Self – Management Strategies as a Pillar in Treatment for Patients With Diabetes Mellitus

SELF – MANAGEMENT STRATEGIES AS A PILLAR IN TREATMENT FOR PATIENTS WITH DIABETES MELLITUS

By

Luisa F. Florez Builes

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Project Advisor: Alexander Turchin MD, MS.
External Content Advisor: Margo Hudson MD
Independent External Expert: Marie McDonnell MD
MMSCI Program Representative: Enid Martinez MD
MMSCI Program Directors:
Ajay Singh MBBS, FRCP, MBA. and Finnian McCausland MBBCh, MMSCI, MRCPI

I have reviewed this thesis. It represents work done by the author under my guidance/supervision.

Primary Mentor: Alexander Turchin MD, MS.

Alexander Turchin

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2. BACKGROUND

As diabetes incidence and prevalence continues to rise, so does the necessity for an efficacious and cost-effective treatment approach that could decrease its complications and mortality rate. Diabetes is one of the most common chronic diseases worldwide. Patients with this condition suffer from sustained hyperglycemia which is associated with acute and chronic complications that could affect multiple body organs.

Diabetes Mellitus can be classified by underlying cause. Type 1 Diabetes Mellitus is an autoimmune disease where the body immune system destroys the pancreas beta cells and prevents them from producing insulin, a hormone that regulates blood glucose levels and allows the body to use it as a source of energy. Patients with this condition are dependent on insulin injections or use of an insulin pump.

Type 2 Diabetes Mellitus has many underlying factors that contribute to the high blood glucose levels commonly associated with overweight and obesity. It has a combination of increased insulin resistance and a progressive decline in beta cell function. Individuals with type 2 diabetes may have a combination of deficient secretion and deficient action of insulin.

While patients with type 2 diabetes have multiple medications available, many of them eventually require insulin at some point during their disease due to the limited glucose-lowering effect, common adverse reactions and contraindications of most non-insulin medications. Insulin has no contraindications and high efficacy for lowering blood glucose; nevertheless, patients with type 2 diabetes frequently delay initiation of insulin therapy. Recent findings show that

often this delay is due to the decline of insulin therapy by the patients when is first recommended by their physician. The clinical course of these patients remains poorly understood. We therefore conducted a retrospective observational analysis to better understand the clinical course of patients with type 2 diabetes who decline insulin therapy.

It is also important to note that patients with both type 1 and type 2 diabetes who use insulin commonly experience dangerous hypoglycemic episodes while still facing a risk of a hyperglycemic state when the disease is not properly controlled. Current strategies to reduce hypoglycemia while achieving glycemic targets have only a modest effect (less pronounced peak concentration insulin) or can be very expensive (continuous glucose monitoring systems). Some digital applications in diabetes care have shown to be effective in improving glycemic control, but none have engaged patients in self-controlling their disease or have shown reduction in hypoglycemic frequency. We are conducting a clinical trial to test whether the Control:Diabetes mobile app can reduce hyper- and / or hypoglycemia in patients with diabetes treated with insulin.

To improve clinical outcomes in this population, the current American Diabetes Association (ADA) guidelines recommends diabetes self-management education and support programs to include behavioral therapy that facilitates the patient to acquire the knowledge, skills, and ability necessary for diabetes self-care. This could be achieved with the use of technology. The Control:Diabetes mobile app was created to teach diabetes-self management through repeated self-feedback.

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Predictors of glycemic control after decline of insulin therapy by patients with type 2 diabetes☆

Luisa Florez [a,b], Maria Shubina [a], Alexander Turchin [a,b,*]

[a] Brigham and Women's Hospital, Boston, MA, United States of America
[b] Harvard Medical School, Boston, MA, United States of America

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ABSTRACT

Aim: Decline of insulin therapy by patients is common but poorly investigated. We conducted this study to determine patient and treatment characteristics predictive of glycemic control after declining clinician recommendation to initiate insulin therapy.
Methods: We retrospectively studied adults with type 2 diabetes mellitus treated at two academic medical centers between 1993 and 2014 who declined their healthcare provider recommendation to initiate insulin.
Results: In a multivariable analysis of 300 study patients adjusted for demographics, comorbidities and clustering within providers, higher baseline HbA1c (OR 1.85; 95% CI 1.40 to 2.39; $p < 0.001$) and lifestyle changes (OR 8.39; 95% CI 3.26 to 21.55; $p < 0.001$) were associated with greater, while non-adherence to diabetes medications (OR 0.014; 95% CI 0.0025 to 0.085; $p < 0.001$) and discontinuation of a non-insulin diabetes medication (OR 0.30; 95% CI 0.11 to 0.80; $p = 0.016$) were associated with lower probability of HbA1c decrease after declining insulin therapy.
Conclusion: We identified patient characteristics and treatment strategies associated with success and failure of glycemic control after insulin therapy decline by the patient. This information can assist in selection of optimal therapeutic approaches for these individuals.

