for the patient: rain. The model incorporates a back-up plan for inclement weather, and suggests an exercise at home (e.g. a 30 minute WiiFit activity) that will achieve his goal. The proposed decision mechanism is inspired by the goal-based clinical decision support planning framework proposed and implemented by Grando, et al. [18], [19] to detect and recover from deviations to standard clinical care plans. In order to specify and reason on SMART goals we have built an ontology using the Ontology Web Language (OWL) using the Protégé tool. Figure 4 depicts a screenshot of the Protégé tool, demonstrating how we model a SMART goal for exercising and the encountered obstacle. The resulting ontology will support the decision rules that recommend behavioral changes, such as a specific, pre-identified home exercise option to use when there is inclement weather. Furthermore, using the ontology's goal achievement status (full, partial and none) the achievement status will be automatically determined and tracked. In our example above, the suggested back-up plan, WiiFit, is considered equivalent to the initial outdoor plan, so our patient achieves the prescribed exercise goal.

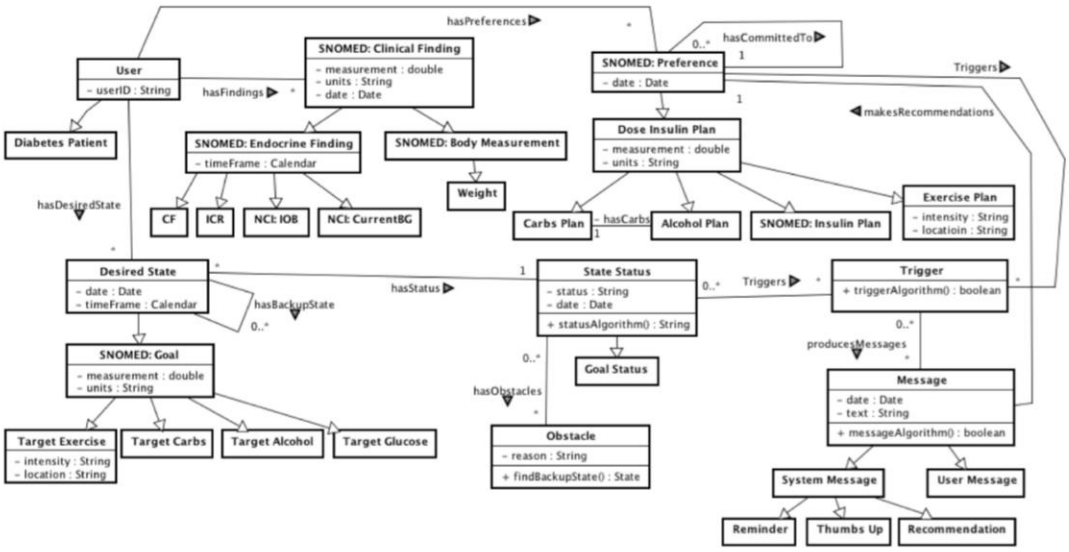

Figure 3- Class diagram depicting iDECIDE's main classes and relationships

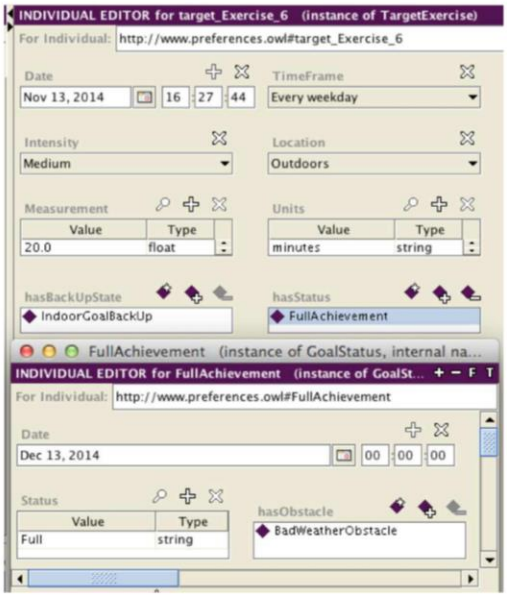

Figure 4- Screenshot from Protégé,, displaying the use case scenario of a patient who chooses the goal of walking outdoors every weekday for 30 minutes with medium intensity. In case of inclement weather, the back-up plan is to exercise at home. The status of the goal achievement (full, partial, none) can be monitored and tracked.

Discussion

Future plans include providing reminders, encouragement messages and alternatives to help patients achieve their SMART goals. For our previous example, iDECIDE could remind at lunchtime the patient to exercise with the personalized message, "Time for your lunchtime break exercise. It feels good to be in shape!" The patient can choose to answer the reminder selecting from a set of predefined options including "I cannot exercise today, the weather is bad." Based on the patient's feedback and back up plans iDECIDE can provide suggestions, I see … do you feel like trying some WiiFit tonight instead? I can send you a reminder if you want."

We are recruiting twenty Arizona Mayo Clinic adult patients with T1D who currently use Medtronic™ insulin pumps to begin a retrospective calibration of the evidenced-based formula used by iDECIDE. We are limiting this study to users of Medtronic™ pumps to streamline the data analysis. Participants will be asked to keep records for one month, including alcohol intake and performed exercise (see Tables 1 and 2). The study was approved by the Mayo Clinic IRB.

Initially we tried to reuse existing retrospective data repositories generated from insulin pumps and patients' diabetes dairies, but the available repositories lacked information on alcohol consumption or they could not be shared due to human subject protection constraints. Following the completion of the study, all participants will provide the data generated during the study period by their insulin pumps and their daily records on alcohol intake and performed exercise. We will input the provided data into iDECIDE. As part of the projected retrospective calibration, domain experts will compare the insulin recommendations generated by iDECIDE against those generated by insulin pumps. We will consider that a recommendation from iDECIDE is as good as the one from the insulin pump when the recommendations are close in range and the postprandial glucose target is achieved. We will say that a recommendation from iDECIDE is better than the one from the insulin pump if iDECIDE recommends a higher (lower) dose and the postprandial reading is higher (lower) than target.

We are adopting a user-centered design approach for iDECIDE. Numerous otherwise well-conceived applications that target patients and health consumers have failed to achieve their desired effect because they have not involved users in the development process. Usability issues identified from the completed usability study will be considered to make appropriate design changes. We also plan to conduct another usability study with diabetes patients at the Arizona Mayo Clinic to further improve the interfaces and functionalities of the mobile app.

iDECIDE does not communicate with continuous glucose monitors or insulin pumps via wireless or Bluetooth technologies because insulin pump and glucose reader manufacturers do not

share the application programming interfaces (APIs) that could facilitate such interactions. iDECIDE currently requires patients to manually input first their glucose reading, meal carbohydrates, alcohol intake and exercise. iDECIDE recommends an insulin dosage to be injected using an insulin pump or syringe. The current study utilizes patients on insulin pumps as a model to test and refine the iDECIDE methodology. Insulin pumps utilize only rapid acting insulin. Future refinement of the system to account for differences in insulin pharmacokinetics will be needed. There are situations where the actions of diabetes patients digress from what was previously entered into the pump's bolus wizard. In these situations there is no technology to account for such behavior. Most patients who use insulin pumps are fairly disciplined and adhere to an established routine, in such cases iDECIDE would be a useful tool.

Table 1– My Diabetic Diary: Tracking alcohol intake

DATE (m/d/y)	TIME (Hour: Min)	TYPE OF DRINK (Beer, wine, etc)	# OF DRINKS	MEASURE (small glass, pint, can, etc)	Did You Input Drink's Carbs Into Insulin Pump?	
__/_/_	__:__				YES carbs:	NO

Table 2– My Diabetic Diary: Tracking exercise performed

DATE (m/d/y)	TIME (Hour: Min)	INTENSITTY – check one			DURATION (minutes)
__/_/_	__ : __	LIGHT	MODERATE	VIGOROUS	

Conclusion

iDECIDE is a novel mobile application prototype that personalizes insulin dose calculations by incorporating two important patient variables that are not currently a part of standard insulin dose calculation algorithms: exercise and alcohol intake. Unlike the proprietary algorithms currently employed by insulin pump manufacturers to calculate insulin dose recommendations, iDECIDE is based on available clinical evidence that can be reviewed and discussed by the patient with the endocrinologist and care team. Also, iDECIDE will empower patients to improve disease management, fitness and nutrition by incorporating SMART goals. The app will help to track the achievement of SMART goals, but also provide reminders, encouragement messages and alternatives to help patients achieve their goals.

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APPENDIX C

JOURNAL PAPERS

C.1 Characterization of Exercise and Alcohol Self-Management Behaviors of Type 1 Diabetes Patients on Insulin Pump Therapy

Original Article

Characterization of Exercise and Alcohol Self-Management Behaviors of Type 1 Diabetes Patients on Insulin Pump Therapy

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Abstract

Background: There is a lack of systematic ways to analyze how diabetes patients use their insulin pumps to self-manage blood glucose to compensate for alcohol ingestion and exercise. The objective was to analyze "real-life" insulin dosing decisions occurring in conjunction with alcohol intake and exercise among patients using insulin pumps.

Methods: We recruited adult type 1 diabetes (T1D) patients on insulin pump therapy. Participants were asked to maintain their daily routines, including those related to exercising and consuming alcohol, and keep a 30-day journal on exercise performed and alcohol consumed. Thirty days of insulin pump data were downloaded. Participants' actual insulin dosing behaviors were compared against their self-reported behaviors in the setting of exercise and alcohol.

Results: Nineteen T1D patients were recruited and over 4000 interactions with the insulin pump were analyzed. The analysis exposed variability in how subjects perceived the effects of exercise/alcohol on their blood glucose, inconsistencies between self-reported and observed behaviors, and higher rates of blood glucose control behaviors for exercise versus alcohol.

Conclusion: Compensation techniques and perceptions on how exercise and alcohol affect their blood glucose levels vary between patients. Improved individualized educational techniques that take into consideration a patient's unique life style are needed to help patients effectively apply alcohol and exercise compensation techniques.

Keywords

alcohol, carbohydrates, diabetes, exercise, insulin dosing, insulin pump, self-management behaviors, type 1 diabetes

Diabetes mellitus is a complex, chronic disease affecting 29.1 million (9.3%) US residents.[1] Chronic hyperglycemia can result in potentially devastating microvascular and macrovascular complications, leading to major morbidity, mortality, and economic consequences in this patient population. Evidence demonstrates that these complications can be prevented by maintaining glycemic control to near normal levels. Achieving and maintaining adequate glycemic control requires consistent medical care, and most importantly, ongoing patient self-management.[2]

While evidence shows that alcohol and exercise affect the absorption of insulin and increase the risk of hypoglycemia, there is a lack of evidence-based decision tools to allow for translation of this information into practice.[3-6] Patients with type 1 diabetes (T1D) must manage their disease by injecting insulin deliverable through syringes, insulin pens, or insulin pumps. Premeal insulin dosage compliance and accuracy is a key factor in achieving target postprandial glucose levels. In 2013 insulin pumps were being used by over 350 000 people in the United States,[7] incorporate proprietary mathematical algorithms called bolus calculators or bolus wizards to determine individualized premeal dosing.[8-10] The benefits achieved through the use of insulin pumps and continuous

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glucose monitors (CGMs) are not necessarily a direct result of wearing the devices but rather due to behavioral and management changes enabled by the information provided by the devices to the users.[11] While bolus calculators and CGMs can lead to better glucose control,[12,13] bolus calculators currently cannot account for the lifestyle complexities of alcohol ingestion and planned exercise.[14-20]

A review of the literature demonstrated a lack of systematic studies analyzing adult T1D patients' self-reported behaviors against their actual behaviors documented from data collected by an insulin pump. Better understanding of these behaviors could help in the design of individualized educational programs, particularly as relates to intensive insulin therapy, and aid in designing better dosing algorithms that account for behaviors related to alcohol consumption and exercise patterns. The aim of this study was to analyze adult T1D patients self-reported versus actual self-management behaviors occurring in conjunction with alcohol intake and exercise.

Materials and Methods

Subject Recruitment

After Institutional Review Board approvals, 19 adult T1D patients were recruited from an academic outpatient endocrinology clinic. Participants were between the ages of 18 and 70, nonpregnant, and English speaking and had been using an insulin pump from a single vendor for at least 1 year. Patients in fragile health, limited life expectancy, a history of mental health problems, advanced vascular disease or microvascular complications, and known history of severe hypoglycemia were excluded. Study personnel identified potential subjects at the time of their scheduled outpatient visit. Subjects were handed a flyer that provided details on the study.

Data Collection

The study team conducted structured interviews to collect participants' self- reported perceptions of how alcohol and exercise affected blood glucose levels and the sources of information they had used to learn about these interactions. In addition, subjects were asked if they accounted for alcohol and exercise in their insulin dosing decisions, and what type of techniques they used to compensate for these behaviors (eg, carbohydrate consumption, reduction in insulin bolus or basal rate, or some combination of these methods).

Participants were asked to maintain their daily routine, and to keep a journal on the time, duration and intensity of exercise performed (eg, at 9:00 AM performed 20 minutes of high-intensity exercise) and the time, type, and amount of alcohol consumed (eg, at 10:20 PM drank a can of light beer) for 4 consecutive weeks. Patients recorded how they compensated for alcohol and exercise on the logs. Participants were called once during the study to assess progress and answer questions. At the end of the data collection period, patients mailed or faxed in their completed alcohol and exercise logs.

The study team also obtained the data contained within the participants' insulin pump during the same 4-week period. The patients uploaded the insulin pump data through a website provided by the insulin pump's manufacturer, which was remotely accessed by study personnel. Once the data were downloaded the patients were encouraged to change their passwords. Alternatively, patients could meet in person with a member of the study team who could download the data from the patients' insulin pump.

Data Analysis

Subjects' perceptions of the effect of alcohol and exercise on glucose levels and their sources of information regarding alcohol and exercise were tabulated. Data from the paper-based diaries were electronically coded and analyzed to quantify for each study participant number of drinks and frequency of exercise. To report patients' observed behaviors for exercise and alcohol we reviewed data downloaded from the insulin pumps and from the participants' paper-based diaries to quantify how often patients used techniques to compensate for alcohol ingestion and exercise activity, such as adjusting insulin (basal rate or bolus) or taking a snack within 30 minutes before exercising. Computer algorithms were written to associate self-reported days and times of alcohol consumption and exercise to the corresponding data collected by the insulin pumps. Using the aggregated data the frequency of compensation techniques related to carbohydrate consumption, insulin boluses delivered, and blood glucose monitoring occurring in close temporal proximity to exercise or alcohol consumption was computed for each study participant. Close temporal proximity was defined as ±30 minutes of alcohol consumption or exercises.

Results

Demographics

Nineteen subjects with T1D were recruited. Mean (SD) age was 48 (15) years, 12 were women, and 18 were of white race. Mean (SD) hemoglobin A1c was 7.3 (1.0)%, self-reported duration of diabetes was 27 (13) years, and duration of insulin pump therapy was 11 (5) years. Seven participants wore a CGMS, and the remaining used capillary glucose monitoring. There were 4249 interactions between the study participants with the insulin pump bolus calculator analyzed. There were 347 exercise events recorded by 17 participants and 155 alcohol events recorded by 11 participants.

Perceived Interactions and Sources of Alcohol and Exercise Information

When subjects were asked about how alcohol or exercise impacted their glucose control, there were no consistent

Table 1. Subject Perceptions on How Exercise and Alcohol Affect Their Blood Glucose.

Activity	No. of subjects	Perception	Sample comments
Exercise	7	It lowers blood glucose	"It lowers my blood glucose"
	7	Various effects, based on type of activity, intensity, and time of day	"Interval training elevates or lowers blood glucose, backpacking raises it" "The effect depends on the time of day and the type of exercise" "Exercise may not drop blood glucose" "Morning exercise raises the blood glucose, but evening exercise lowers it"
	5	No reported data	
Alcohol	8	Various effects, based on number of drinks and drink type	"Alcohol raises blood glucose initially and lower it hours later" "Beer raises blood sugar" "I feel I have to take insulin if I have beer, but no insulin if I have hard alcohol" "Almost always raises it" "If I have more than a few drinks the blood glucose lowers, if I have hard alcohol it raises and then lowers"
	1	No effect or minimal effect	"I don't see much effect"
	2	Lack of knowledge	"I don't know, I need more information"
	8	No reported data or N/A	"I don't drink"

Table 2. Subject Self-Reported Sources of Education on How Exercise and Alcohol Affect Their Blood Glucose.