1. Introduction

Diabetes is one of the most common chronic diseases, with a worldwide prevalence of 6.4% that is projected to increase to 7.7% by the year 2030.[1,2] The number of people diagnosed with diabetes worldwide has risen from 108 million in 1980 to 422 million in 2014.[3] In the United States, diabetes prevalence is even higher at 12.6%; it is the seventh leading cause of death and contributes to many others.[4,5] In addition to acute complications such as diabetic ketoacidosis and hyperosmolar hyperglycemic non-ketotic state, diabetes can lead to a number of micro- and macrovascular sequelae, including retinopathy, nephropathy, coronary artery disease (CAD) and cerebrovascular accident (CVA).[3,6]

Type 2 diabetes mellitus (T2DM) is characterized by a combination of increased insulin resistance and a decline in beta cell function.[7,8] Patients with T2DM who have elevated blood glucose levels are at high risk for acute and chronic complications[9,10]; lowering blood glucose decreases these risks.[11–13] Consequently, current guidelines recommend that most patients achieve hemoglobin HbA1c levels = 7.0% (53 mmol/mol) or lower.[14–16] As the disease continues to progress, repeated intensification of treatment is usually necessary to achieve these targets.[17]

Multiple medications are available to treat T2DM. However, many of them have limited glucose-lowering effect, common adverse reactions and/or contraindications that restrict their use.[18] Insulin, on the other hand, has no contraindications and high efficacy for lowering blood glucose. As a result, many patients with T2DM require insulin at some point during the course of their disease. Nevertheless, insulin therapy is often delayed.[19] While historically delays in initiation of insulin therapy were thought to be primarily due to clinical inertia,[20,21] recent findings show that many patients with diabetes decline insulin therapy offered to them by their clinicians.[22] The clinical course of patients who have declined insulin therapy remains poorly understood. We have therefore conducted this study aiming to establish the factors associated with a greater risk of poor glycemic control following insulin therapy decline by the patient.

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* Corresponding author at: Division of Endocrinology, Brigham and Women's Hospital, 221 Longwood Avenue, Boston, MA 02115, United States of America.
E-mail address: aturchin@bwh.harvard.edu (A. Turchin).

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2. Materials and methods

2.1. Study design

We conducted a retrospective analysis to determine patient characteristics predictive of glycemic control after they declined their healthcare providers' recommendation to start insulin treatment.

2.2. Study cohort

We studied adults with T2DM, treated by primary care physicians or endocrinologists affiliated with Brigham and Women's Hospital (BWH) and Massachusetts General Hospital (MGH) who declined an insulin therapy recommendation between January 1, 1993, and December 31, 2014. Patients were considered to have declined insulin therapy recommendation if the provider's EMR note documented both the recommendation of insulin therapy and the patient's rejection of that recommendation in the absence of an insulin prescription. We compared 150 randomly selected patients whose HbA1c subsequently decreased to 150 randomly selected patients whose HbA1c increased or stayed the same after rejecting insulin therapy. Patients were included in the analysis if they were at least 18 years old, declined insulin treatment recommended by their providers for the first time, had no prior history of insulin usage, had HbA1c ≥ 7.0% (53 mmol/mol) at baseline and a follow-up HbA1c measurement at least three months after declining insulin therapy. Patients were excluded if they had a diagnosis of type 1 diabetes or were pregnant. This study was approved by the Partners HealthCare institutional review board, and the requirement for written informed consent was waived.

2.3. Study measurements

Patients' medical history and demographic information were obtained from the Electronic Medical Record (EMR) system at Partners HealthCare, which includes records from BWH and MGH. To identify characteristics predictive of glycemic control, we manually collected demographic information (age, sex, race/ethnicity, primary language, marital status, health insurance and median household income by zip code), baseline measurements (HbA1c, BMI and the number of non-insulin diabetes medications), pre-existing medical conditions (sustained elevated HbA1c, coronary artery disease, cerebrovascular accident, and mental illness) and characteristics of diabetes treatment after declining insulin therapy (lifestyle changes, weight changes, treatment adherence, starting or increasing the doses of a non-insulin diabetes medication, discontinuing or decreasing the doses of a non-insulin diabetes medication, and starting insulin after an initial rejection). Discontinuation or addition of a non-insulin medication was recorded only if the decision was made by the healthcare provider; self-discontinuations of diabetes medications by the patient were recorded as treatment non-adherence. Sustained HbA1c elevation was defined as HbA1c ≥ 7.0% (53 mmol/mol) for at least 12 months prior to having declined insulin with no HbA1c < 7.0% (53 mmol/mol) during this time. Direction of HbA1c change between baseline and the first measurement at least three months after the initial decline of insulin therapy (decreased vs. increased or remained the same) served as a binary primary outcome.

2.4. Statistical analysis

Summary statistics were analyzed using measures of central tendency (means, standard deviations, and medians) for continuous variables and using frequencies and proportions for categorical variables. To identify predictors of HbA1c decrease, we constructed a multivariable logistic regression model that included patient demographics, baseline characteristics and post-insulin decline treatment, and was also adjusted for clustering within individual providers. Multiple imputation was used to account for missing data (BMI and median household income by zip code). Significance threshold was adjusted for multiple hypothesis testing using the Simes-Hochberg method.[23,24] All analyses were performed using SAS, version 9.4 (Cary, NC).

3. Results

We identified 300 patients who rejected insulin treatment recommended by their providers for the first time by randomly selecting 150 patients whose HbA1c decreased after they declined insulin therapy and 150 patients whose HbA1c did not. Baseline characteristics were similar between the two groups (Table 1) with the exception of the baseline HbA1c that was higher for patients whose HbA1c subsequently decreased (9.5% (80 mmol/mol) vs. 8.5% (69 mmol/mol); $p < 0.001$).

Mean follow-up HbA1c was 7.7% (61 mmol/mol) among patients whose HbA1c decreased after they declined insulin therapy recommendation and 9.5% (80 mmol/mol) among the rest. In univariate analysis (Table 1), patients whose HbA1c decreased following decline of insulin therapy were more likely to implement lifestyle changes (27.3% vs. 7.3%; $p < 0.001$) or to initiate a non-insulin diabetes medication (47.3% vs. 31.3%; $p = 0.006$); additionally, individuals who started a non-insulin diabetes medication had, on average, achieved a decrease of 0.4% in HbA1c. Patients whose HbA1c decreased after they declined insulin therapy were also less likely to be non-adherent to diabetes medications (1.3% vs. 26.7%; $p < 0.001$) or to discontinue a non-insulin diabetes medication (8.0% vs. 16.0%; $p = 0.049$) after they declined insulin therapy. There were no statistically significant differences in BMI changes or insulin initiation rate after the initial decline between the two groups.

In a multivariable analysis (Table 2) adjusted for demographics, comorbidities and clustering within providers, we found that higher baseline HbA1c (OR 1.83; 95% CI 1.40 to 2.39; $p < 0.001$) and lifestyle changes implemented after the initial decline of insulin therapy (OR

Table 1
Characteristics of study patients.

	HbA1c decreased n = 150	HbA1c did not decrease n = 150	p-Value
Baseline			
Age, mean (SD), y	62 (14.1)	62.5 (13.2)	0.72
Female sex, no (%)	79 (52.6)	81 (54)	0.90
White race, no (%)	99 (66)	97 (64.6)	0.90
English as primary language, no (%)	120 (80)	119 (79.3)	1
Married, no (%)	70 (46.6)	72 (48)	0.90
Government insurance, no (%)	86 (57.3)	83 (55.3)	0.81
Median household income, mean (SD), $1000s	62.6 (23.5)	66.8 (26.0)	0.14
HbA1c, mean (SD), %/mmol/mol	9.5/80 (1.9)	8.5/69 (1.3)	<0.001
BMI, mean (SD), kg/m^2	32.9 (5.9)	33.1 (6.5)	0.78
Non-insulin diabetes medications, mean (SD)	1.7 (0.74)	1.8 (0.75)	0.19
Sustained elevated HbA1c, no (%)	99 (66)	108 (72)	0.31
CAD, no (%)	24 (16)	27 (18)	0.75
CVA, no (%)	9 (6)	5 (3.3)	0.41
Mental illness, no (%)	24 (16)	31 (20.6)	0.37
Study year, mean (SD)	13.4 (3.7)	13.1 (4.2)	0.43
Post insulin decline			
HbA1c, mean (SD), %/mmol/mol	7.7/61 (1.3)	9.5/80 (1.8)	<0.001
Lifestyle changes, no (%)	41 (27.3)	11 (7.3)	<0.001
Weight loss >5%, no (%)	7 (4.6)	12 (8)	0.34
Weight loss <5%, no (%)	57 (38)	47 (31.3)	0.27
Weight gain, no (%)	44 (29.3)	46 (30.6)	0.89
Non-adherence, no (%)	2 (1.3)	40 (26.7)	<0.001
Non-insulin diabetes medication started or increased, no (%)	71 (47.3)	47 (31.3)	0.006
Non-insulin diabetes medication discontinued or decreased, no (%)	12 (8)	24 (16)	0.049
Insulin started, no (%)	15 (10)	18 (12)	0.71
No changes, no (%)	16 (10.6)	25 (16.6)	0.17

Table 2
Effects of patient and treatment characteristics on glycemic control.

	Odds ratio	95% CI	p-Value
Baseline			
Age	1	0.97–1.03	0.60
Female sex	1.39	0.75–2.57	0.29
White race	1.26	0.58–2.71	0.55
English as primary language	1.25	0.52–3.03	0.61
Married	0.84	0.46–1.52	0.57
Government insurance	1.31	0.65–2.66	0.43
Median household income	0.98	0.97–1.00	0.06
HbA1c	1.83	1.40–2.39	**<0.001**
BMI	0.99	0.94–1.05	0.95
Non-insulin diabetes medications	1.2	0.77–1.86	0.41
Sustained HbA1c elevation	0.65	0.34–1.25	0.20
CAD	0.66	0.33–1.32	0.24
CVA	1.18	0.28–4.96	0.81
Mental illness	0.67	0.30–1.45	0.31
Study year	1.06	0.97–1.15	0.15
Post insulin decline			
Lifestyle changes	8.39	3.26–21.55	**<0.001**
Weight loss >5%	1.05	0.27–3.96	0.93
Weight loss <5%	0.92	0.31–2.69	0.88
Weight gain	0.53	0.17–1.60	0.26
Non-adherence	0.014	0.002–0.08	**<0.001**
Non-insulin diabetes medication started or increased	1.73	0.84–3.59	0.13
Non-insulin diabetes medication discontinued or decreased	0.3	0.11–0.80	**0.016**
Insulin started	1.26	0.49–3.26	0.62
No changes	0.48	0.12–1.85	0.29

Boldfaced p-values were significant after Simes-Hochberg adjustment for multiple hypothesis testing.