Activity	No. of subjects	Source of education
Exercise	19	Trial and error
	2	Literature/online reading
	2	Provider education
	1	Other diabetes patients
Alcohol	12	Trial and error
	3	Literature/online reading
	1	Provider education
	5	Other diabetes patients
	4	N/A

responses observed (Table 1). There were 7 participants who all stated that exercise lowers blood sugar independently of the type and time of exercise, another 7 whose responses varied on how glucose reacted to different exercise types (variety of endurance, athletic, aerobic, and anaerobic types of exercises were mentioned) and times (eg, morning, evening), and another 5 without responses. With respect to alcohol (Table 1), 8 participants stated that their reactions to alcohol depended on factors like the number of drinks (eg, only compensating when consuming 2 or more drinks) or type of drinks (eg, differentiating between drinks with high or low alcohol concentration), 1 who stated there was no effect on glucose, 2 who did not know, and 8 who did not respond.

Participants also reported deriving information on how exercise and alcohol affected their blood glucose from a number of different sources (Table 2). Most participants indicated they learned about the interactions from trial and error and had developed their own heuristics. Few participants reported having received information or education from providers on approaches to compensate for alcohol or exercise when self-managing blood glucose. Two participants indicated that they would like to receive more information on the way alcohol affects blood glucose.

Overall Self-Management Behaviors

Current American Diabetes Association (ADA) Standards of Care Guidelines suggest that patients should consider checking blood glucose prior to exercise and recommend that to avoid hypoglycemia the insulin dose and/or carbohydrate intake may need to be altered.[21] Many health care organizations suggest that alcohol should be consumed with a meal containing carbohydrates to avoid hypoglycemia.[22-24] Data entered into the subjects' insulin pumps indicated self-management techniques did not match current recommendations (Figure 1). When comparing self-management techniques for exercise versus alcohol, participants consumed carbohydrates (40.9% vs 20.6%), delivered an insulin bolus (38.3% vs 26.8%), or checked their blood glucose (60.7% vs 27.3%) more consistently with exercise than when consuming alcohol.

Similar to Hendricks et al,[25] study participants' adherence to ADA recommendations for alcohol consumption and exercise[21] were quantified. According to the guidelines "adults with diabetes should be advised to perform at least 150 min/week of moderate-intensity aerobic physical activity (50-70% of maximum heart rate), spread over at least 3 days/week with no more than 2 consecutive days without exercise." Weekly adherence to this guideline by study participants was 38.4% (45.4), with 5/17 subjects reporting 100% adherence and 10/17 subjects at 0%. The ADA also recommends "adults with diabetes who drink alcohol should do so in moderation (no more than one drink per day for

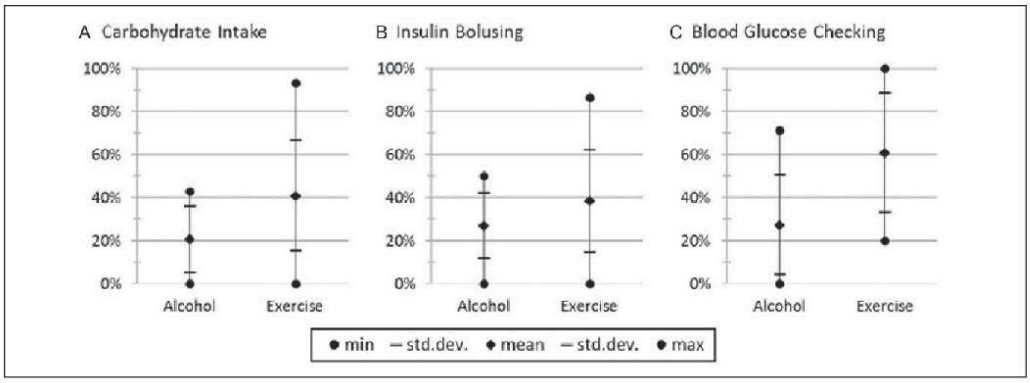

Figure 1. (A) Carbohydrate intake, (B) insulin bolusing, and (C) blood glucose checking within ±30 minutes of exercise or alcohol consumption. For instance, as depicted in (A), in temporal proximity of alcohol events subjects consumed carbs with 20.6% mean, 15.3% standard deviation, and 0-42.9% range. In contrast, in proximity to exercise events subjects consumed carbs with 40.9% mean, 25.5% standard deviation, and 0-93.3% range.

adult women and no more than two drinks per day for adult men)." The mean (SD) adherence to the ADA guidelines for daily alcohol moderation was 94.6 (9.2)% within the range of 70 to 100%.

Observed Versus Actual Behaviors Associated With Exercise and Alcohol

Next we contrasted subjects' reported self-management techniques against observed behaviors for exercise and alcohol, as derived from analysis of corresponding data contained with the subjects' insulin pumps. Self-described compensatory self-management techniques for exercise and alcohol consumption were categorized as no compensation, adjusting insulin (reducing basal rates or boluses), ingesting snacks, or removing the pump. When examining behaviors related to exercise, discordance was seen between what subjects claimed they did versus actual behavior. For instance, 16 subjects reported they would adjust insulin pump settings when exercising, while only 7 were observed to have done so (Table 3). Another 2 indicated they would take a snack, but 5 were noted to employ this technique. While 2 study participants reported always adjusting basal insulin, no patients were observed always adjusting their basal settings. Although 2 patients reported sometimes removing the pump during exercise, the pump disconnection was not explicitly recorded in the insulin pump data we had access to, hence we were not able to quantify this behavior.

Similar discrepancies were noted between what subjects said they would do and what they actually did when reviewing self-management behaviors related to alcohol ingestion (Table 3). For example, 5 subjects indicated they would not compensate for alcohol use, while 8 were actually observed not making any adjustments. There were 10 subjects who indicated they would adjust insulin when drinking alcohol, but only 3 were noted to have done so.

Discussion

Qualitative studies of children, adolescent, and adult diabetes patients have been performed with the purpose of understanding behavioral diabetes care.[25-29] While in general qualitative studies are limited by small sample sizes and do not generate statistically significant data, their findings are crucial to give a glimpse into patients' beliefs, attitudes, behaviors, culture, and lifestyle. With diabetes in particular, understanding patients' behaviors is very important to discover the reasons behind nonadherence to treatment or poor glycemic control, and to identify the best ways to deliver effective interventions.

With respect to self-care, qualitative studies have shown that many patients lack understanding of how medications, food, and exercise affect blood glucose control and what kind of information needs to be taken into account (carbohydrate content of food, activity level, etc) to self-manage diabetes effectively.[30,31] In terms of physical activity, the qualitative study by Hendricks et al interviewed 49 emerging adults (18 to 26 years old) to understand their exercise habits and to determine their compliance with the ADA recommendations on physical activity.[25] The ADA recommends at least 30 minutes of daily physical activity for youth. In the Hendricks et al study[25] 41% of participants engaged in exercise at least once daily; 55% of those individuals who engaged in daily exercise demonstrated a mean duration of 30 minutes or more. Mean exercise duration was 29.56 minutes/day and ranged from 0 to 157 minutes.

Table 3. Patient Self-Reported Compensation Techniques and Observed Behaviors for Exercise and Alcohol.

Activity	Compensation technique	Comments	No. of subjects who reported using the technique	No. of subjects who actually used the technique
Exercise	No compensation		1	1
	Adjust insulin (basal rate or bolus) sometimes or always	"When I perform strenuous exercise I reduce basal rate" "When I play hockey I take a bolus of 1 ½ unit, then I remove the pump" "When involved in anaerobic exercise I take insulin, if it is aerobic exercise I don't take insulin"	16	7
	Remove pump	"Sometimes I remove my pump"	2	-
	When needed, take snack before exercising	"If my blood sugar is less than 200 in the evening I eat a snack or I reduce the basal rate to half and I get to 100"	2	5
	No data		2	9
Alcohol	No compensation		5	8
	Adjust insulin by compute drinks' carbs, sometimes or always	"I was told by my endocrinologist to not compute drinks' carbs when I take 1 or 2, otherwise yes" "I feel I have to take insulin when I drink beer but no insulin when I drink hard alcohol"	10	3
	No data or NA	"I don't drink"	4	8

To eliminate inaccuracies from self-reported data and to obtain statistically significant results by increasing the sample sizes, quantitative studies are taking full advantage of the data generated by diabetes technology as was conducted here. Blood glucose monitors, CGMs, and insulin pumps can objectively store data that reflect what patients actually do, as opposed to what patients say they are doing (self-reported data). Driscoll and Young-Hyman[32] provide a detailed review of the use of such technology in assessing adherence to diabetes self-management behaviors. Their 2014 review focused on patients' adherence to the ADA Clinical Practice Recommendations[33] with an emphasis on studies that assessed patient adherence to glucose monitoring, insulin administration, medical nutrition therapy, and physical activity. The review by Driscoll and Young-Hyman did not discuss alcohol consumption. In terms of physical activity, their review highlighted the lack of studies that quantify physical activity and suggest the future use of accelerometers to objectively measure physical activity.

The goal of this study was to address the lack of systematic qualitative and quantitative studies to understand adult T1D patients' self-management practices occurring in conjunction with alcohol intake and exercise. Results indicated that subjects varied in their understanding of how exercise and alcohol affected their glucose control, and in how they compensated for the impact of these common lifestyle choices in their diabetes management. These results are consistent with patients' trial and error approaches to fine-tune self-management techniques based on unique personal and situation specific factors that affect blood glucose control in the presence of alcohol and exercise. In addition, there was no one means by which they obtained information on these important topics. Documented adjustments in carbohydrate intake, insulin doses, and glucose monitoring occurred at frequencies lower than what might be expected. In the case of alcohol consumption, very few instances of changes in self-management behavior were noted.

The results demonstrate the need for a revision of current educational strategies to help patients incorporate their personal lifestyle preferences into proper alcohol and exercise compensation techniques. A number of approaches could be utilized, such as the use of social media, or incorporating more individualized training during diabetes self-management education sessions. Another approach could be the development of software applications (apps) that assist patients in making decisions about how to change carbohydrate intake or adjust insulin doses in the event of an exercise or alcohol event. An automatic approach to help prevent hypoglycemic events, including those caused by exercise or alcohol, is to incorporate into insulin pumps a threshold suspend feature that is designed to automatically stop insulin delivery when the blood glucose sensor value reaches or falls below a patient-specific preset threshold.

Further research will be needed to better understand and explain the findings observed here and their practical implications. This study revealed that many patients described using a behavioral technique that was inconsistent with their actual behaviors. While it is clear that subjects were often acting in a manner different than that reported, it is unclear if these study subjects were conscious of these inconsistencies.

Figure 2. Screenshots of a smartphone app to report (a) plans for exercise and (b) food intake and alcohol.

Future work could aim to better understand real-life insulin pump behaviors and look for explanations for observed behaviors from study participants by recontacting and interviewing them using sets of detailed scenario-based questions that replicate the most frequently observed behaviors. It would also be interesting to review patient data with the subjects to see if they were aware of their inconsistencies. Similar detailed scenario-based questions that could help to understand reasons for patients' common self-management behaviors could be posted to diabetes patients online communities, like Glu (https://myglu.org) or PatientsLikeMe (https://www.patientslikeme.com), that are designed to accelerate research and amplify the collective voice of thousands of diabetes patients.

An important limitation of our study was the use of paper-based records for collecting participant's self-reported data on exercise, alcohol, and carbohydrate intake. It is possible that subjects were not recording all their exercise or alcohol events. There are methods available to improve on the accuracy of the data collected that are currently being employed in a follow-up study currently underway. For instance, to achieve higher accuracy in the reported data on exercise wristband heart rate accelerometers are being provided to subjects that measure the intensity and duration of exercise. In this follow-up study, participants are being asked to use a smartphone app (iDECIDE) to self-report data on perceptions on how alcohol/exercise affect insulin absorption and sources of education, and food and alcohol consumed and exercise performed. The authors expect to take advantage of the ubiquity of smartphones to obtain more precise records on food and alcohol consumed and exercise performed (see Figure 2). Another limitation is the small sample size, although each subject did generate multiple behaviors that could be analyzed.

Conclusion

Despite the limitations, the reported analysis of real-life diabetes self-management decisions provided insight on behaviors occurring in conjunction with alcohol intake and exercise among patients using insulin. The results of this study revealed the need for improved individualized educational techniques and decision support systems to assist patients with incorporating exercise and alcohol into daily life and management of their blood glucose. Further research should focus on understanding reasons behind observed patients' disease management behaviors and ways to change undesirable behaviors into evidence-based recommended glucose control techniques that could lead to better diabetes self-management.

Abbreviations

ADA, American Diabetes Association; CGM, continuous glucose monitor; T1D, type 1 diabetes.

Declaration of Conflicting Interests

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C.2 Self-Management Behaviors in Adults on Insulin Pump Therapy: What Are Patients Really Doing?

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Self-Management Behaviors in Adults on Insulin Pump Therapy: What Are Patients Really Doing?

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Abstract

Background: Successful diabetes management requires behavioral changes. Little is known about self-management behaviors (SMB) in adults on insulin pump (IP) therapy.

Objective: Analyze and characterize observed common diabetes SMB in adult participants with type 1 diabetes (T1D) using IPs and to correlate behaviors with glycemic outcomes based on participant's individual glucose targets.

Materials and Methods: One month of IP data from adults with T1D were downloaded. Computer programs were written to automatically quantify the observed frequency of expected behaviors such as: insulin bolusing, checking blood glucose (BG), and recording carbohydrate intake, and other interactions with the IP.

Results: Nineteen participants were recruited and 4,249 IP interactions were analyzed to ascertain behaviors. Intersubject variability of adherence to minimally expected behaviors was observed: daily documentation of carbohydrates and BG checks in 76.6 (31.7)% and 60.0 (32.5)%, respectively, and bolusing without consulting the IPBC in 13.0 (16.9)% of delivered boluses, while daily insulin bolus delivery was consistent 96.8 (5.7)%. Higher frequency of adherence to daily behaviors correlated with a higher number of glucose readings at target.

Conclusion: Results indicate variability in SMB and do not always match recommendations. Case-scenarios based on observed real-life SMB could be incorporated into interviews/surveys to elucidate ways to improve SMB.

Keywords

type 1 diabetes, self-management behaviors, insulin dosing, insulin pump, bolus calculator

Optimizing glucose control in patients with type 1 diabetes mellitus (T1D) is known to reduce microvascular and macrovascular complications.[1] The intensive insulin therapy needed to accomplish glycemic goals can be delivered either via multiple daily injections or continuous subcutaneous insulin infusion devices, also referred to as insulin pump (IP) therapy. However, intensive insulin therapy alone is not sufficient to achieve desired glycemic goals. Successful diabetes self-management requires behavioral changes to achieve glucose targets. The 2016 American Diabetes Association (ADA) Standards of Care Guidelines outline the behaviors required for daily self-management, including recommendations to monitor blood glucose (BG) 6-10 times per day, and dose prandial insulin 3-4 times per day as it relates to carbohydrate intake.[2]

As technology for diabetes has advanced, so have the informatics capabilities of IPs and BG monitors. Devices store objectively measured data that can be downloaded and used to quantify behaviors and outcomes. IPs store data such as the bolus amount suggested by the insulin pump bolus calculator (IPBC), the bolus amount selected by the patient, carbohydrates entered into the IP by the patient, and BG levels from a connected BG monitor and/or a continuous glucose monitoring system (CGMS).

Adherence to self-management behaviors (SMB) such as carbohydrate intake, administering insulin boluses to cover

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meals, and monitoring of BG have been studied in children, youth and emerging adults (18-26 years old) with various criteria, methods and sources of data, including users of IPs.[3-7] Although IP therapy has been found to improve glycemic control, suboptimal adherence even with this technology can result in poor glycemic control.[4,8] There is a lack of studies that describe SMB in adults with T1D. The objective of this study was to use IP data to analyze and characterize common behaviors related to insulin bolus dosing, BG monitoring and carbohydrate intake observed in adults with T1D, and to correlate those behaviors with glycemic outcomes.

Methods

Study Recruitment

After Institutional Review Board approval, we recruited adults with T1D from an outpatient academic endocrinology practice. We identified potential participants at routine quarterly visits and they were contacted to set up a recruiting appointment. After participant consent we remotely gathered data after 30 days of participation. Therefore, data were collected after the appointment with the provider and well before the next quarterly appointment.

Participant Selection

We adopted the following as inclusion criteria: patients who had been under the care of the endocrinology team for at least 1 year, 18-70 years of age, nonpregnant, English speaking, and using the same IP manufacturer, Medtronic. We used as exclusion criteria: fragile health, limited life expectancy, records of mental health problems, advanced vascular disease or micro-vascular complications, known history of severe hypoglycemia or advanced atherosclerosis. The inclusion/exclusion criteria and duration of the study was defined as part of a broader study that collected data to retrospectively compare insulin bolus algorithms.[9,10]

Data Collection and Standardization

Participants' IP data were downloaded in its source format (ie, spreadsheet). IP data included carbohydrates recorded by the participant, BG levels from CGMS or capillary BG monitor or both, amount of insulin suggested and delivered by the pump, and personalized pump settings and BG targets which may have varied over the course of a 24-hour period. Computer programs were written to automate the process of quantifying the IP behaviors and glycemic outcomes.