8.39; 95% CI 3.26 to 21.55; $p < 0.001$) were associated with greater probability of HbA1c decrease, while non-adherence to diabetes medications (OR 0.014; 95% CI 0.0025 to 0.085; $p < .001$) and discontinuation of a non-insulin diabetes medication (OR 0.30; 95% CI 0.11 to 0.80; $p = 0.016$) were associated with lower probability of HbA1c decrease after initial decline of insulin therapy by the patient. After the Simes-Hochberg procedure with a false discovery rate of 25% the same variables remained statistically significant.

The most common reasons for discontinuation of a non-insulin diabetes medications after the initial decline of insulin therapy recommendation by the patient (Table 3) were replacement with insulin (presumably due to lack of efficacy), side effects or worsening renal function.

4. Discussion

In this study, we found that characteristics of patients who had declined their healthcare providers' recommendation to start insulin therapy could indicate their subsequent glycemic control. Individuals with higher baseline HbA1c were more likely to achieve a decrease in their blood glucose levels. This could be explained by greater motivation of the patients who recognize they are at higher risk of complications of diabetes and may also be symptomatic from their hyperglycemia, as well as their physicians who may be treating them more aggressively[25,26] On the other hand, a "regression to the mean" could also be a contributing factor. Higher baseline HbA1c could have been a transient event, caused by a temporary lapse in diet or medication, that improved after their restoration.

Treatment of these patients after they had declined insulin therapy was also an important factor in their subsequent glycemic control. Our results were consistent with previously published studies that suggest that the initiation of a new class of non-insulin diabetes medication added to the initial therapy generally lowers HbA1c around 0.4 to 1.0%.[27] Intensification of alternative anti-hyperglycemic therapy is a reasonable step in patients who may benefit from treatment with insulin but decline it; even if a single non-insulin diabetes medication fails to achieve glycemic goals, multiple agents together may be successful.[14] Furthermore, a number of recently introduced diabetes agents, including GLP-1 receptor agonists and SGLT2 inhibitors have additional short-and long-term clinical benefits besides lowering blood glucose and may for some patients be preferable to treatment with insulin.[14,28,29]

Another aspect of post-insulin therapy decline treatment that was strongly associated with improving glycemic control was the implementation of lifestyle changes. Current guidelines recommend lifestyle management as a fundamental aspect of diabetes care, including diabetes self-management education and support (DSMES), medical nutrition therapy (MNT), physical activity, smoking cessation counseling, and psychosocial care.[14] Effect of lifestyle counseling on blood glucose levels is supported by both clinical trials[30,31] and real-world evidence.[32,33] Our evidence suggests lifestyle changes could improve glycemic control even after a significant progression of the disease and have an impact on the patient clinical outcome. However, given the retrospective nature of the analysis and the observed dramatic effect of lifestyle counseling, it is possible that a reporting bias was also a contributing factor.

We also identified several factors that were associated with worsening glycemic control after the decline of insulin therapy recommendation. One of these was the discontinuation of non-insulin diabetes medications. In both groups, these were most commonly stopped because they were being replaced with insulin (likely due to lack of efficacy) or side effects. On the other hand, a numerically larger proportion of patients whose HbA1c did not decrease following decline of insulin therapy discontinued non-insulin medications due to worsening of their renal function, which could have contributed to the poor glycemic control of this group. Consequently, the causal relationship between discontinuation of non-insulin diabetes medications and glycemic deterioration could have been bi-directional. Another important factor that was associated with a lack of improvement in glycemic control was non-adherence to diabetes medications. While reporting bias could have accounted for some of the magnitude of the observed effect, non-adherence to diabetes therapy is well established as a significant contributor to suboptimal glycemic control and is an important risk factor for chronic complications and high mortality rates among patients with T2DM.[34–36]

We also found that some of the post-insulin decline treatment characteristics were not associated with changes in blood glucose level, as might have been expected. Weight loss, whether under or in excess of 5% of body mass, did not show a statistically significant association with HbA1c changes. This could have been due to the time it takes both to lose the weight – not an instantaneous process – and for the HbA1c to achieve equilibrium. As the outcome HbA1c could have been measured as early as three months after the patient's entry into the study (decline of insulin therapy), there may not have been sufficient time for the weight loss to manifest itself in HbA1c changes. On the other hand, catabolic weight loss due to insulin deficiency is a less likely explanation, as all patients in our study had type 2 diabetes.

Table 3
Reasons for discontinuation of non-insulin diabetes medications during follow-up.

	HbA1c decreased n = 12	HbA1c did not decrease n = 24	p-Value[a]
Initiation of insulin, no (%)	4 (33.3)	9 (37.5)	1.0
Deterioration of kidney function, no (%)	1 (8.3)	3 (12.5)	1.0
Side effects, no (%)	3 (25.0)	6 (25.0)	1.0
Initiation of chemotherapy, no (%)	1 (8.3)	0	0.33
Not specified, no (%)	3 (25.0)	6 (25.0)	1.0

[a] p-Values were calculated using Fisher's exact test.