We identified over 4000 interactions with the IP in this study. Using code, we removed duplicate BG readings that occurred in within 4 minutes of each other since CGMS sent readings every 5 minutes. We included in the analysis values that were entered manually, recorded from IP connected BG meters and CGMS. We did not identify any means to identify BG readings that resulted from user-error, and as such, no BG values recorded with the IP were excluded after the data cleaning process.

Minimally Expected Self-Management Behaviors

As in O'Connell et al[4] and Driscoll et al[5] the minimally expected daily SMB for glycemic control were defined as: counting carbohydrates 3 or more times per day (assuming at least 3 meals per day), delivering an insulin bolus 3 or more times per day to correspond to those meals, and checking BG 4 or more times per day (once for each meal and before bedtime). These behaviors were quantified on a daily basis for each participant and 2-sided, unequal t-tests were used between those using capillary glucose monitoring and CGMS. Fisher's exact test was used to compare adherent days to nonadherent days when considering BG readings that were within target. These parameters were assessed because they could be directly derived from IP/CGMS data.

The correlation of the above 3 diabetes SMB was analyzed with BG outcomes. Glycemic control was addressed on a daily basis by categorizing BG as low, at target or high based on each participant's personalized BG targets. The number of BG readings within the target range for the participant over the course of a 24-hour day were compared to the total number of BG readings. BG readings were obtained from manual entry, synchronized glucose meter or CGMS. All data are reported as mean and standard deviation (SD) where applicable.

Insulin Bolusing Behaviors

How often participants selected the same, smaller or larger insulin bolus that was suggested by IPBC was evaluated. In addition, the number of times the IPBC was accessed was counted and this value was used to calculate the percentage of IPBC overrides.

Finally, participants may have opted to deliver insulin boluses without consulting the IPBC. They may have changed the waveform (eg, normal to square), which is considered an advanced IP feature. The delivered boluses for each participant were counted and used to calculate the percentage of delivered boluses that were self-determined (ie, the participant did not access the IPBC for a suggestion before delivering an insulin bolus) and how often the bolus waveform was changed.

Results

Participant Characteristics

There were 19 participants recruited; 7 employed CGMS and the remainder utilized capillary glucose monitoring (Paradigm System), with 13 participants using 1 or more BG meters that communicated with the IP. Four IPs were

Table 1. Observed Frequency of Investigator-Defined Minimally Expected Daily Behaviors, Differentiating Between the Group of Participants Under Capillary Glucose Monitoring and the Group Using CGMS.

BG behavior	Capillary glucose monitoring	CGMS	*P* value	Group total
Documented carbohydrates 3 or more times/day, %	72.3 (33.3) 0.0-100	84.0 (29.7) 17.2-100	.44	76.6 (31.7) 0.0-100
Administered insulin bolus 3 or more times/day, %	97.4 (5.6) 80.6-100	95.6 (6.2) 82.8-100	.53	96.8 (5.7) 80.6-100
Documented BG 4 or more times/day, %	55.8 (36.1) 0.0-94.4	67.8 (26.4) 37.9-96.4	.45	60.0 (32.5) 0.0-96.4
All 3 behaviors/day, %	48.4 (35.5) 0.0-88.9	61.5 (32.9) 6.9-93.6	.43	53.2 (34.3) 0.0-93.6
Documented carbohydrates/day, #	3.8 (1.5) 1.1-6.0	4.2 (1.8) 1.4-6.7	.62	3.9 (1.6) 1.1-6.7
Administered insulin bolus/day, #	6.5 (2.3) 3.8-11.8	9.4 (4.8) 3.9-18.3	.17	7.5 (3.6) 3.8-18.3
Documented BG/day, #	4.2 (2.5) 1.2-11.1	4.5 (1.4) 3.2-7.2	.72	4.3 (2.1) 1.2-11.1

Values are reported as mean (SD), range.

used by the participants: 9 on MiniMed 530G-551, 1 on MiniMed 530G-751, 5 on ParadigmRevel-523, and 4 on ParadigmRevel-723. The average participant age was 48 (15) years and the self-reported duration of T1D and duration of IP therapy was 27 (13) and 11 (5) years, respectively. Mean HbA1c was 7.3 (1.0). There was a higher percentage of recruited women (63%) and most were white (95%). We analyzed an average of 32 (4.8) days of data from each participant and a total of 4,249 interactions with the IPBC.

Daily Minimally Expected Self-Management Behaviors

Intersubject variability to the 3 minimally expected daily behaviors was observed (Table 1). Carbohydrates were entered into the IPBC 3 or more times per day an average of 76.6 (31.7)%. Levels of adherence were similar between those on CGMS and capillary glucose monitoring, 84.0 (29.7)%, and 72.3 (33.3)%, respectively. Five participants showed adherence to this behavior 100% of the time, while 1 participant showed a maximum of 2 carbohydrate entries per day. Carbohydrates were documented an average of 3.9 (1.6) times per day.

Participants delivered insulin boluses an expected 3 or more times per day an average 96.8 (5.7)%. There were 11 participants whose observed bolus adherence was 100%; all but 1 participant achieved 90% or better adherence. On average participants delivered an insulin bolus 7.5 (3.6) times per day. Although not statistically significant, participants on CGMS delivered an average of 9.4 (4.8) boluses per day while participants using capillary glucose monitoring averaged 6.5 (2.3) boluses per day.

Adherence to glucose checks was similar for participants on CGMS when compared to those on capillary glucose monitoring even though providers at the Mayo Clinic advise patients on CGMS to calibrate with a capillary glucose check a minimum of 2 times per day. On average, participants on CGMS checked BG 4.5 (1.4) times per day and those on capillary glucose monitoring checked 4.2 (2.5) times per day. None of the participants were perfectly adherent to checking or recording BG and only 3 achieved 90% or better adherence.

When all 3 minimally expected behaviors were considered together participants were simultaneously adherent to all 3 investigator-defined guidelines on average 52.3 (34.3)% of days. None of the participants were found to be 100% adherent and 2 individuals never engaging in the 3 recommendations simultaneously. Adherence of all 3 behaviors between CGMS and capillary glucose monitoring was similar, 61.5 (32.9)% and 48.4 (35.5)%, respectively.

Relationship Between Daily Minimally Expected Behaviors and Glucose Targets

As depicted in Figure 1, when participants entered carbohydrates 3 or more times per day they achieved their individualized target BG in 4.6 (4.1)% of the recorded BG values during the 24-hours. Days when that behavior was not observed the target BG was achieved 0.8 (1.7)%. When participants were observed bolusing 3 or more times per day it resulted in 5.2 (3.7)% BG readings at target, days when blousing was less than 3 the target BG was recorded 0.1 (0.3)%. On days that participants checked BG 4 or more times per day they achieved target BG 3.5 (3.0)% versus 1.8 (3.3)% on days that expected behavior was not observed. When participants were adherent to all 3 minimally expected behaviors BG was at target 3.3 (3.0)%, and 2.4 (3.2)% on days they failed to meet all 3 behaviors. Although these findings were not significant (Fisher's exact test), there was a

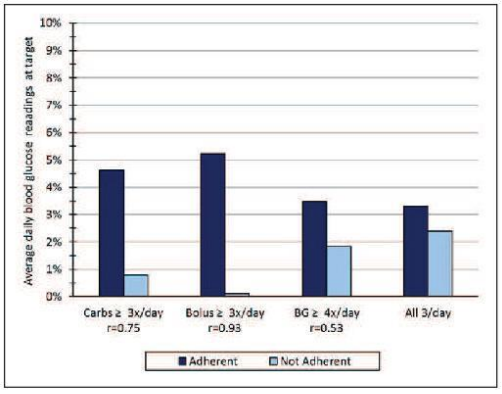

Figure 1. Comparison of blood glucose control for observed adherent/nonadherent days based on investigator-defined optimal behaviors and percentage of blood glucose readings at target for the day.

high correlation between the observed frequency of behaviors and the percentage of BG readings that were at target. Increasing the number of daily insulin boluses had the largest impact on increasing the number of BG readings at target for the day, r = 0.93. Consuming carbohydrates and checking BG had correlation values of r = 0.75 and r = 0.53, respectively.

Daily Insulin Bolusing Behaviors

Table 2 provides results for additional behaviors that were observed and analyzed. Over the course of the month participants accessed the IPBC on average 198.7 (94.3) times and insulin boluses were delivered 220.7 (78.7) times during the same time period. Two-thirds, 66.6 (16.1)%, of the IPBC recommendations resulted from participants entering carbohydrates. Correction BG readings were provided by participants in 74.8 (24.4)% of the IPBC recommendations. Nine participants frequently entered BG corrections (>90%) while 4 participants entered BG corrections less than 50% of the time.

Participants chose to deliver the same bolus amount as suggested by the IPBC in 85.7 (12.7)% of delivered boluses (Table 2). There were 8 participants who very often (>90%) chose the same bolus as the IPBC, while 1 participant chose a different bolus in 51% of the delivered boluses. Participants were nearly even on their preference for choosing a larger or smaller bolus, 7.4 (6.1)% and 6.9 (9.3)%, respectively.

In 6.4 (10.8)% of the delivered boluses participants changed the waveform from normal to dual or square. A majority of the participants (n = 14) never or rarely (<5.0%) changed the bolus waveform while 3 participants changed the waveform in over 25% of the boluses they delivered. Participants occasionally chose to deliver an insulin bolus without consulting the IPBC, which constituted 13.0(16.9)% of the delivered boluses. While 10 participants never or rarely (<5.0%) delivered an insulin bolus without consulting the IPBC, 2 participants delivered approximately 50% of their insulin boluses without accessing the IPBC.

Table 2. Overview of the Insulin Pump Bolus Calculator (IPBC), Insulin Bolus Decisions, and Additional Information Regarding the Optimal Behaviors.

Access IPBC	Value
IPBC recommendation provided, #	198.7 (94.3), 62-449
BG control guidelines	
Carbohydrates entered to IPBC, %	66.6 (16.1), 38.8-100
Boluses delivered, #	220.7 (78.7), 109-380
BG entered to IPBC, %	74.8 (24.4), 35.8-100
Bolus recommendations from IPBC	
Select same bolus suggested by IPBC, %	85.7 (12.7), 49.1-100
Select larger bolus than suggested by IPBC, %	7.4 (6.1), 0.0-18.5
Select smaller bolus than suggested by IPBC, %	6.9 (9.3), 0.0-32.7
Other bolus decisions	
Select square or dual bolus waveform, %	6.4 (10.8), 0.0-30.4
Bolus without consulting IPBC, %	13.0 (16.9), 0.0-52.7

Values are reported as mean or % (SD), range.

Monthly Frequency of Expected Self-Management Behaviors

In addition to the daily analysis of participant's behavior (Tables 1 and 2), we analyzed for each participant the monthly frequency of 5 distinct behaviors: 1) disregarding BG readings and only accounting for carbohydrates when using the IPBC, 2) bolusing without consulting the IPBC, 3) changing the bolus waveform to dual/square, 4) choosing insulin boluses different from those suggested by the IPBC, and 5) frequent bolusing: 4 or more boluses in a 5-hour time period or delivering 10 or more boluses during a 24-hour period. As shown in Table 3, we categorized each participant as never (0 events), rarely (1-4 events), occasionally (5-14 events), regularly (15-90 events), or excessively (more than 90 events) showing a behavior over the course of 1 month.

We observed that 15 participants occasionally or regularly chose a different insulin bolus than the one recommended by the IPBC and that 4 participants rarely or never chose a different bolus. All the behaviors reported in Table 3 were automatically computed, except for the frequency of bolusing which was manually counted on a subset of the participants: 7 on CGMS and 2 on capillary glucose monitoring. Out of the subset of 9 participants, 3 occasionally or regularly bolused frequently while 6 rarely or never bloused frequently.

Table 3. Categories of Insulin Compensation Techniques Observed in Study Participants, Including (1) Disregarding BG Readings and Only Accounting for Carbohydrates When Using the IPBC, (2) Bolusing Without Consulting the Pump, (3) Changing the Insulin Bolus Delivery From Waveform to Square, (4) Choosing Insulin Boluses Different From Those Suggested by the IPBC, and (5) Bolusing 4 or More Times in a 5-Hour Period or Delivering 10 or More Boluses During a 24-Hour Period.

Behavior	Never (0 events)	Rarely (1-4 events)	Occasionally (5-14 events)	Regularly (15-90 events)	Excessively (90+ events)
Compute carbs only (n = 19)	7	2	1	5	4
Bolus without consulting pump (n = 19)	7	3	1	7	1
Change waveform to dual/ square (n = 19)	10	3	0	5	1
Clinically different bolus selected (n = 19)	3	1	7	8	0
Frequent boluses (n = 9)	4	2	2	1	0

Using the IPBC to adjust for carbohydrate meal content while omitting a current BG reading was done regularly or excessively by 9 participants, while 9 rarely or never omitted a current BG reading and 1 occasionally did so. Bolusing without consulting the IPBC was done regularly or excessively by 8 participants and 10 rarely or never delivered a bolus without the IPBC and 1 occasionally bolused without the IPBC. There were 13 participants that never or rarely changed the bolus waveform and 6 who regularly or excessively changed the bolus waveform.

Discussion

Diabetes behavior studies have mainly relied on self-reported data gathered from interviews, surveys and questionnaires.[3,7,11] These methods have been used to gather qualitative data, which contribute to the understanding of behavioral diabetes such as insights about the beliefs, motivations, perceptions and expectations of the patient which can be used to inform changes to therapy regimens that can improve adherence.[12,13] There are limitations to self-reported data such as recall bias (ie, inaccurately remember and report behaviors) and social desirability (ie, over-report favorable behavior and under-report poor behavior). White coat adherence may be a source of bias when measurement instruments are delivered during patient-provider encounters since patients may improve their SMB in the days or weeks leading up to the appointment.[14,15] In our case data were collected after the appointment with the provider and months before the next appointment.

Although we were able to assess the adherence to diabetes management recommendations and other SMB by using device recorded data, this study was limited by a small sample size which lacked the power to detect differences between groups. The demographics of this cohort may not be representative of the general T1D population based on race and HbA1c. Another limitation of this study is that participants may have used 1 or more glucose meters that did not communicate with the IP and subsequently the use of those devices would not have been captured by the IP.

Consistent with other studies, we found that there was variability of observed behaviors across participants and that there was a direct correlation between daily adherence to expected SMB and better glycemic control.[3-7] Although this cohort had an average of 11 years' experience with IP therapy, advanced features, such as changing the bolus waveform to dual or square, were used infrequently.

The ADA guidelines suggest that treatment regimens may be intensified if patients are adherent to their current regimen, or in the case of poor adherence the routine should be simplified to improve adherence.[2] Clinicians relying only on self-reported assessments may overestimate patients' adherence since it has been shown that patients who struggle with adherence are less likely to honestly report their deficiencies in SMB.[11,16] While clinicians mainly rely on quantified data coming from diabetes technology, this type of data has limitations, too. Actual behaviors may be different from what was documented in the IP. For instance, a participant had a meal and delivered a bolus without entering carbohydrates and without requesting advice from the IPBC. This may partially explain why the behavior with the highest frequency was delivering insulin boluses.

In this study we found that increasing the frequency of insulin boluses, calculating carbohydrate consumption and checking BG had a positive impact on glycemic control with the delivery of insulin boluses having the greatest impact. Providing real-time monitoring via the IP, or other appropriate device (eg, smartphone app with wireless connection to IP) on these minimally expected behaviors could empower patients and improve daily diabetes self-management and glycemic control.

For providers, presenting information gathered by IPs in ways that are clinically relevant and actionable could be empowering, too. Availability of precise and complete BG data that are presented in a structured manner enables providers to more efficiently and accurately identify glucose patterns which can lead to more accurate therapeutic

decisions.[17-19] Take for instance Table 3, where we classified the frequency of 5 observed behaviors by monthly frequency (never, rarely, occasionally, regularly and excessively), instead of daily means and SDs (Table 2). This way to visualize the data could help the clinician to better identify patients that behaved in a certain way more often or less often than the average patient. For instance, if during the last month the patient never changed the bolus waveform, the clinician could spend time during the next clinical encounter reviewing how to change the bolus delivery in the IP and discussing potential meal types that could benefit from a square insulin delivery to improve glycemic control. For the example of the patient who frequently boluses (15-90 monthly events when the patient delivers 10 insulin boluses per day or more than 5 boluses within 4 hours), the clinician can review the patient's settings to identify if the basal rate needs to be changed to reduce frequency of insulin bolusing. It remains as an open question to understand which are the best ways to present patients' diabetes SMB to providers to facilitate their decision process.