Initiation of insulin therapy after the patient originally declined it also was not associated with improvement in blood glucose control. While this contrasts from published evidence that suggests that the addition of basal insulin to any non-insulin combination is a highly effective approach,[37] it is worth noting that our study included patients who were originally disinclined to take insulin. It would therefore not be unexpected if these individuals did not actually start insulin therapy when it was ultimately prescribed by their clinicians, or were only partially adherent to it. Even in general population of patients with T2DM non-adherence to diabetes medications reaches as high as 60% and many patients do not adhere to either oral or injectable treatment after the first six months of therapy.[34] It would therefore not be surpring if in our study population of individuals reluctant to initiate insulin therapy this number would be even higher. Non-adherence to insulin, in particular, could also be explained by its continuously rising costs, which create a substantial economic burden on patients with diabetes.[38]

A number of previous studies on decline of insulin therapy aimed to define the concept and causes of psychological insulin resistance from the perspective of patients with T2DM. This phenomenon can result from a variety of beliefs that include cognitive appraisal, emotional reactions, and supportive relational factors.[39,40] These studies have pointed out the need for adequate psychological insulin resistance measurement tools such as questionnaires,[41] and proper patient training to decrease decline of insulin therapy.[40] However, many of them did not include patients who actually declined insulin therapy (most asked patients who have not been treated with insulin to comment on a hypothetical scenario of insulin therapy recommendation). Furthermore, none of them studied patient outcomes after decline of insulin therapy.

As we are starting to gather systematic information about decline of insulin therapy by patients, it may seem intuitive that such decisions would inexorably lead to poor clinical outcomes. However, many patients who reject insulin therapy subsequently see an improvement of their glycemic control. The present study, for the first time, identifies patient and treatment characteristics that are associated with either increase or decrease in blood glucose levels following decline of insulin therapy by the patient. While some of these may in retrospect seem obvious (e.g. association of lifestyle changes with lower and non-adherence with higher blood glucose levels), others were less apparent (e.g. lack of association between eventual initiation of insulin and glycemic control). This study will therefore serve as one of the initial building blocks for an evidence-based approach to treatment of patients with type 2 diabetes who decline insulin therapy.

Our study had a number of strengths. It included a racially and socioeconomically diverse population receiving attention in primary care settings where most patients with diabetes in the United States are treated. The availability of comprehensive electronic medical record data over an extended period offered a unique viewpoint into a previously unexplored but apparently common phenomenon of the decline of insulin therapy by patients.

The present study leveraged these strengths to add to the existing literature a novel perspective on decline of insulin therapy by patients – analysis of its outcomes. For the first time, we were able to identify baseline patient characteristics and subsequent therapeutic actions that are associated with improved glycemic control after decline of insulin therapy recommendation by the patient. These findings could help guide clinicians to optimize a patient-centered approach to individuals who declined insulin therapy. Even when insulin therapy is the best recommended course of action, other alternative approaches may exist that will help the patient achieve blood glucose control; the findings of this study offer initial data on strategies that are more likely to be successful under these circumstances.

4.1. Limitations

The findings of this study should be interpreted in light of its limitations. As an observational analysis, it could only identify associations rather than causal relationships. Therefore the findings of the study may not be rigorous enough to definitively justify modifications of existing clinical practice. The study may not have been powered to detect the relationship between glycemic control and some of the variables, such as the initiation of non-insulin diabetes medications. While we incorporated multiple potential confounders in the multivariable analysis and also adjusted for clustering within individual providers, it is possible that some confounders were not included. Not matching the two study groups on baseline HbA1c levels may have introduced a bias because the same diabetes medications (added after the initial decline of insulin therapy by the patient) would have a greater glucose-lowering effect in patients with higher HbA1c. Potentially relevant information, such as the intensity of lifestyle changes or the magnitude of medication non-adherence, was not available for most study patients. Reporting bias could have affected some aspects of the analysis; for example, the relationship between HbA1c changes and lifestyle changes or medication non-adherence. Finally, this study was conducted in academically affiliated practices in eastern Massachusetts. Therefore, our findings may not be applicable to other settings.

4.2. Future directions

In view of the limitations discussed above, the initial findings provided by the present study need to be confirmed by subsequent research to provide more definitive guidance to clinicians and patients. These future investigations could take form of larger observational studies, patient and provider surveys or – ideally – interventional trials that could test the efficacy of different treatment methods after decline of insulin therapy recommendation by the patient on their glycemic control. Data presented in this study could help formulate the questions to be addressed by subsequent investigations and assist in their design.

5. Conclusion

Our results suggest that after declining of insulin therapy by patients, specific patient characteristics (e.g. baseline glucose levels) and therapeutic actions (e.g. lifestyle changes and treatment adherence) could lead to better glycemic control. These findings could help guide clinicians to optimize a patient-centered approach to individuals who declined insulin therapy in order to achieve glycemic targets. Further prospective interventional investigations are needed to establish the optimal treatment strategies and outline a provider-patient discussion approach that ensures that individuals make fully informed choices while optimizing clinical outcomes.

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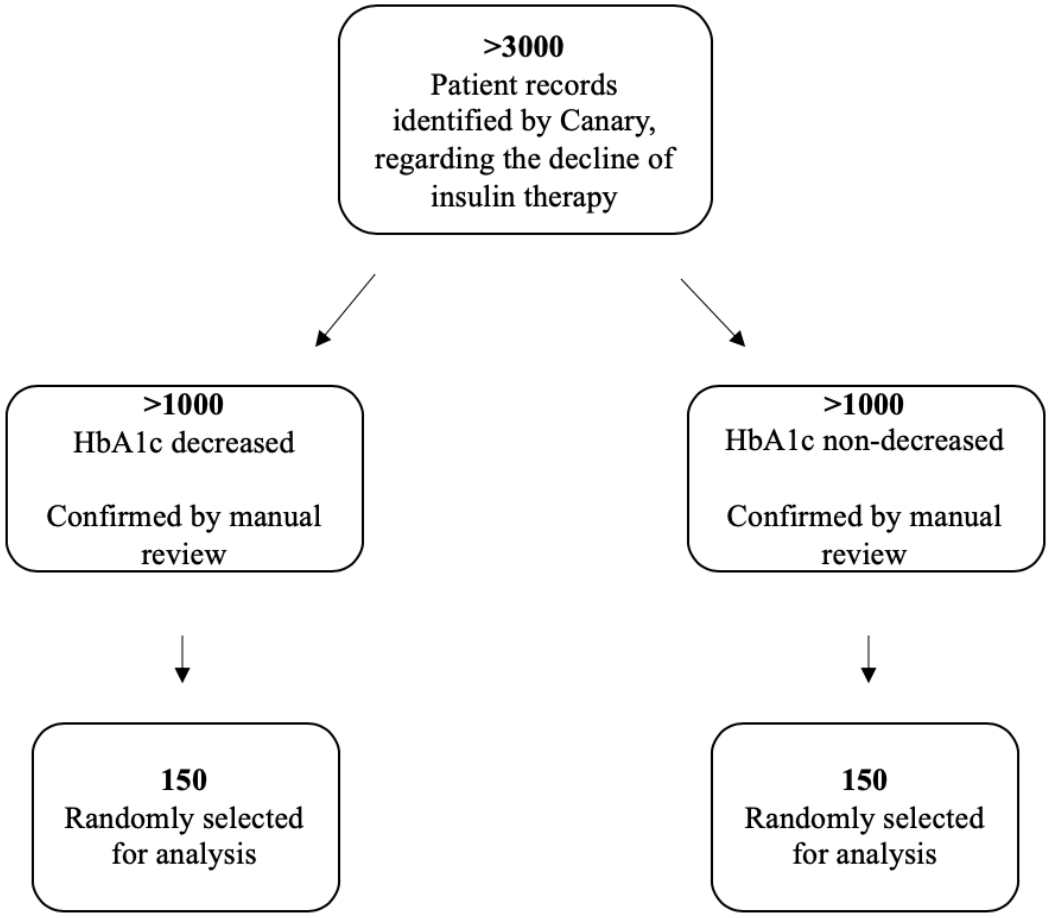
3.1. Appendix 1. Study Cohort Selection



Title: Effect of Control:Diabetes Mobile App on Blood Glucose Levels and Risk of Hypoglycemia in Patients with Diabetes

Authors: Luisa Florez MD, Saveli I. Goldberg PhD, Alexander Turchin MD, MS.

Author Affiliations:

Brigham and Women's Hospital, Boston, Massachusetts (Florez, Turchin)

Massachusetts General Hospital (Goldberg)

Harvard Medical School, Boston, Massachusetts (Florez, Turchin)

Corresponding Author:

Alexander Turchin, MD, MS

Division of Endocrinology, Brigham and Women's Hospital

221 Longwood Avenue, Boston, MA 02115

Email: aturchin@bwh.harvard.edu

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4.1. ABSTRACT

Aim

Digital applications could improve glycemic control in patients with type 1 and type 2 diabetes. We conducted this study to determine if the Control:Diabetes mobile app can reduce hyper- and / or hypoglycemia in patients with diabetes treated with insulin.

Methods

We conducted a pilot, single-arm non-blinded clinical trial of using Control:Diabetes app in adults with type 1 and type 2 diabetes mellitus who were using insulin and had poor glycemic control or/and high hypoglycemia frequency.

Results

Preliminary results from 10 patients who have continuously used the Control:Diabetes mobile app for at least 3 weeks showed that frequency of hypoglycemia decreased from 4.4% to 3.1% between the first week and the last week of using the Control:Diabetes app (p-value=0.26). There was no difference in the median blood glucose levels between the first and last week of using the app. Blood glucose prediction accuracy improved from the first week (median difference between forecast and the subsequent measurement = 44.5 mg/dL) to the last week (37.5) (p-value = 0.10).

Conclusion

In the preliminary results of a pilot study, using the Control:Diabetes mobile app was associated with a trend for reduction in frequency of hypoglycemic episodes that did not reach statistical significance, but no change in the overall blood glucose levels.

KEY WORDS: Type 1 Diabetes Mellitus, Type 2 Diabetes Mellitus, Insulin Therapy, Mobile Applications, Self-Management, Glycemic Control, Hypoglycemia.

4.2. INTRODUCTION

Diabetes is a common chronic illness that can lead to significant disability and premature death. Individuals with both type 1 and type 2 in the US have a substantial reduction in longevity,[1, 2] and their lives can be impaired by multiple complications. Over 30 million people have diabetes in the U.S,[3] and incidence of the disease has been increasing both in the U.S. and worldwide.[4] It is therefore important that treatment for this morbid and lethal disease be optimized.