Conclusion

This study quantified observed SMB of adults on IP therapy by analyzing objectively recorded data from IPs. A limitation of our research is that we did not collect information on the reasons behind observed participants' behaviors. Nevertheless, the results from this quantitative study have guided on-going research that aims to survey patients on their knowledge on how carbohydrates, alcohol and exercise influence BG control and correlate those findings with observed SMB. Furthermore, we have future plans to use case-scenarios based on instances from real-life behaviors reported in this study to guide interviews with patients that will provide more information on beliefs and motives to exhibit identified SMB. Lessons learned from the described studies could help identify potentially undesirable patients' behaviors and gaps in patients' diabetes education that could be addressed through improved educational material and decision support systems.

Abbreviations

ADA, American Diabetes Association; BG, blood glucose; CGMS, continuous glucose monitoring system; IP, insulin pump; IPBC, insulin pump bolus calculator; SD, standard deviation; SMB, self-management behaviors; T1D, type 1 diabetes.

Authors' Note

DG and MAG equally contributed to this article.

Declaration of Conflicting Interests

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Original Article

A Methodology to Compare Insulin Dosing Recommendations in Real-Life Settings

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Abstract

Background: We propose a methodology to analyze complex real-life glucose data in insulin pump users.

Methods: Patients with type 1 diabetes (T1D) on insulin pumps were recruited from an academic endocrinology practice. Glucose data, insulin bolus (IB) amounts, and self-reported alcohol consumption and exercise events were collected for 30 days. Rules were developed to retrospectively compare IB recommendations from the insulin pump bolus calculator (IPBC) against recommendations from a proposed decision aid (PDA) and for assessing the PDA's recommendation for exercise and alcohol.

Results: Data from 15 participants were analyzed. When considering instances where glucose was below target, the PDA recommended a smaller dose in 14%, but a larger dose in 13% and an equivalent IB in 73%. For glucose levels at target, the PDA suggested an equivalent IB in 58% compared to the subject's IPBC, but higher doses in 20% and lower in 22%. In events where postprandial glucose was higher than target, the PDA suggested higher doses in 25%, lower doses in 13%, and equivalent doses in 62%. In 64% of all alcohol events the PDA would have provided appropriate advice. In 75% of exercise events, the PDA appropriately advised an IB, a carbohydrate snack, or neither.

Conclusions: This study provides a methodology to systematically analyze real-life data generated by insulin pumps and allowed a preliminary analysis of the performance of the PDA for insulin dosing. Further testing of the methodological approach in a broader diabetes population and prospective testing of the PDA are needed.

Keywords

alcohol, bolus calculator, exercise, insulin pump, postprandial blood glucose, retrospective analysis

Current standards of care for patients with type 1 diabetes (T1D) advocate for tight control of blood glucose (BG).[1] One treatment challenge for patients with T1D is optimization of postprandial glucose levels.[2-4] To help patients achieve improved glucose regulation, continuous subcutaneous insulin infusion devices (CSII, aka "insulin pumps") sometimes coupled with continuous glucose monitoring systems (CGMs), have been developed. Although devices can assist patients in making insulin dosing decisions through the use of bolus calculators, it is unknown how accurate the bolus recommendations are in real-life scenarios when complex lifestyle choices, such as exercise and alcohol intake, have to be considered in decision making. Recent data suggests that patients are often confused and inconsistent when trying to factor in these behaviors when deciding insulin doses.[5,6]

Models exist to study insulin delivery recommendations in controlled, simulated settings. Before undergoing clinical trials, a common practice to facilitate the design, development and testing of diabetes technology is to use in silico methods.[7-12] Recently, Wong et al proposed a method to retrospectively compare insulin bolus (IB) recommendations using Intensive Care Unit (ICU) data.[13] They concluded that in silico comparisons appear to be an efficient nonclinical method for allowing rapid and inexpensive identification of computer-based protocols that justify expensive and burdensome clinical trials.

Although models exist to study IB recommendations in controlled environments, there is a lack of methods capable of analyzing glucose data simultaneously with patient behaviors. The aims of this study were to (1) develop an analytic method to retrospectively compare prandial IB recommendations, (2) apply the proposed method in a real-life setting to test the performance of an evidence-based proposed decision aid (PDA) against the bolus calculator of an insulin pump, and (3) share lessons learned from collecting, aggregating and analyzing real-life data generated by insulin pumps and self-reported patient behaviors.

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Methods

Description of the iDECIDE Evidence-Based Insulin Bolusing Dosing Decision Aid

iDECIDE (PDA) is an evidence-based decision aid to recommend IB doses, carbohydrate intake, or both, by taking into account carbohydrates and alcohol consumed, and/or exercise plans.[14] The PDA was deployed as a smartphone app to help patients with T1D incorporate varied lifestyle choices simultaneously into decisions about prandial insulin dosing. The PDA is based on the formula proposed by Colin[15] to include alcohol,[16,17] exercise,[18-21] and the absorption rate of rapid-acting insulin to calculate IOB.[22] The PDA corrects to the nearest target glucose setting when the blood glucose is out of range, and does not account for the CGMS trendline. Exercise is accounted for based on body weight and duration and intensity of exercise, while the drink type and volume consumed are necessary to adjust for alcoholic beverages.

When the user launches the app the first time he is prompted to set up a diabetes profile: weight, insulin-to-carbohydrate ratios, target BG levels, correction factors and active insulin time.[23] Although participants did not set up their user profile for the study, those that did not use paper logs interacted with the self-reporting module to log (1) exercise, describing duration and intensity, (2) food intake, specifying food type, serving size and carbohydrate content, and (3) alcohol intake, indicating number of drinks, size, and type of drink (Figure 1). In addition, when self-reporting plans, the user is expected to enter the BG reading. The PDA subsequently recommends an IB or carbohydrate intake by incorporating current evidence on the way food and alcohol carbohydrates and exercise influence BG, but these recommendations were assessed retrospectively and were not provided to the participants (Figure 1).

Figure 1. Screenshots of the iDECIDE app. (A) Self-reported exercise plans. (B) Self-reported plans for food and alcohol consumption. (C) Summary of relevant preprandial information. (D) Advice to take 5 grams of snack carbohydrates to avoid exercise-induced hypoglycemia.

Participant Recruitment

Following Institutional Review Board approval, 31 study participants were recruited from an outpatient academic endocrinology practice. Patients with T1D 18 years or older who had been under the care of the endocrinology team while on CSII therapy using a Medtronic (Minneapolis, MN) insulin pump for at least one year were eligible to participate.

Data Collection

Participants were asked to continue their usual fitness and nutrition routine. For 30 days, participants recorded their exercise activity and alcohol consumption via paper logs or the self-reporting module of the PDA, according to subject's preferences. Exercise was recorded by start time, duration and intensity, and categorized as light, moderate or vigorous. Alcohol was recorded by tracking drink time, type, volume, and number (eg, 6PM, 1 pint of beer, no carbohydrates entered). Carbohydrate content was entered in the insulin pump. After 30 days, logs were manually encoded into tables or downloaded from a secure cloud-based server.

Self-reported data on exercise and alcohol was used as input for the PDA. For exercise, the PDA recommends an IB or carbohydrate intake by considering body weight and intensity and duration of exercise.[18-21] For alcohol, the PDA accounts for the carbohydrates of the alcoholic drinks based on type, volume and count.

CSII data from the corresponding 30-day timeframe was downloaded in tabular format. CSII device data included carbohydrates recorded by the participant, glucose levels either from a continuous glucose monitoring system (CGMS) or capillary BG monitor or both, amount of insulin delivered, pump settings, and the IB suggested by the insulin pump bolus calculator (IPBC).

Retrospective Comparison of Two Insulin Bolus Calculators

To evaluate the performance of the PDA against conventional approaches to prandial insulin dosing, the

authors adapted methodology from Wong et al.[13] For this study, the conventional approaches to insulin dosing were defined as either use of the IPBC or participant's self-determined doses. The PDA's recommendations were compared against those made by the participant's IPBC, or against the participant when they either overrode or neglected to get advice from their IPBC (Figure 2).

The "appropriateness" of an IB was defined as one that brings the postprandial glucose to the desired target.[13] The method assumes that a conventional insulin dosing calculator, *BCa* (ie, IPBC or the participant), has made an IB recommendation. The point in time when *BCa* made the IB suggestion and when the insulin was delivered is referred to as the initial time, t_i. The method assumes that a proposed insulin dosing calculator, *BCp* (eg, PDA), is retrospectively executed at the same data point, t_i, to compare at time t_{i+1} the effect on BG of the insulin suggestion from *BCp* against the actual suggestion that was made by *BCa*. We considered that one calculator "outperformed" another calculator if there was a major performance enhancement over the competitor. For instance, in the case of a low postprandial BG we consider that a lower insulin dose recommendation outperformed higher insulin dose advice, potentially avoiding a hypoglycemic event.

Applying this methodology requires that each preprandial BG at t_i can be paired with a corresponding postprandial BG at t_{i+1}. For meal events and BG corrections, we defined t_{i+1} to be the first BG reading obtained 3 hours ± 15 minutes, after t_i. This time frame was chosen considering that the majority of the carbohydrate load and the rapid-acting insulin analog bolus would have been absorbed and BG levels would have stabilized.[16] The BG readings at t_{i+1} were broken into three categories, based on predetermined individual target BG levels obtained from the insulin pump settings of each participant. The analysis determines which calculator provided at time t_i an IB recommendation that would have placed the participant closer to their target BG based on the category of the actual BG reading at t_{i+1}. In the case of a target postprandial BG reading, we considered that a smaller insulin recommendation outperforms a larger recommendation because it could have avoided a hypoglycemic event.

The method outlined in Figure 2 was used to compare the appropriateness of two calculators, *BCa* and *BCp*, and assumes that *BCa* (IPBC) has made IB recommendations that were delivered to the patient. A variation of that method is needed to assess the appropriateness of recommendations from *BCp* (PDA) when there is no available data from *BCa* (ie, no recommendation from the IPBC).

Assessing the Appropriateness of an Insulin Bolus Recommendation for Alcohol and Exercise

Conventional IPBCs do not provide IB recommendations for alcohol. For these cases the method explained in Figure 3 was adopted. The postprandial time frame of interest, t_{i+1}, was defined as the first BG reading obtained within 3 hours ± 15 minutes. This time frame neglects to consider any delayed effects from alcohol induced hypoglycemia and primarily focuses on the carbohydrates associated with alcoholic beverages.

As with alcohol ingestion, when participants exercised there were no recommendations made by the IPBC. For those cases, we used the method in Figure 4. We modified the window of t_{i+1} to be the first BG reading within 15 minutes of finishing exercise as recorded by the participant to detect any immediate effects of exercise-induced hypoglycemia. For example, if the participant finished exercising at 8:30 AM, we used the first available BG between 8:30 and 8:45 AM. In the case of exercise, the PDA's recommendations could be a carbohydrate snack in addition to an IB dose. For exercise scenarios, the appropriateness of the IB and/or carbohydrate was defined as in Figure 4.

Data Analysis

Computer programs were written to automate the process of collating and analyzing the data generated by the insulin pumps with the self-reported patient behaviors. In addition, assessing the performance of the PDA at t_{i+1} against the IPBC, or against participants' self-dosing choices when the IPBC was not used as anticipated was automated. Comparisons were made according subject glucose targets (below, at, or above target).

Results

Participant Characteristics and Data

There were 31 participants recruited for the study, with 4 withdrawals. Of the remaining 27 participants, a subset of 15 participants (Table 1) had preprandial glucose readings paired with t_{i+1} BG readings, with 13 of them on CGMS (9 on Minimed 530G-551, 3 on Minimed 530G-751, and 1 on Paradigm Revel-723).

A total of 2104 events had postprandial glucose readings that allowed for a comparison between the IPBC and the PDA, and there were 419 events where the PDA was compared against cases where the participants did not use their IPBC, they overrode the IPBC recommendations, or they did not provide a prandial BG. There were 235 exercise and 105 alcohol events that had sufficient data for analysis. Most exercise events, 56%, were moderate intensity. There were few alcohol events, 14%, where participants accounted for the carbohydrates associated with the beverage.

IPBCs allow different settings (BG target, insulin-to-carbohydrate ratio, and correction factor) throughout the day and the PDA accounted for these different settings for each participant at each time of day. While participants used different Medtronic insulin pumps, all used the same formula for computing IB recommendations, and an adaptation of Mudaliar et al[24] for computing active insulin.

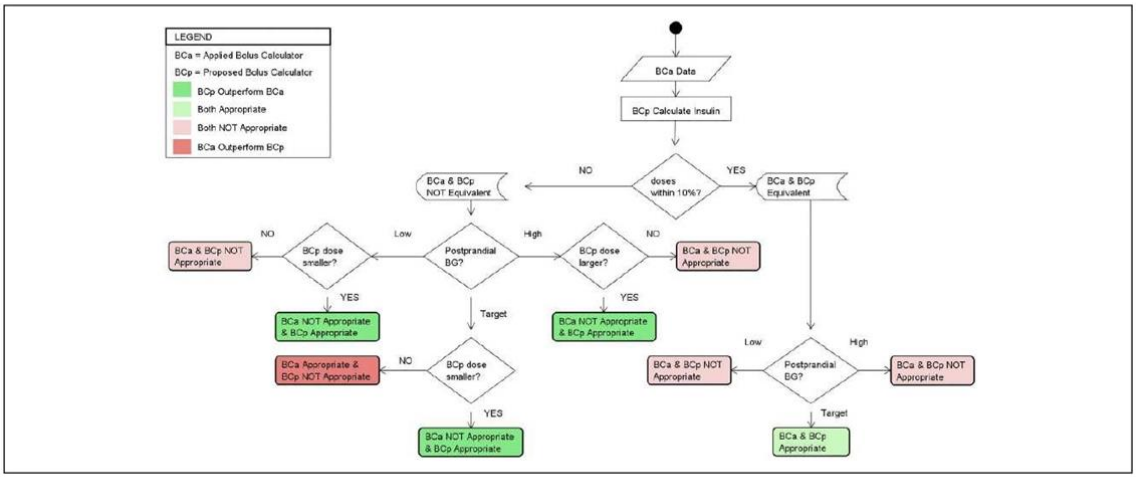

Figure 2. Method used to retrospectively compare recommendations from two insulin bolus calculators, *BCa* and *BCp*. If the recommendations from *BCa* and *BCp* were within 10% of each other they were considered to be equivalent. If the BG at t_{i+1} was low, then the smaller of the two recommendations from *BCa* and *BCp* was considered appropriate; if they were equivalent then neither was considered appropriate. If the BG at t_{i+1} was at target, then the smaller of the two recommendations from *BCa* and *BCp* was defined as appropriate, preferring recommendations that could avoid hypoglycemic events; if they were equivalent then both were considered appropriate. If the BG at t_{i+1} was above target, then the larger of the two recommendations from *BCa* and *BCp* was deemed appropriate; if they were equivalent then neither was considered appropriate. We considered that one calculator outperformed the other if there was a major performance enhancement over competitor calculator. In the case of on target postprandial BG, we consider that a lower insulin dose recommendation outperformed higher insulin dosing advice, potentially avoiding a hypoglycemic event.

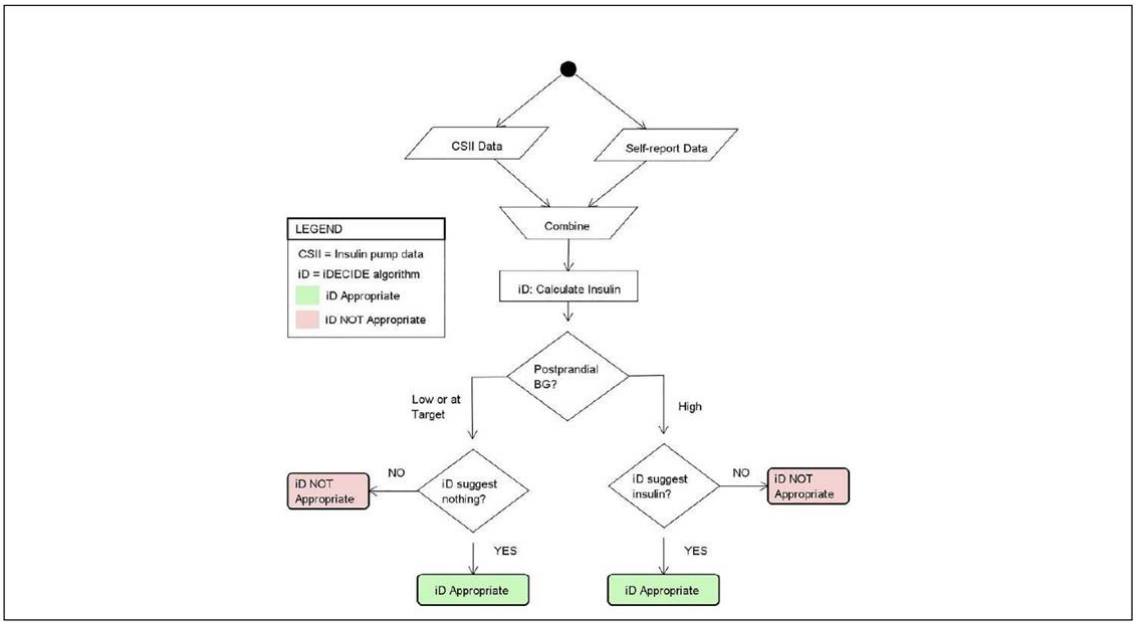

Figure 3. Method used for assessing the appropriateness of the recommendations from the proposed decision aid (PDA), when patients choose to consume alcohol, for which the insulin pump bolus calculator does not provide insulin dosing recommendations. If the BG at t_{i+1} is low or at target and the PDA did not recommend insulin the recommendation from the PDA was appropriate; if the PDA recommended insulin the recommendation was not considered appropriate. If the BG at t_{i+1} is high and the PDA recommended insulin the recommendation from the PDA was appropriate; if the PDA did not recommend insulin the recommendation was not considered appropriate. Given that our PDA is not compared against another calculator, outperformance is not defined.

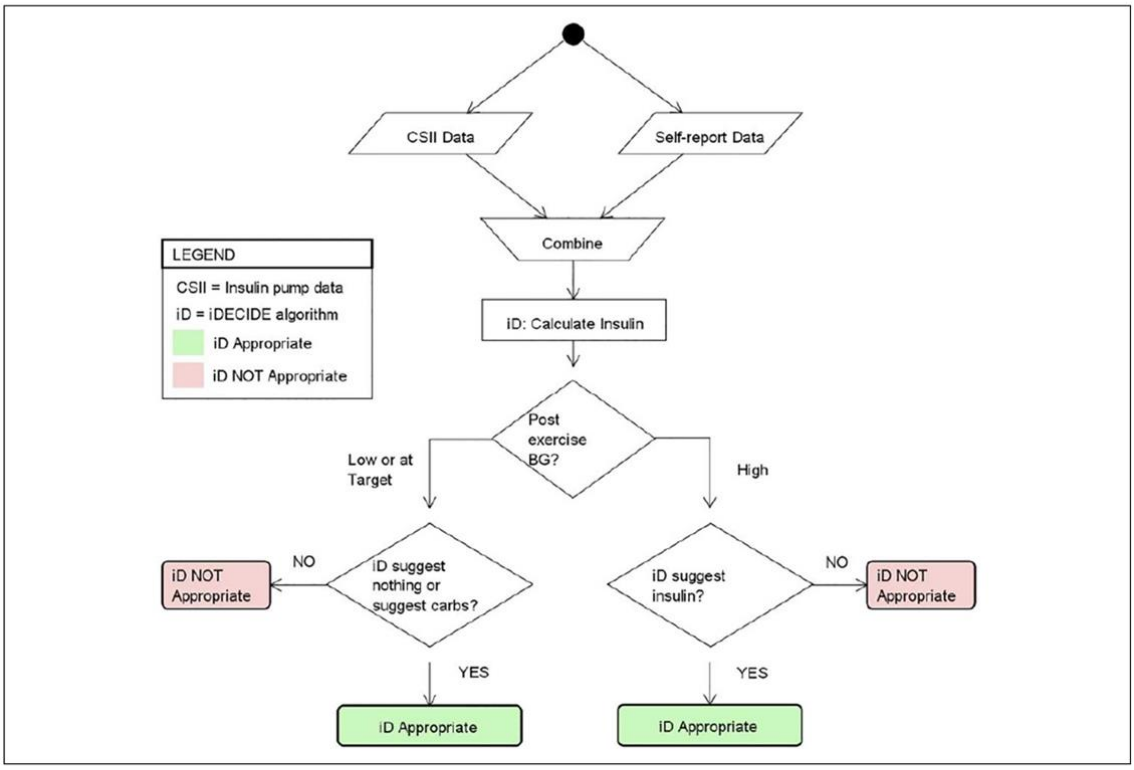

Figure 4 Method used for assessing the appropriateness of the recommendations from the proposed decision aid (PDA) when patients choose to exercise, for which the insulin pump bolus calculator does not provide insulin dosing or carbohydrate intake recommendations. If the BG at t_{i+1} was low or at target and the PDA suggested nothing or suggested consuming carbohydrates the recommendation from the PDA was considered appropriate; if the PDA recommended insulin, then the recommendation was deemed not appropriate. If the BG at t_{i+1} was high and the PDA suggested insulin the recommendation from the PDA was considered appropriate; if the PDA suggested no insulin or recommended consuming carbohydrates, then the recommendation was not considered appropriate. Given that the PDA is not compared against another calculator, outperformance is not defined.

Table 1. Demographics of 15 Subjects With Type 1 Diabetes.

Characteristic	Value
Age (years)	48.7 (13.9)
% women	73.3
% white	93.3
Hemoglobin A1C	7.5 (1.2)
Diabetes duration (years)	26.9 (11.8)
Duration on insulin pump (years)	11.5 (5.3)
Daytime low/high target BG	89.9 (8.6) / 112.3 (10.8)
# Analyzable exercise events/day	1.1 (0.34)
# Analyzable alcohol events/day	0.2 (0.18)

Data are mean (SD) or %.

The Medtronic 530G includes a threshold suspend feature, that is designed to automatically stop insulin delivery when the CGMS value falls below a patient-specific preset threshold. There were 5 insulin suspension events that occurred in close temporal proximity to events of interest; such low frequency did not warrant removing data from the analysis.

Comparison of iDECIDE Against the IPBC or Patient

We used the method described in Figure 2 to compare the appropriateness of the PDA's recommendations against events when the patient followed the IPBC recommendations for BG correction doses and/or carbohydrate loads that included a prandial and postprandial BG.

First assessed was how iDECIDE (PDA) compared against the IPBC (Table 2). The IPBC brought the participants to target glucose levels in 13% (278/2104) events, below target 10% (207/2104) and above target 77% (1619/2104). When considering very low and very high postprandial BG, the BG was below 70 mg/dl in 3% (55/2104) and over 180 mg/dl in 35% (737/2104). When considering instances where glucose was below target, the PDA would have recommended an appropriately smaller dose in 14% (28/207), but a larger dose in 13% (27/2017) and an equivalent IB in 73% (152/207). For glucose levels at target, the PDA would have suggested an equivalent IB in 58% (162/278) compared to the subject's IPBC, but a

Table 2. Results From the Retrospective Comparison of the Appropriateness of the Recommendations From the Proposed Decision Aid (PDA) Against the Insulin Pump Bolus Calculator (IPBC), and From the PDA Against the Patient's Self-Dosing Choices.

		PDA insulin recommendations			
Event type	Postprandial BG (mg/dl)	Larger dose	Smaller dose	Equivalent dose	Total
IPBC	Low (<target)	27[a]	28[b]	152[c]	207
	Target (participant target)	56[a]	60[b]	162[d]	278
	High (>target)	406[b]	212[a]	1001[c]	1619
	Total	489	300	1315	2104
Participant	Low (<target)	10[a]	23[b]	21[c]	54
	Target (participant target)	18[a]	24[b]	4[d]	46
	High (>target)	107[b]	86[a]	126[c]	319
	Total	135	133	151	419

[a]IPBC (or participant) was appropriate and the PDA recommendation was not appropriate, IPBC (or participant) outperformed the PDA.
[b]PDA recommendation was appropriate and IPBC (or participant) was not appropriate, PDA outperformed the bolus calculator (or patient). When the PDA recommends a lower insulin dose recommendation than the bolus calculator (or participant) and the postprandial BG is on target, the PDA could potentially avoid a hypoglycemic event and therefore outperformed the bolus calculator (or participant).
[c]Events where the PDA and IPBC (or participant) recommendations were not appropriate.
[d]Events where the PDA and IPBC (or participant) recommendations were appropriate.

higher dose 20% (56/278) and lower in 22% (60/278). In events where postprandial glucose was higher than target, the PDA would have suggested a higher dose in 25% (406/1619), a lower dose in 13% (212/1619), and an equivalent dose in 62% (1001/1619). Overall, the PDA would have recommended an equivalent dose compared to the IPBC in 63% (1315/2104) of IB decisions.

We used the method described in Figure 2 to compare the appropriateness of iDECIDE (PDA) against decisions made by the participant (Table 2). The participants self-dosing led to above target postprandial glucose in 76% (319/419), below target in 13% (54/419) while participants only achieved target glucose levels in 11% (46/419). There were 3% (14/419) of the events with a postprandial BG below 70 mg/dl and 37% (154/419) over 180 mg/dl. When considering instances where glucose was below target, the PDA would have recommended an appropriately smaller dose in 43% (23/54), a larger dose in 19% (10/54), and an equivalent IB dose in 38% (21/54). For glucose levels at target, the PDA would have suggested an equivalent IB amount in 9% (4/46) compared to the subject's own decision, but a higher dose 39% (18/46) and lower in 52% (24/46). In situations where postprandial glucose was greater than target, the PDA would have suggested a higher dose in 34% (107/319), a lower dose in 27% (86/319), and an equivalent dose in 39% (126/319). Overall, the PDA would have recommended an equivalent IB in only 36% (151/419) of instances compared to when the participants made their own decisions.

Assessment of the Appropriateness of iDECIDE's Recommendations for Exercise and Alcohol

In cases of exercise and alcohol the pump does not suggest insulin. In these cases, the PDA is only assessed based on the BG outcomes since it could not be compared against the IPBC. We used the method described in Figure 3 to assess the appropriateness of the PDA's recommendations when alcohol consumption was recorded. As reported earlier, patients self-reported accounting for the carbohydrate content of the beverage in 15 of the 105 events. As indicated in Table 3, in 64% (67/105) of overall alcohol events the PDA would have provided appropriate advice. The PDA performed well when the postprandial BG was high with 78% (64/82) appropriate IB recommendations, but had poor performance when the postprandial BG was at target with only 5% (1/19) recommendations deemed appropriate.

Table 3. Results From Assessing the Appropriateness of the Recommendations Regarding Insulin Dosing for Alcohol Consumption From the Proposed Decision Aid (PDA).

	PDA recommendations		
Postprandial BG	Appropriate	Not appropriate	Total
Low (<target)	2	2	4
Target (participant target)	1	18	19
High (>target)	64	18	82
Total	67	38	105

We used the method described in Figure 4 to assess the appropriateness of the PDA's recommendation before exercise (Table 4). The PDA appropriately suggested insulin or to ingest carbohydrates in 75% (176/235). Similar to the alcohol results, the PDA performed well when post exercise BG was high 87% (154/178), but only made appropriate suggestions in 37% (10/27) and 40% (12/30) when the post exercise BG was low or target, respectively. There were 26 exercise events that had a duration of 90 minutes or longer and the PDA made appropriate recommendations in only 27%.

Discussion

Although advances in in silico models technology have allowed for incorporation of new features into existing technologies to improve BG control, these often don't account for variables that affect BG (eg, exercise, stress, sleep, and illness). Decision aids that assist patients with

Table 4. Results From Assessing the Appropriateness of the Recommendations Regarding Insulin Dosing and Carbohydrate Ingestion for Exercise From the Proposed Decision Aid (PDA).

	PDA insulin dose and carbohydrate recommendations		
Post exercise BG	Appropriate	Not appropriate	Total
Low (<target)	10	17	27
Target (participant target)	12	18	30
High (>target)	154	24	178
Total	176	59	235

T1D to make better prandial insulin dosing decisions are needed, particularly when patients must account for multiple simultaneous lifestyle variables that may impact BG levels.

One of the main differences between this study and others that retrospectively evaluated the performance of prandial insulin dosing recommendations is the source of the clinical data. For instance, previous studies have compared the effectiveness of insulin dosing recommendations in controlled environments such as in the ICU,[13,25] where glucose control is closely monitored and tracked and lifestyle behaviors are not a factor. In contrast, this study focused on free-living outpatients who made their own choices about insulin therapy, and where individual lifestyle choices have the potential to impact treatment decisions and outcomes.

One of the analytic challenges we encountered when developing, testing, and comparing the effectiveness of insulin dosing recommendations is the complex nature of data generated by free-living participants. In our study, many of the self-management and daily living activities recorded by the participants occurred in tight temporal succession and could not be assessed as isolated events. This required development of a new analytic approach to evaluating the data. An unexpected positive outcome of this study was gaining a better understanding of patients' self-management behaviors as they interact with insulin pumps.[5,6]

The methodology outlined here permitted an assessment of how our PDA would perform when used in different scenarios. When compared to the IPBC embedded in the subject's insulin pump, the PDA in general was noninferior, recommending IB doses equivalent to the IPBC standard in 63% of decisions overall and nearly equivalent number of smaller doses when glucose levels were below or at target. There were some instances where the PDA was superior to the IPBC, such as when it would have recommended larger doses in 91% more cases when postprandial glucose levels were above target. Initial analysis of the PDA in cases where the doses were too large or small, provided insights which were used to improve performance with continuing analysis necessary for further refinement of the recommendations.[26,27] For instance, we used an initial setting of 3 hours of active insulin time to calculate IOB. To improve performance, this was later adjusted to 4 hours which reduced the number of inappropriate recommendations that could have led to hypoglycemia. In the future, the PDA will adapt to the insulin action time specified for each patient.

Employing the analytic paradigms developed here, we also assessed the performance of the PDA when there was a lack of recommendations from the IPBC with exercise and alcohol events. In these analyses the postprandial glucose was used as the outcome measure. For cases involving alcohol consumption, the PDA may have offered an advantage when deciding a compensatory insulin bolus. The PDA could have improved postexercise BG when the duration was 90 minutes or less and the PDA should be restricted to such events until further study.

There are limitations to the study. This study incorporated self-reported data for exercise, meal and alcohol behaviors. It is possible participants did not record all these events, or may have recorded them inaccurately. Also, participants' insulin pump settings were not adjusted for the study. Inappropriate insulin pump settings, such as basal rates, could have influenced the results. Sample sizes for alcohol and exercise events were small with respect to the larger comparisons involving the IPBC. The study also did not consider late-onset hypoglycemia that can arise from engaging in exercise, and possibly when consuming alcohol. To automate the analysis, we opted against determining an appropriate postexercise timeframe on a case-by-case basis and instead focused on the immediate effects of exercise by employing a standard 15-minute postexercise timeframe. Considering BG levels outside of the time-frames used for analysis in this study is another important factor to consider in the future when assessing and calibrating IB calculators.

In addition, the analysis was done retrospectively. A prospective analysis, where the PDA makes suggestions in real time, would help further delineate its capabilities, improve performance and assess user acceptance. A recent analysis suggests that mobile apps can offer advantages in diabetes management, but more rigorous studies are needed.[28] Finally, the analytic methods tested here were for a very specialized group of patients (T1D on insulin pumps) and we did not conduct an analysis of the outcomes in relation to A1c scores. Testing these methodologies in a wider selection and more diverse population of patients (eg, T1D patients on multiple daily insulin injections or patients with type 2 diabetes) would be needed to test the generalizability of the approach.

Conclusion

We introduced an analytic method to use prospective real-life data to retrospectively compare insulin dosing recommendations. This method was used to assess the recommendations of an evidence-based decision aid. Additional prospective testing of the proposed decision aid with a bigger patient cohort is being planned to further validate the proposed method.

Abbreviations

BG, blood glucose; CGMS, continuous glucose monitoring system; CSII, continuous subcutaneous insulin infusion devices; IB, insulin bolus; ICU, intensive care unit; IPBC, insulin pump

bolus calculator; PDA, proposed decision aid; T1D, type 1 diabetes.

Authors' Note

DG and MAG share first authorship of this article.

Declaration of Conflicting Interests

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APPENDIX D

USABILITY STUDIES

D.1 First Study: Usability Protocol

ASU Knowledge Enterprise Development
ARIZONA STATE UNIVERSITY

SOCIAL BEHAVIORAL INSTRUCTIONS AND TEMPLATE		
NUMBER	DATE	PAGE
HRP-503a	8/8/2016	1 of 3

Instructions and Notes:
- Depending on the nature of what you are doing, some sections may not be applicable to your research. If so, mark as "NA".
- When you write a protocol, keep an electronic copy. You will need a copy if it is necessary to make changes.

1 Protocol Title
iDECIDE Usability Testing

2 Background and Objectives
Provide the scientific or scholarly background for, rationale for, and significance of the research based on the existing literature and how will it add to existing knowledge.
- Describe the purpose of the study.
- Describe any relevant preliminary data.