When the disease is not controlled, patients with type 1 and type 2 diabetes face a constant state of hyperglycemia, which is associated with multiple acute and chronic complications, including blindness, kidney failure, amputations and cardiovascular events.[5, 6] On the other hand, when insulin therapy is required, always in type 1 diabetes and at some point, during the course of the disease in type 2 diabetes, hypoglycemia can become a common complication. The average patient suffers two episodes of mildly symptomatic hypoglycemia per week and one episode of severe (temporarily disabling) hypoglycemia per year.[7] Severe hypoglycemia can lead to injury and death;[8] it is estimated that 4 to 10% of all deaths in patients with type 1 diabetes are due to hypoglycemia.[9, 10]

While a number of preventative measures can be undertaken to decrease these risks, some, like changing basal insulins to the ones with a less pronounced peak concentration, have only a modest effect, and others, as continuous glucose monitoring systems, can be very expensive. Therefore, there is a strong need for an efficacious and cost-effective approach to reducing the

incidence of hyper- and hypoglycemia in patients with diabetes (both type 1 and type 2) who are treated with insulin.

Digital applications have many of the right ingredients for success in this area. Millions of people throughout the world now carry smartphones and some diabetes apps have been shown to be effective in improving glycemic control.[11-13] While a very large number of diabetes mobile apps exists, their utilization by patients remains limited. Less than 20% of patients with diabetes report using mobile apps to help take care of their condition, and many stops using the apps after trying them.[14] The existing diabetes apps offer a variety of standard functions, including documentation, communication, reminders and app-driven suggestions, but none endeavor to actively engage patients in taking control of their diabetes.[15, 16] In particular, no diabetes apps have been shown to reduce the risk of hypoglycemia. More innovative approaches to mobile health applications are therefore needed to further advance digital diabetes care and decrease the incidence of these medical conditions.

We created the Control:Diabetes mobile app to teach users how to treat their disease through repeated self-feedback by using two educational psychology techniques. Cognitive task analysis is a technique that disassembles complex cognitive tasks into smaller and simpler components that are easier to learn individually. It has been successfully used in a variety of fields, ranging from mine detection to intraoperative anesthesia.[17] However, it has not been used to train patients to manage their own chronic condition, such as diabetes. Operant conditioning is a technique that involves teaching a specific behavior by providing direct incentives.[18] This unique combination of fundamental educational methods represents a novel, patient-centered approach to diabetes

care that recognizes that empowering the individual with diabetes is the key to success in treatment of this complex disease that is not easily reduced to one-size-fits-all prescriptions from a time-starved clinician.

The app encourage patients to: a) predict their blood glucose level at a particular time point in the future (e.g. the next morning); then b) enter their actual blood glucose levels when that time (the next morning) comes; and c) enter reasons for the discrepancy between prediction and reality, if the prediction was significantly (e.g. > 20%) different from the actual measurement. We hypothesize that by repeatedly encouraging disassembly of blood glucose changes into individual reasons (cognitive task analysis) while providing an incentive in the form of being able to more accurately predict blood glucose levels (operant conditioning), the app will prompt the patient to learn how various internal and environmental factors affect their blood glucose. They will then be able to adjust their behavior and medications to improve their blood glucose control. We have therefore conducted this study aiming to test whether the Control:Diabetes mobile app impact their blood glucose levels and can reduce hyper- and / or hypoglycemia in patients with diabetes treated with insulin.

4.3. MATERIALS AND METHODS

4.3.1. Study design

We conducted a single arm open label clinical trial that to determine whether patients with diabetes mellitus treated with insulin, and elevated blood glucose and / or frequent hypoglycemia, will achieve better glycemic control and / or lower frequency of hypoglycemia, after using the Control:Diabetes mobile app.

4.3.2. Study Subjects

We studied adults with type 1 and type 2 diabetes, who used the Control:Diabetes mobile app. Participants were recruited between October 2019, and July 2020. We studied participants who used the mobile app for at least 3 weeks. Patients were included in the analysis if they fulfilled all of the following criteria: a) were at least 18 years old; b) diagnosed with either type 1 and type 2 diabetes; c) were treated with multiple daily insulin injections (MDII) or continuous subcutaneous insulin infusion (CSII); d) had HbA1c between 7% and 10.5% (as reported by the participant) and/or self-reported frequency of symptomatic hypoglycemia ≥ 3 times / week, and e) owned a smartphone running either Android or iOS operating system with an active data plan. Patients were excluded if they were using a closed loop insulin delivery system (e.g. Medtronic 670G or OpenAPS).

We recruited participants through advertisements on diabetes support groups using the Facebook social media platform. Individuals who completed the qualification survey and fulfilled the inclusion and exclusion criteria for the study were contacted by email by a member of the study team to schedule the initial telephone call. During this phone call each participant was asked to confirm their intent to join the study by giving verbal informed consent. Subjects who provided consent completed an additional phone survey, were guided through the installation of the Control:Diabetes app on their smartphone and were trained in using the app. All study subjects were enrolled by Partners investigators. There were no in-person visits. This study was approved by the Partners HealthCare institutional review board.

4.3.3. Study Measurements

All study subjects used the Control:Diabetes mobile app as *exposure* in this clinical trial. On a single screen the user was able to see the pattern of their predicted and actually measured blood glucose, treatment (entered by the user) and the reasons for discrepancy between the predicted and actual blood glucose (Figure 1). The app also includes a separate screen where the user can view reports allowing them to monitor their progress in accuracy of blood glucose level prediction.