Diabetes is recognized as very complex disease that requires daily insulin management. Treatment goals include optimization of postprandial glucose levels (glucose measurement following a meal) within a desired range—avoiding excessive highs or lows and reducing variability. Insulin pumps, currently being used by over 350,000 people in US, incorporate proprietary mathematical algorithms using bolus calculators to determine individualized pre-meal dosing. While bolus calculators can lead to better glucose control, they currently cannot account for the lifestyle complexities of alcohol ingestion and planned exercise, nor do they possess the flexibility to assist patients in the management of other related health goals, such as losing weight or keeping fit. To address the need for personal treatment management systems, we propose to build the Smartphone application, iDECIDE, to assist and educate diabetes patients on treatment options that are tailored to their preferences and goals. iDECIDE will help diabetes patients select the pre-meal insulin dose based on the next meal's anticipated carbohydrate and alcohol content and exercise plans to achieve tailored clinical goals. Recommendations will be supported with lay-based explanations to help patients learn how each of these choices affects their overall well-being and goals.
The aim of this study is to perform a preliminary formative usability test with 10 participants, to improve the design and functionality of the current mobile application iDECIDE prototype. Although iDECIDE will generate insulin dosage recommendations for fictitious patient cases, actual study participants will receive no treatment recommendation from iDECIDE.

3 Inclusion and Exclusion Criteria
Describe the criteria that define who will be included or excluded in your final study sample. If you are conducting data analysis only describe what is included in the dataset you propose to use.
Indicate specifically whether you will target or exclude each of the following special populations:
- Minors (individuals who are under the age of 18)
- Adults who are unable to consent
- Pregnant women
- Prisoners
- Native Americans
- Undocumented individuals

Inclusion criteria: English speakers, 18 years old or older. The participants will be either faculty, staff or students (graduate or undergraduate level) at the ASU Department of Biomedical Informatics (BMI).
Exclusion criteria: unsatisfaction of the inclusion criteria.

4 Number of Participant
Indicate the total number of participants to be recruited and enrolled: 10

5 Recruitment Methods
- Describe when, where, and how potential participants will be identified and recruited.
- Describe materials that will be used to recruit participants. (Attach copies of these documents with the application.)

Potential participants will be recruited through the student, faculty and staff email list of the Department of Biomedical Informatics at ASU. Participants will be also recruited by personal contact and the word of mouth. Each potential recruit will be informed that their participation is strictly voluntary and that they are free to discontinue participating without any penalty.

6 Procedures Involved

Describe all research procedures being performed and when they are performed. Describe procedures including:

- Surveys or questionnaires that will be administered. (Attach all surveys, interview questions, scripts, data collection forms, and instructions for participants.)
- What data will be collected including long-term follow-up?
- Lab procedure and tests and related instructions to participants
- The period of time for the collection of data.
- Describe the amount and timing of any compensation or credit to participants.
- If the research involves conducting data analysis only, describe the data that that will be analyzed.

We expect that the interaction with each participant will take at most 60 minutes. All interviews will be conducted at the Department of Biomedical Informatics housed at the Arizona Mayo Clinic Campus is Scottsdale, AZ. All the participants will undergo the same protocol. First they will be consented and then they will be informed of the goals of the study, which is to assess the usability of a mobile application. They will be assured that this study does not in any way evaluate their performance. The participants will not be compensated with money, but they will be offered snacks. We will provide a smartphone with the iDECIDE application installed. The participants will read a script describing a fictitious diabetes patient case and a brief explanation of SMART goals, see attached forms for scripts. After that, the participants will be given approximately 5 minutes to become familiar with the app. They will then be asked to complete a set of 7 brief tasks using the app which will be presented on the same documentation as the diabetic patient script and SMART goal explanation. The first five tasks are specific to the fictitious diabetes patient. IDECIDE will generate an insulin dosage recommendation as a result of completing tasks for the fictitious patient case. The final two tasks will be open to the participant to complete based on their preferences and iDECIDE will not generate treatment recommendations for the patient.

During the study sessions, the subjects will be asked to think aloud while exploring the app and while performing the tasks. The audio and video (participant's face and screen-capture of the smartphone) will be recorded during the session. The technology will non-intrusively monitor how the user interacts with the iDECIDE smartphone app to complete the given tasks. Data from the audio/video recordings will be analyzed to develop a better understanding of how participants use iDECIDE, and software improvements will be identified.
There will be two brief questionnaires that will be administered after the tasks are completed. The first questionnaire will be used to gather information about the participant's use of mobile devices and smartphone apps. The second questionnaire will collect information regarding the participant's experience using iDECIDE. See attached forms for the questionnaire forms.

7 Risks to Participants

List the reasonably foreseeable risks, discomforts, or inconveniences related to participation in the research. Consider physical, psychological, social, legal, and economic risks.

The proposed study can be classified as negligible-risk. We collect participants' information on their habits on using smartphones and smartphone apps, in particular apps for improving fitness, nutrition and well-being. We request …. from participants their personal views on the interfaces design and functionalities of the iDECIDE tool, and we record their interactions with the tool. All the collected information is kept strictly confidential.

8 Potential Benefits to Participants

Realistically describe the potential benefits that individual participants may experience from taking part in the research. Indicate if there is no direct benefit. Do not include benefits to society or others.

Participants may not directly benefit from the proposed study. However, in the future the results of this study may benefit diabetes patients.

9 Prior Approvals

Describe any approvals – other than the IRB - that will be obtained prior to commencing the research. (e.g., school, external site, or funding agency approval.)

Besides this IRB approval, no other prior approvals are being requested.

10 Privacy and Confidentiality

Describe the steps that will be taken to protect subjects' privacy interests. "Privacy interest" refers to a person's desire to place limits on with whom they interact or to whom they provide personal information.

Describe the following measures to ensure the confidentiality of data:

- Where and how data will be stored?
- How long the data will be stored?
- Who will have access to the data?
- Describe the steps that will be taken to secure the data (e.g., training, authorization of access, password protection, encryption, physical controls, certificates of confidentiality, and separation of identifiers and data) during storage, use, and transmission.

For each participant we will record and save the files generated from the audio/video/screen-capture from the interviews. As part of the interview demographic data is collected. We will manage the data securely in the Department of Biomedical Informatics at ASU, limiting access only to the personnel approved on this protocol. In addition, the data obtained from recruited participants will be on an encrypted hard drive.

11 Consent Process

Indicate the process you will use to obtain consent. Include a description of:

- Where will the consent process take place
- How will consent be obtained

Non-English Speaking Participants

- Indicate what language(s) other than English are understood by prospective participants or representatives.
- If participants who do not speak English will be enrolled, describe the process to ensure that the oral and/or written information provided to those participants will be in that language. Indicate the language that will be used by those obtaining consent.

Waiver or Alteration of Consent Process (written consent will not be obtained, required information will not be disclosed, or the research involves deception)

- Review the "CHECKLIST: Waiver or Alteration of Consent Process (HRP-410)" to ensure you have provided sufficient information for the IRB to make these determinations.

Participants who are minors (individuals who are under 18)

- Describe the criteria that will be used to determine whether a prospective participant has not attained the legal age for consent to treatments or procedures involved in the research under the applicable law of the jurisdiction in which the research will be conducted.

The consent process will take place at the ASU Department of Biomedical Informatics, Mayo Clinic Scottsdale Johnson Research Bldg, 13212 E. Shea Blvd., Scottsdale, AZ 85259. Informed consent will be obtained prior to the start of the subject's participation. Subjects will be asked to review the document carefully and ask questions if they are unclear on any matter. Consent forms will be in English; we will only recruit English speaking participants.

12 Process to Document Consent in Writing

If your research presents no more than minimal risk of harm to participants and involves no procedures for which written documentation of consent is normally required outside of the research context, the IRB will consider a waiver of the requirement to obtain written documentation of consent.

(If you will document consent in writing, attach a consent document. If you will obtain consent, but not document consent in writing, attach the short form consent template or describe the procedure for obtaining and documenting consent orally.)

13 Training

Provide the date(s) the members of the research team have completed the CITI training for human participants. This training must be taken within the last 3 years. Additional information can be found at: http://researchintegrity.asu.edu/training/humans

Maria Adela Grando, PhD completed her CITI training for human research on 01/16/2014.
David Kaufman, PhD completed his CITI training for human research on 06/09/2014.
Danielle Groat, completed her CITI training for human research on 09/04/2013.

D.2 First Study: User Tasks

Task 1: Enter the Mike's body weight of 162 pounds.

Task 2: Enter the insulin to glucose ratio for Mike of 20 units/ (mg/dL) from 6:00 a.m. to 2:00 p.m.

Task 3: Calculate how much insulin/carbohydrates Mike would need when consuming 35 grams of carbohydrates and one can of beer. Assume his current blood glucose reading is 152 mg/dL.

Task 4: Calculate how much insulin/carbohydrates Mike would need when consuming 9 grams of carbohydrates and engaging in 40 minutes of moderate exercise. Assume the current blood glucose reading is 113 mg/dL.

Task 5: Enter a SMART goal for Mike to use less than 18 units of insulin per weekday. Name the goal "Weekday Insulin."

The previous tasks were related to Mike. These next two tasks let us see how you would use the app for defining your own SMART goals.

Task 6: Based on your preferences enter a SMART goal related to consuming alcoholic beverages.

Task 7: Based on your preferences enter a SMART goal related to exercise.

D.3 First Study: Demographics and usability questionnaire

Demographic Questionnaire

1. Have you ever used a smartphone? If yes continue to question 2, if no then continue to page 2.
    a. Yes
    b. No

2. What is the operating system and phone that you currently use?
(e.g.: iOS 7 on iPhone 5 or Android Jelly Bean on Samsung Galaxy)

3. How long have you used a smartphone?

4. Please indicate if you have performed any of the following functions on a smartphone:
    a. Access the internet
    b. Text
    c. Use apps
    d. Made reservations
    e. Other(s):

5. Have you ever used apps for tracking fitness, nutrition or well-being habits? If yes continue to question 6, if no then continue to page 2.
    a. Yes
    b. No

6. How long have you been using health-related apps?

7. If you stopped using health-related apps can you please explain why?

Experience Questionnaire

Please mark your choices with an X.

	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
1. The app had a clear, clean, uncluttered screen design.					
2. The app kept screen changes to a minimum during the completion of a task.					
3. The app minimized the number of steps it took to complete tasks.					
4. Information presented on screen was easy to comprehend quickly.					
5. Information needed for a specific task was grouped together on a single screen.					
6. Data could be entered once then used in multiple places.					
7. I felt confident that I could make a mistake without losing my work.					

8. Is there any additional functionality you think should be included in iDECIDE?

9. Describe things you disliked about iDECIDE.

10. Describe things you liked about iDECIDE.

D.4 Second Study: User Tasks

Task 1: Enter information on Claire's health and fitness habits.

- She feels she does not know enough about exercise/healthier lifestyle and would like to learn more;
- Exercises at most 1 hour per week;
- Rarely smokes;
- Has up to 7 drinks per week;
- Rarely eats fruits and veggies, and
- Would like to lose weight.

Task 2: Enter the following information about Claire to set up her profile:

Gender: Female
DOB: 1/1/1973 (Age: 42)
Height: 5'6"
Weight: 168 lbs.
Target Weight: 150 lbs.
Weight achievement time: about 4 months from today

Endocrine Findings:
Correction Factor (CF): 80 from 8AM to 12PM and
Correction Factor (CF): 90 from 12PM to 8AM
Insulin to Carb Ratio (ICR): 20 during 24 hours
Target Glucose: 90 to 110 mg/dL during 24 hours

Task 3: Select the suggestions related to exercise goal and set the goal for Claire to walk briskly during her lunch break:

Name: Walk at Lunch
Intensity: Moderate
Duration: 30 minutes
Start Time: 12:30 p.m.
Repeat every week for days: Mon, Tue, Wed, Thu, Fri

Task 4: On Tuesday, Claire is busy and has no time for exercising during lunchtime. She receives a message from iDECIDE asking reasons for not exercising. She inputs lack of time as the reason.

Task 5: The same Tuesday at 6pm the evening Claire plans to go for a light walk of 20 minutes. Her glucose reading is 107 mg/dL. Input Claire's plan.

Task 6: Enter Claire's plan to eat one slice of steak with 1 cup of mash potatoes and a diet coke of 240 ml for lunch. Her glucose reading is 107 mg/dL

The previous tasks were related to Claire. This next task will let us see how you would use the app for defining your own goals.

Task 7: Based on your preferences enter a goal related to consuming alcoholic beverages.

D.5 Second Study: Demographics and usability questionnaire

Identical to D.3.

APPENDIX E

FIRST ROUND OF RECRUITMENT OF MAYO PATIENTS WITH TYPE 1 DIABETES: MAYO CLINIC IRB APPROVAL #14-004649

E.1 Study Protocol

IRB Minimal Risk Protocol Template

Note: If this study establishes a human specimen repository (biobank) for research purposes, do not use this template. Use the Mayo Clinic Human Specimen Repository Protocol Template found on the IRB home page under Forms and Procedures at http://intranet.mayo.edu/charlie/irb/

First-time Use: Use this template to describe your study for a new IRB submission.

1. Complete the questions that apply to your study.
2. Save an electronic copy of this protocol for future revisions.
3. When completing your IRBe application, you will be asked to upload this template to the protocol section.

Modification: To modify this template after your study has been approved:

1. Open your study in IRBe. Click on the study 'Documents' tab and select the most recent version of the protocol. Save it to your files.
2. Open the saved document and activate "Track Changes".
3. Revise the protocol template to reflect the modification points, save the template to your files
4. Create an IRBe Modification for the study and upload the revised protocol template.

General Study Information

Principal Investigator: Dr. Curtiss Cook

Study Title: Calibration of an evidence-based pre-meal insulin dosing equation to account for patient's lifestyle preferences

Protocol version number and date: Version 1, 2 June 2014

Purpose

The purpose of this non-therapeutic study is to collect data to allow calibration of software that would eventually be utilized in mobile technology for prandial insulin dose calculations. This feasibility data would then be used in an FDA IND application in preparation for formal clinical trials.

Hypothesis: postprandial glucose control can be optimized by incorporating patient preferences on alcohol intake and exercise into a standard formula used to compute pre-meal insulin bolus.

Specific aims

The specific aims of this project are:

1. Data collection from type 1 diabetes (T1D) patients: Patients with T1D on insulin pump therapy will be recruited. Demographic data and information on disease characteristics will be abstracted from electronic

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medical record. Participants will then be asked to record information on alcohol intake and exercise over a 4-week period.

2. Calibration and evaluation of iDECIDE using collected data: After four weeks, we will collect from the subjects the generated baseline insulin pump data and the generated records on alcohol intake and exercise. We will then use that information for a retrospective calibration of iDECIDE. We will evaluate the performance of iDECIDE by comparing the postprandial glucose outcomes recorded in the insulin pumps and the outcomes projected by iDECIDE. Based on the feedback from this evaluation iDECIDE will be calibrated. Patients will not be asked to make any changes in their therapy above and beyond what they are already performing in their standard diabetes self-management practices.

Background

Patients with type 1 diabetes mellitus (T1D) often have difficulty achieving desired postprandial glucose levels, often overestimating or underestimating the amount of insulin to be taken with the meal. An important driver of postprandial glucose control is carbohydrate intake, however, other variables currently not accounted for in standard algorithms that can affect a desired postprandial glucose level are lifestyle variables related to alcohol intake and amount of exercise. It is **hypothesized that postprandial glucose control can be optimized by incorporating patient preferences on alcohol intake and exercise into a standard formula used to compute the pre-meal insulin bolus.**

To develop the model, we propose to recruit subjects with T1D on insulin pump therapy. Insulin pumps are medical devices that deliver insulin continuously via the subcutaneous route, but also allow for the patient to deliver meal time boluses. Current insulin pumps incorporate proprietary equations to calculate pre-meal insulin dosage based on well-established parameters. However, current equations do not incorporate the latest medical evidence to further personalize pre-meal insulin dosing, such as an individual's preference for exercise and alcohol intake. Evidence shows that these personal lifestyle choices have a short-term impact on glucose levels, which in turn could alter a patient's decision on the amount of insulin to deliver with a meal. The proposed solution is to incorporate these parameters into the current equation, evaluate how including these variables affects decision making on prandial insulin dosing, and then correlate this decision with the next premeal glucose level.

There are a multitude of mobile applications for diabetes management that allow users to track carbohydrate intake, exercise, medication and insulin dosage. We are developing a smartphone app, iDECIDE, for Patient-centered ***DECI***sion support based on ***DE***vice data. iDECIDE differs from these current mobile applications in that it is evidence based, a criterion largely missing in current mobile applications. Furthermore, the development of iDECIDE is grounded on well-established cognitive-based decision principles from the field of Clinical Decision Support Systems.

Patients on insulin pump therapy make ideal subjects to calibrate the iDECIDE software. These patients are typically well trained in insulin pump devices, and monitor glucose values frequently throughout the day yielding a rich source of data on glucose levels, insulin doses, and amount of carbohydrates consumed. Additionally, the glucose and insulin pump parameters can be downloaded and the data exported to an analytic file. This can be done either in the presence of the patient at the point of care, or even remotely if the patient desires.

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Subject Information – charts, records, images, or specimens are considered 'subjects'

Target accrual: *Proposed number of subjects to be included in your study at your site. "Subjects" may include Mayo Clinic charts, records, or specimens,* ***and/or*** *charts, records, or specimens received at Mayo Clinic from external sources for collaborating analysis by the investigator under this IRB application*:

Subject population: 20 subjects

Inclusion Criteria: Arizona Mayo Clinic type 1 diabetes outpatients, older than 18 years old, younger than 60 years old, non-pregnant, English speakers, who use Medtronic insulin pumps, who has been using insulin pumps for at least one year, and who have kept in consistent contact with the Mayo Clinic Division of Endocrinology health care team during the last year.

Exclusion Criteria: patients with fragile health, limited life expectancy, records of mental health problems, advanced vascular disease or micro vascular complications, known history of severe hypoglycemia or advanced atherosclerosis.

Will a Certificate of Confidentiality be obtained? *If yes, provide an explanation.*
NA

Study Design

Methods: *Describe, in detail, the research activities that will be conducted under this protocol*:
For those participants that consent to participate in the study, study personnel will collect the following information from the electronic medical record:

- Medical history: age, gender, current treatment of diabetes (including years with diabetes, medication), ketoacidosis information (frequency, severity and cause), hypoglycemic episodes, history of diabetes-related complications (in particular vascular disease or micro vascular complications)
- Social history: exercise habits (frequency and type of exercise), alcohol use history and frequency of alcohol use
- Physical examination: height, weight, body mass index
- Laboratory evaluation: results of last A1C
- Referrals: mental health referrals

Study personnel will identify potential subjects at the time of their routine clinical visit. Following informed consent, study personnel will provide each participant with paper forms (Attachments 1 and 2) to record daily alcohol intake and the amount of exercise. Study personnel will explain to the participants how to complete those diaries and provide them take-home educational material (see Attachment 3). Participants will be asked to collect data for 4 consecutive weeks. At the end of the data collection period, we will also obtain and download the data generated by the insulin pump, during the proceeding 4 weeks. We will link the data obtained from the participants' insulin pumps with the collected clinical information and de-identify it. After that we will destroy the information that could link the de-identified data to the patient's identity.

We will also de-identify medical device identifiers and serial numbers. We will use the de-identified information to calibrate the iDECIDE tool

Resources: *Describe the available resources to conduct the research (personnel, time, facilities, mentor commitment, etc.)*:

The entire study team has completed Human Subject Protection training. Dr. Curtiss Cook is the Chair of the Division of Endocrinology at Mayo Arizona. Dr. Grando is an Assistant Professor at the Department of Biomedical Informatics at the Arizona State University. Dr. Grando is a Mayo Research Affiliate.

Dr. Thompson will be responsible for the overall supervision of this study and to oversee the team of investigators that will calibrate and evaluate iDECIDE. Dr. Adela Grando will be responsible for the study design and implementation.

Check all that apply. If none apply, leave blank:

☒ This is a multisite study involving Mayo Clinic and non-Mayo Clinic sites.
When checked, describe the research procedures/activities being conducted **only** at Mayo Clinic:

☐ Mayo Clinic staff will be engaged in research activity at a non-Mayo Clinic site. *When checked, provide the location and a detailed description of the Mayo Clinic research staff involvement.*

☒ This study is to establish and/or maintain an ongoing database or registry for research purposes only.

☒ The research involves contact or interaction with subjects, for example, surveys, questionnaires, observation, blood draw.

☐ The study involves audiotaping or videotaping

Blood Collection

If this study involves prospective blood collection by finger, heel, ear stick or venipuncture, complete the following:

☐ **From healthy, non-pregnant, adult subjects who weigh at least 110 pounds**. For a minimal risk application, the amount of blood drawn from these subjects may not exceed 550ml in an 8-week period and collection may not occur more frequently than 2 times per week.
Volume per blood draw: _____ml
Frequency of blood draw (e.g. single draw, time(s) per week, per year, etc.) _____

☐ **From other adults and children considering age, weight, and health of subject.** For a minimal risk application, the amount of blood drawn from these subjects may not exceed the lesser of 50 ml or 3 ml per kg in an 8-week period, and collection may not occur more frequently than 2 times per week.

Volume per blood draw: _____ml
Frequency of blood draw (e.g. single draw, time(s) per week, per year, etc.) _____

Review of Chart, Images, Specimens

Provide the date range for collection of data and/or specimens that will be included in your research dataset. (*Example: 01/01/2000 to 12/31/2012*)

Date range: From _06/01/2014 to 06/01/2015

Check all that apply:

☐ This study involves only data and/or specimens that exist at the time this application is submitted to the IRB (IRB submission date). No data or specimens will be collected beyond this date.

☒ This study involves only data and/or specimens that will be collected after submission to the IRB.

☐ The study involves data and/or specimens that exist at the time of submission to the IRB **and** data and/or specimens that will be collected after submission to the IRB, for example a study that includes collection of existing data and prospective collection of specimens.

☐ Data and/or specimens used in this study are collected under another IRB protocol. *When checked, provide the IRB number(s) from which the research material will be obtained and check the box below to attest that subjects have provided consent for future use of their data and/or specimens, as described in this protocol.*

IRB Number(s):

□Subjects have provided consent for use of their data and/or specimens, as described in this protocol.

☐ Other data sources will be utilized in this study. When checked, provide all data sources:

Data Confidentiality, HIPAA Subject Identifiers

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Review the list of subject identifiers below and, if applicable, check the box next to each subject identifier being recorded at the time you are collecting/abstracting data/specimens for use in this study.

Subject Identifiers: Individually identifiable information, including demographic data, that identifies the individual or for which there is reasonable basis to believe it can be used to identify the individual. NOTE: Identifiers apply to subjects enrolled in your study and to the subject's relatives, household members, employers, etc.

Internal refers to subject identifiers that will be included in the dataset maintained by the study team.
External refers to subject identifiers that will be shared with persons outside of the immediate study team, for example, sent to an external collaborator or shared with a national registry.

SUBJECT IDENTIFIERS **Check all that apply**	INTERNAL IDENTIFIER	EXTERNAL IDENTIFIER
Name		
Social Security number		
Medical record/patient registration number, lab accession, specimen or radiologic image number	X	
Study number, subject ID, or any other unique identifying number, characteristic or code that can be used to link the identity of the subject to the data		
Dates: All elements of dates [month, day, and year] directly related to an individual. Their birth date, date of death, date of diagnosis, etc. **Note:** Recording a year only is not a unique identifier.	X	X
Medical device identifiers and serial numbers		
Biometric identifiers, including finger and voice prints, full face photographic images and any comparable images		
Web Universal Resource Locators (URLs), Internet Protocol (IP) address numbers, email address		
Street address, city, county, precinct, zip code, and their equivalent geocodes		
Phone or fax numbers		
Account, member, certificate or professional license numbers, health beneficiary numbers		
Vehicle identifiers and serial numbers, including license plate numbers		
If None of the above identifiers will be recorded or maintained in the dataset and/or sent outside of the study team, please check "None".	☐ None	☐ None

Statistical Information

Note: Power analyses and study endpoints are not needed for a pilot or feasibility studies.

☒ No statistical information. *If checked, please explain*:
This is a pilot study for the calibration of the iDECIDE tool.

E.2 Interview Questions

RECRUITMENT NOTES

Recruitment Date	
Patient Name	
Patient Telephone	
Patient Birthday	
Patient Study ID	
Exercise frequency, duration and type	
Exercise education	**Do you know how exercise affects your blood glucose? How did you learn about it?** **Do you take exercise into account when deciding insulin dosage?** **ALWAYS[ ] NEVER [ ] SOMETIMES [ ]**
Alcohol frequency, number and type	
Alcohol education	**Do you know how alcohol affects your blood glucose? How did you learn about it?** **Do you usually input into the insulin pump carbs from alcoholic drinks?** **ALWAYS[ ] NEVER [ ] SOMETIMES [ ]**
Medtronic data collection	**[ ] CARELINK SOLUTION User Name:** **User Password:** **[ ] IN PERSON** **DATE:**
Diaries data collection	**[ ] FAX [ ] MAIL [ ] SCANNED & EMAIL** **DATE:**

E.3 Self-Tracking Logs

PARTICIPANT NUMBER:
STARTING DATE: **ENDING DATE:**

MY DIABETES DIARY FOR TRACKING ALCOHOL INTAKE

DATE	TIME (Hour: Min)	TYPE OF DRINK (Beer, wine, etc)	NUMBER OF DRINKS	MEASURE (Small glass, pint, can, etc)	DID YOU INPUT DRINK'S CARBS INTO INSULIN PUMP?	
_ / _ /_	__:__				[ ] YES, ____carbs	[ ]NO
_ / _ /_	__:__				[ ] YES, ____carbs	[ ]NO
_ / _ /_	__:__				[ ] YES, ____carbs	[ ]NO

MY DIABETES DIARY FOR TRACKING EXERCISE

DATE	STARTING TIME (Hour: Min)	INTENSITY			DETAILS ON EXERCISE TYPE (OPTIONAL)	DURATION IN MINUTES
_ / _ /_	___:____	[ ] LIGHT	[ ] MODERATE	[ ] VIGOROUS		
_ / _ /_	___:____	[ ] LIGHT	[ ] MODERATE	[ ] VIGOROUS		
_ / _ /_	___:____	[ ] LIGHT	[ ] MODERATE	[ ] VIGOROUS		

APPENDIX F

SECOND ROUND OF RECRUITMENT OF MAYO PATIENTS WITH TYPE 1 DIABETES: MAYO CLINIC IRB APPROVAL #15-006155

F.1 Study Protocol

IRB Minimal Risk Protocol Template

Note: If this study establishes a human specimen repository (biobank) for research purposes, do not use this template. Use the Mayo Clinic Human Specimen Repository Protocol Template found on the IRB home page under Forms and Procedures at http://intranet.mayo.edu/charlie/irb/

First-time Use: Use this template to describe your study for a new IRB submission.

1. Complete the questions that apply to your study.
2. Save an electronic copy of this protocol for future revisions.
3. When completing your IRBe application, you will be asked to upload this template to the protocol section.

Modification: To modify this template after your study has been approved:

1. Open your study in IRBe. Click on the study 'Documents' tab and select the most recent version of the protocol. Save it to your files.
2. Open the saved document and activate "Track Changes"
3. Revise the protocol template to reflect the modification points , save the template to your files
4. Create an IRBe Modification for the study and upload the revised protocol template.

General Study Information

Principal Investigator: Dr. Bithika Thompson

Study Title: Calibration of a pre-meal insulin dosing equation using retrospective data collected through accelerometers and insulin pumps

Protocol version number and date: IRB Application # 15-006155, November 12, 2015.

Purpose

The purpose of this non-therapeutic study is to collect data to allow calibration of software that would eventually be utilized in mobile technology for prandial insulin dose calculations. This feasibility data would then be used in an FDA IND application in preparation for formal clinical trials. This study is similar to IRB #14-004649 except that it adds using an accelerometer by subjects to more accurately determine actual exercise activity and it replaces paper-based diaries of alcohol intake and exercise performed for electronic records input through a smartphone app.

Hypothesis: postprandial glucose control can be optimized by incorporating patient preferences on alcohol intake and exercise into a standard formula used to compute pre-meal insulin bolus.

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Specific aims

The specific aims of this project are:

1. Data collection from type 1 diabetes (T1D) patients: Patients with T1D on insulin pump therapy will be recruited. They will be provided an accelerometer. Demographic data and information on disease characteristics will be abstracted from electronic medical record. Participants will then be asked to record information on alcohol intake and exercise over a 4 week period and to wear an accelerometer as a wristband.

2. Calibration and evaluation of iDECIDE using collected data: After four weeks we will collect from the subjects the generated baseline insulin pump data and the generated records on alcohol intake and exercise, as recorded by the smartphone app that we will install in their phones. We will also collect data from the accelerometers they wore. We will then use that information for a retrospective calibration of iDECIDE. We will evaluate the performance of iDECIDE by comparing the postprandial glucose outcomes recorded in the insulin pumps and the outcomes projected by iDECIDE. Based on the feedback from this evaluation iDECIDE will be calibrated. Patients will not be asked to make any changes in their therapy above and beyond what they are already performing in their standard diabetes self-management practices.

Background

Patients with type 1 diabetes mellitus (T1D) often have difficulty achieving desired postprandial glucose levels, often overestimating or underestimating the amount of insulin to be taken with the meal. An important driver of postprandial glucose control is carbohydrate intake, however, other variables currently not accounted for in standard algorithms that can affect a desired postprandial glucose level are lifestyle variables related to alcohol intake and amount of exercise. It is **hypothesized that postprandial glucose control can be optimized by incorporating patient preferences on alcohol intake and exercise into a standard formula used to compute the pre-meal insulin bolus.**

To develop the model, we propose to recruit subjects with T1D on insulin pump therapy. Insulin pumps are medical devices that deliver insulin continuously via the subcutaneous route, but also allow for the patient to deliver meal time boluses. Current insulin pumps incorporate proprietary equations to calculate pre-meal insulin dosage based on well-established parameters. However, current equations do not incorporate the latest medical evidence to further personalize pre-meal insulin dosing, such as an individual's preference for exercise and alcohol intake. Evidence shows that these personal lifestyle choices have a short-term impact on glucose levels, which in turn could alter a patient's decision on the amount of insulin to deliver with a meal. The proposed solution is to incorporate these parameters into the current equation, evaluate how including these variables affects decision making on prandial insulin dosing, and then correlate this decision with the next premeal glucose level.

There are a multitude of mobile applications for diabetes management that allow users to track carbohydrate intake, exercise, medication and insulin dosage. We are developing a smartphone app, iDECIDE, for Patient-centered ***DECI***sion support based on ***DE***vice data. iDECIDE differs from these current mobile applications in that it is evidence based, a criterion largely missing in current mobile applications. Furthermore, the development of iDECIDE is grounded on well-established cognitive-based decision principles from the field of Clinical Decision Support Systems.

Patients on insulin pump therapy make ideal subjects to calibrate the iDECIDE software. These patients are typically well trained in insulin pump devices, and monitor glucose values frequently throughout the day yielding a rich source of data on glucose levels, insulin doses, and amount of carbohydrates consumed. Additionally, the data recorded by the insulin pump, the provided smartphone app and the accelerometer can be downloaded and the data exported to an analytic file. This can be done either in the presence of the patient at the point of care, or even remotely if the patient desires.

Subject Information – charts, records, images, or specimens are considered 'subjects'

Target accrual: *Proposed number of subjects to be included in your study at your site. "Subjects" may include Mayo Clinic charts, records, or specimens,* ***and/or*** *charts, records, or specimens received at Mayo Clinic from external sources for collaborating analysis by the investigator under this IRB application*:

Subject population: 15 subjects

Inclusion Criteria: Mayo Clinic Arizona type 1 diabetes outpatients, older than 18 years and younger than 70, non-pregnant, English speakers, who use Medtronic insulin pumps and glucose continuous monitoring sensors, own a smartphone and who have kept in consistent contact with the Mayo Clinic Division of Endocrinology health care team during the last year.

Exclusion Criteria: subjects who do not satisfy the inclusion criteria.

Will a Certificate of Confidentiality be obtained? *If yes, provide an explanation.*
NA

Study Design

Methods: *Describe, in detail, the research activities that will be conducted under this protocol*:
The proposed research is a continuation of the approved and completed study, IRB# 14-004649, that resulted in a preliminary calibration of the iDECIDE insulin dosing formula. In this new study we will replace the paper-based alcohol and exercise diaries used in IRB# 14-004649 for electronic diaries implemented as a smartphone app that we will install in participant's smartphones. Also, to further improve the accuracy of the self-reported data on exercise we will ask participants to use an accelerometer that will independently record duration and intensity of exercise.

For those participants that consent to participate in the study, study personnel will collect the following information from the electronic medical record:

- Medical history: age, gender, current treatment of diabetes (including years with diabetes, medication), ketoacidosis information (frequency, severity and cause), hypoglycemic episodes, history of diabetes-related complications (in particular vascular disease or micro vascular complications)
- Social history: exercise habits (frequency and type of exercise), alcohol use history and frequency of alcohol use

- Physical examination: height, weight, body mass index
- Laboratory evaluation: results of last A1C

Mayo Clinic study personnel will identify potential subjects at the time of their routine clinical visit. Subjects will be handed a flyer that provides details on the study (see Attachment 1). The Mayo Clinic team will share with the Arizona State University the subject's name for identification during an initial interview. The subject will receive the email and phone number of the Arizona State University team and will initiate contact. By phone or email the subject and the recruiter will agree on a date and place to meet (possibly different from the patient appointment date). The Arizona State University team and the subject will meet at the Mayo Clinic at Scottsdale or at the Arizona State University Department of Biomedical Informatics at Scottsdale. Both are located next to each other. The Arizona State University team will recruit subjects though a written informed consent, survey them on glucose control self-management (see Attachment 2) and will install a smartphone app in the their phones to self-report daily alcohol intake and the amount of exercise. Recruited participants will also receive a wristband accelerometer. Arizona State University study personnel will explain to the participants how to use the app and the accelerometers and will set them up. Participants will be asked to collect data for 4 consecutive weeks. At the end of the data collection period, the information recorded by the insulin pumps, the smartphone app and the accelerometers will be remotely collected by the study team. The Arizona State University team could contact the recruited subject periodically during the study, through email or phone, to clarify doubts or concerns. At the end of the study subjects will be sent through email an optional survey (see Attachment 3) to evaluate the usability of the provided app. Identical to procedures followed in IRB# 14-004649,patients will download the insulin pump data through the Medtronic Carelink Solution password protected account, which will be remotely accessed by the recruiters. Once the data has been downloaded the patients will be encouraged to change their passwords. Alternatively, patients can meet in person with the recruiter at Mayo Clinic, so the recruiters can download the data from the patient's insulin pump.

The data generated by the accelerometer is automatically synchronized with a Fitbit account, no downloaded is required. Study personnel will access that data remotely using the participant's password protected account. Once the data has been downloaded the patients will be encouraged to change their passwords. The data recorded by the smartphone app will be remotely access by study personnel. Once the data has been downloaded the remote connections with the app will be removed.

The data generated by the smartphone app will be locally saved in the participant's phone and a copy of that data will be securely transmitted using up-to-date encryption technology to a remove server at the Arizona State University. The server is password protected and kept in a locked room. Only members of the study team have access to the server room. In case the patient experiences difficulties using the app, they will be able to upload the same information collected by the app using paper-based logs (see Attachment 4).

We will link the data obtained from the participants' insulin pumps, smartphone app and accelerometer with the collected clinical information and de-identify it. After that we will destroy the information that could link the de-identified data to the patient's identity. We will also de-identify medical device identifiers and serial numbers. We will use the de-identified information to calibrate the iDECIDE tool. The Arizona State University team will store all the information in a password protected server, in a locked room. All the files will be encrypted.

The Mayo Clinic team will have access to the participant's insulin pump data as they usually do while providing care. The Mayo Clinic will have no access to the data from the smartphone app or the accelerometer.

Resources: *Describe the available resources to conduct the research (personnel, time, facilities, mentor commitment, etc.)*:

The entire study team has completed Human Subject Protection training. Dr. Bithika Thompson is a Senior Associate Consultant at the Division of Endocrinology at Mayo Clinic Arizona. Dr. Curtiss Cook is the Chair of the Division of Endocrinology at Mayo Clinic Arizona and adjunct faculty at ASU's Department of Biomedical Informatics. Dr. Grando is an Assistant Professor at the Department of Biomedical Informatics at the Arizona State University. Dr. Grando is a Mayo Research Affiliate and an Adjunct Assistant Professor at the Mayo Clinic Arizona's Department of Medicine. Hiral Soni, BS and Danielle Groat, BS are graduate students at the Arizona State University Department of Biomedical Informatics and Mayo Research Affiliates.

Dr. Thompson and Curtiss will be responsible for the overall supervision of this study and to oversee the team of investigators that will calibrate and evaluate the iDECIDE formula. Dr. Adela Grando will be responsible for the study design and implementation. Hiral Soni and Danielle Groat will recruit participants, and perform the data analysis needed to calibrate the iDECIDE formula.

Check all that apply. If none apply, leave blank:

☒ This is a multisite study involving Mayo Clinic and non-Mayo Clinic sites.
When checked, describe the research procedures/activities being conducted **only** at Mayo Clinic:
Downloading of preexisting insulin pump data.

☐ Mayo Clinic staff will be engaged in research activity at a non-Mayo Clinic site. *When checked, provide the location and a detailed description of the Mayo Clinic research staff involvement.*

☐ This study is to establish and/or maintain an ongoing database or registry for research purposes only.

☐ The research involves contact or interaction with subjects, for example, surveys, questionnaires, observation, blood draw.

☐ The study involves audiotaping or videotaping

Blood Collection

If this study involves prospective blood collection by finger, heel, ear stick or venipuncture, complete the following:

☐ **From healthy, non pregnant, adult subjects who weigh at least 110 pounds**. For a minimal risk application, the amount of blood drawn from these subjects may not exceed 550ml in an 8 week period and collection may not occur more frequently than 2 times per week.

Volume per blood draw: _____ml

Frequency of blood draw (e.g. single draw, time(s) per week, per year, etc.) _____

☐ **From other adults and children considering age, weight, and health of subject.** For a minimal risk application, the amount of blood drawn from these subjects may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period, and collection may not occur more frequently than 2 times per week.

Volume per blood draw: _____ml

Frequency of blood draw (e.g. single draw, time(s) per week, per year, etc.)_____

Review of Chart, Images, Specimens

Provide the date range for collection of data and/or specimens that will be included in your research dataset. (*Example: 01/01/2000 to 12/31/2012*)

Date range: From 09/01/2015 to 09/01/2016

Check all that apply:

☐ This study involves only data and/or specimens that exist at the time this application is submitted to the IRB (IRB submission date). No data or specimens will be collected beyond this date.

☒ This study involves only data and/or specimens that will be collected after submission to the IRB.

☐ The study involves data and/or specimens that exist at the time of submission to the IRB **and** data and/or specimens that will be collected after submission to the IRB, for example a study that includes collection of existing data and prospective collection of specimens.

☐ Data and/or specimens used in this study are collected under another IRB protocol. *When checked, provide the IRB number(s) from which the research material will be obtained and check the box below to attest that subjects have provided consent for future use of their data and/or specimens, as described in this protocol.*

IRB Number(s):

□Subjects have provided consent for use of their data and/or specimens, as described in this protocol.

☐ Other data sources will be utilized in this study. When checked, provide all data sources:

Data Confidentiality, HIPAA Subject Identifiers

Review the list of subject identifiers below and, if applicable, check the box next to each subject identifier being recorded at the time you are collecting/abstracting data/specimens for use in this study.

Subject Identifiers: Individually identifiable information, including demographic data, that identifies the individual or for which there is reasonable basis to believe it can be used to identify the individual. NOTE: Identifiers apply to subjects enrolled in your study and to the subject's relatives, household members, employers, etc.

Internal refers to subject identifiers that will be included in the dataset maintained by the study team.
External refers to subject identifiers that will be shared with persons outside of the immediate study team, for example, sent to an external collaborator or shared with a national registry.

SUBJECT IDENTIFIERS **Check all that apply**	INTERNAL IDENTIFIER	EXTERNAL IDENTIFIER
Name	X	X
Social Security number		
Medical record/patient registration number, lab accession, specimen or radiologic image number	X	
Study number, subject ID, or any other unique identifying number, characteristic or code that can be used to link the identity of the subject to the data	X	
Dates: All elements of dates [month, day, and year] directly related to an individual. Their birth date, date of death, date of diagnosis, etc. **Note:** Recording a year only is not a unique identifier.	X	X
Medical device identifiers and serial numbers	X	
Biometric identifiers, including finger and voice prints, full face photographic images and any comparable images		
Web Universal Resource Locators (URLs), Internet Protocol (IP) address numbers, email address		X
Street address, city, county, precinct, zip code, and their equivalent geocodes		
Phone or fax numbers		X
Account, member, certificate or professional license numbers, health beneficiary numbers		
Vehicle identifiers and serial numbers, including license plate numbers		
If None of the above identifiers will be recorded or maintained in the dataset and/or sent outside of the study team, please check "None".	None	None

Statistical Information

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Note: Power analyses and study endpoints are not needed for a pilot or feasibility studies.

☒ No statistical information. *If checked, please explain*:
This is a pilot study for the calibration of the iDECIDE tool.

Statistical Considerations

Power Statement: NA

Data Analysis Plan:
The amount to insulin that should have been delivered (as calculated by iDECIDE) to reach the patient designated glucose target will be compared to the actual amount of insulin bloused by the patient.

Endpoints

Primary: Calibration of iDECIDE formula using accelerometer data.

Secondary:

F.2 Compensation Techniques Survey

iDECIDE Recruitment Survey

* Required

1. Your name *

_____

2. Your date of birth * Example: December 15, 2012

_____

3. Your weight *

_____(lbs)

4. Your gender * Check all that apply.

[ ] Female
[ ] Male

5. Do you use fitness apps or wearable devices to track your meals, exercise and alcohol related activities? Provide details *

_____

Meal Activities Related Questions

6. How do you know about the effects of carbs on blood glucose? * (Please select all that apply)

[ ] Physician/ Nurse
[ ]Website
[ ]From other patients
[ ]Trial and error
[ ]Pamphlets or books
[ ]I don't know much about the effects
[ ]Other: _____

7. How do you calculate your meal's carbs? *(Please select all that apply)

[ ]Food label
[ ]Online food database
[ ]Personal estimation
[ ]Clinician's or Educator's suggested approach
[ ]I don't calculate
[ ]Other: _____

8. How do you compensate for carbs intake? *(Please select all that apply)

[ ]Insulin bolus, following Insulin Pump advice
[ ]Insulin bolus, my own estimation
[ ]Insulin bolus, following online calculator recommendations
[ ]Basal adjustment
[ ]Square delivery adjustment
[ ]I don't compensate
[ ]Other: _____

9. Do you skip carbs calculations for any reason? Provide details *

_____

Exercise Related Questions

10. Do you exercise? *
[ ]Yes
[ ]No

11. How frequently do you exercise? *
[ ]Daily
[ ]4 to 6 days a week
[ ]2 to 3 days a week
[ ]Once a week
[ ]I don't exercise

12. How long do you exercise in one session? *
[ ]More than 60 minutes
[ ]Between 30 to 60 minutes
[ ]Less than 30 minutes
[ ]Varies
[ ]I don't exercise

13. What is your preferred time for exercising? * (Please select all that apply)
[ ]Morning
[ ]Afternoon
[ ]Evening
[ ]Varies
[ ]I don't exercise
[ ]Other: _____

14. What type of exercise do you prefer? * (Please select all that apply)
[ ]Cardio
[ ]Circuit training
[ ]Aerobics
[ ]Strength training
[ ]Stretching and balance
[ ]Hiking
[ ]I don't exercise
[ ]Other: _____

15. If you exercise, when do you check your blood glucose? *(Please select all that apply)
[ ]Before
[ ]After
[ ]During
[ ]I don't check blood glucose
[ ]Other: _____

16. How do you know about the effects of exercise on blood glucose? *(Please select all that apply)
[ ]Physician/ Nurse
[ ]Website
[ ]From other patients
[ ]Trial and error
[ ]Pamphlets or books
[ ]I don't know much about the effects
[ ]Other: _____

17. How do you compensate for your blood glucose levels related to exercise? * (Please select all that apply)

	Before exercise	During exercise	After exercise	I don't compensate
Remove Insulin pump				
Eat snack/food				
Adjust basal rate				
Bolus Insulin				

18. Do your blood glucose levels affect your exercise decisions? *(Please select all that apply)
[ ] I exercise when blood glucose is high
[ ] I exercise when blood glucose is in target range
[ ] I skip exercise when blood glucose is low
[ ] I don't decide on exercise based on blood glucose levels
[ ] I don't exercise
[ ]Other: _____

19. Which of the following related to exercise affect your blood glucose? *

	Has effect	No effect	I don't know
Intensity of exercise			
Type of exercise			
Duration of exercise			
Time of exercise			
Pre-exercise blood glucose			
Pre-exercise snack/food			

Alcohol Intake Related Questions

20. Do you consume alcohol? *
[ ]Yes
[ ]No

21. How often do you consume alcohol? *
[ ]Daily
[ ]More than 4 times a week
[ ]Less than 4 times per week, or 4 times per week
[ ]Occasionally
[ ] I don't drink
[ ]Other: _____

22. Have you notice any effect of alcohol intake on your blood glucose? *(Please select all that apply)
[ ]Alcohol increases my blood glucose
[ ]Alcohol decreases my blood glucose
[ ]Alcohol increases and then decreases my blood glucose
[ ]Alcohol decreases and then increases my blood glucose
[ ]Alcohol has no effect on my blood glucose

[ ]I don't know
[ ]Other: _____

23. What type of alcohol do you consume? *(Please select all that apply)
[ ]Beer
[ ]Wine
[ ]Spirits/ Hard alcohol
[ ]Mixed drinks
[ ]I don't drink
[ ]Other: _____

24. If you consume alcohol, when do you check your blood glucose? *(Please select all that apply)
[ ]Before
[ ]After
[ ]During
[ ]I don't check blood glucose
[ ]Other: _____

25. How do you know about the effects of alcohol on blood glucose? * (Please select all that apply)
[ ]Physician/ Nurse
[ ]Website
[ ]From other patients
[ ]Trial and error
[ ]Pamphlets or books
[ ]I don't know much about the effects
[ ]Other: _____

26. How do you compensate for your blood glucose levels related to alcohol? * (Please select all that apply)

	Before Alcohol	During Alcohol Intake	After Alcohol	I don't compensate
Remove Insulin Pump				
Eat food				
Adjust basal rate				
Bolus insulin				

27. How do you calculate carbs when you consume alcohol? *(Please select all that apply)
[ ]Drink label
[ ]Online database
[ ]Personal estimation
[ ]Clinician's or Educator's suggested approach
[ ]I don't calculate
[ ]Other: _____

28. Do you compensate for your alcohol's carbs? *
[ ]Always
[ ]Sometimes
[ ]Depends on drink type/count
[ ]Only when the blood glucose is high
[ ]Never
[ ]Other: _____

29. Which of the following related to alcohol affect your blood glucose? *

	Has effect	No effect	I don't know
Time of consumption			
When combined with food			
Type of drink			
Number of drinks			
Blood glucose levels			
Pre-alcohol food			

General Questions

30. Do you disconnect you Insulin Pump for any reason other than exercise? Provide details *

_____

31. Do you change your Insulin Pump endocrine settings (Basal rate, Preset factors) for any reason without clinician's advise? Provide details *

_____

32. Do you change the insulin bolus delivery waveform pattern in the Insulin Pump? Provide details *

_____

33. Do you override bolus suggestions from the Insulin Pump for any reason? Provide details *

_____

34. Do you bolus to compensate for blood glucose without any carbs intake? Provide details *

_____

35. Do you bolus to compensate for carbs without adjusting for blood glucose levels? Provide details *

_____

F.3 Post-study Usability Survey

iDECIDE Survey

* Required

1. My overall experience with iDECIDE during the study was *

[ ]Excellent
[ ]Moderately Satisfying
[ ]Neutral
[ ]Slightly Unsatisfactory
[ ]Very disappointing
[ ]Other: ____

Refer to the image below for the next 3 questions.

2. I found the exercise, meal/drinks tab to be *

(Reference: Image above the question)

[ ]Useful
[ ]Not useful
[ ]Confusing
[ ]Other: _____

3. iDECIDE helped me keep track of my exercise, meal and alcohol plans *

1 2 3 4 5
Disagree Agree

4. I felt that using iDECIDE to add exercise and/or meal/drinks plans was *

(Selection of tabs, steps in task completion, etc.)

1 2 3 4 5
Difficult Easy

Refer to this image to answer question 5.

5. The iDECIDE Home Button was useful for me *

1 2 3 4 5
Disagree Agree

6. Please rate the following attributes of iDECIDE *

	Excellent	Good	Fair	Poor	Very poor
Design					
Functions are easy to follow					
Display clarity					
Screen clutter					
Selection of font					
Selection of colors					
Use of icons					

7. During the study period, how often did the iDECIDE app crash or stop working? *

[ ]Never
[ ]Rarely
[ ]Sometimes
[ ]Often
[ ]Frequently
[ ]Other: _____

8. Compared to other apps I have used, I would rate the overall quality of iDECiDE as *

1 2 3 4 5
Poor Excellent

9. My comments on iDECIDE and improvement suggestions. (Optional)

_____

10. I would recommend using iDECIDE to my family and friends, *

1 2 3 4 5
Disagree Agree