The Control:Diabetes mobile app was first developed in 2018 by Dr. Alexander Turchin's study team. The first prototype included the same idea of predicting the blood glucose, adding the actual measurement and explaining the difference between them using the same psychology educational techniques (cognitive task analysis and operant conditioning).

The prototype was shared with several individuals with diabetes. In a survey-based evaluation of the app, patients reported that it was: a) easy to use (4/5); b) very helpful to learn how food, exercise, medication, etc. impact their blood sugar (5/5); c) very helpful to lower blood sugar (5/5); and d) helpful to decrease the incidence of low blood sugar (4/5); and that they were "very likely" (5/5) to continue using it for a longer period of time. Based on this feedback and on the study team experience with the prototype, a full specification for the initial version of the app has been developed by a software development company (First Line Software) that was contracted to build the app on both Android and iOS platforms in accordance with HIPAA security requirements.

The full version used in this clinical trial included all the prototype's educational techniques and basic functions, with some additions that included: a) actual measurement reminders at the time when the user previously predicted a blood glucose value, and b) point based rewards to encourage and engage the user into using the app. Before starting this clinical trial, the Control:Diabetes app was selected as one of the finalists in the Boston Scientific Connected Patient Challenge IV.

Non-identifiable data entered by the user through the app (predicted blood glucose values, measured blood glucose values, reasons for discrepancies between predictions and real measurements, medications) were securely transmitted to a central SQL Server database inside the Partners HealthCare firewall. Other medical history data obtained by either the qualification or the phone survey (including the number of hypoglycemic episodes during the previous two weeks, the last measured HbA1c, number or years diagnosed with either type 1 or type 2 diabetes, and presence of diabetes complications), and the identifiable data entered by the participants in the qualification survey (name, date of birth, telephone number, device ID, patient demographics, etc.) were saved in the Partners HealthCare REDCap database. Each installation of the app was assigned a unique ID that was used to anonymously track data entered through the same app installation. For study participants, this unique ID was linked to the identifiable information entered into the REDCap database.

As *co-primary outcomes* we compared both; a) the change in blood glucose (as recorded by the patient in the app) between the first week and the last week of the study; and b) the change

in the hypoglycemic frequency (blood glucose < 70 mg/dl) between the first week and the last week of the study (as recorded by the patient in the app).

We also conducted secondary analyses of the data recorded by the app to determine whether their predictions of blood glucose levels have become more accurate over the course of the study.

4.3.4. Statistical Analysis

Summary statistics were analyzed using measures of central tendency (means, standard deviations, and medians) for continuous variables and using frequencies and proportions for categorical variables. To compare the difference between the blood glucose levels at the first week and the last week of the study we used Wilcoxon rank test. Fisher exact test was used to compare the frequency of hypoglycemia between the first week and the last week of the study. To compare accuracy of the blood glucose level predictions between the first and the last week of the study we also used Wilcoxon test. All analyses were performed using SAS, version 9.4 (Cary, NC).

We based the sample size calculation on the number of subjects needed to detect a difference in blood glucose levels over the study period compared to baseline (i.e. each subject will serve as their own comparator) with at least a 10 mg/dL superiority margin. Assuming standard deviation of blood glucose change of 20 mg/dL and a true difference between the study-end and baseline blood glucose levels of 20 mg/dL, a sample size of 34 subjects achieves 80%

power to detect superiority using a one-sided t-test at the significance level of 0.025. Assuming a 50% dropout rate after the run-in period, we plan to enroll a total of 70 subjects into the study.

4.4. RESULTS

We have recruited 32 participants, ten of whom have continuously used the Control:Diabetes mobile app for at least 3 weeks (Figure 2). We have analyzed data from these 10 participants.

All of study participants were white females. Their mean age was 50 years. Most (80%) had type 1 diabetes and 20% had type 2 diabetes. Most (70%) used insulin pump and 30% used multiple daily insulin injections as primary treatment. All participant characteristics, including demographics, diabetes characteristics, treatment characteristics and comorbidities are shown in Table 1.

There was no difference between the median blood glucose during the first (149 mg/dL) and the last week (143 mg/dL) week of the study ($p = 0.35$). The frequency of hypoglycemia decreased from 4.4% to 3.1% between the first week and the last week of the study but did not reach statistical significance ($p = 0.26$). The median difference between blood glucose forecasts and the actual measurements during the last week (37.5 mg/dL) was lower than during the first week (44.5 mg/dL) but did not reach statistical significance ($p = 0.10$). (Table 2).

There were 12 participants who dropped out of the study and stopped using the app before 3 weeks. All of them were white, as the participants who completed the study. Four of the participants who dropped out (33.3%) were men and the rest (66.7%) were women. Their mean

age was 44.7 years. Most (83.3%) had type 1 diabetes and 16.7% had type 2 diabetes. Most (83.3%) used insulin pump and 16.7% used multiple daily insulin injections as primary treatment. There were no significant baseline differences from the studied population that could explain why they dropped out.

We analyzed the reasons for study dropout for the six participants who reported them. One of them could not add the reason for the discrepancy between the forecast and the actual measurement and therefore did not find usefulness in the predicting exercise. Two of the participants stated they forgot to use the app and would prefer the app to send more notifications and reminders. Finally, two other participants found the exercise to be a lot of work and would prefer their continuous glucose monitoring system to be able to save their numbers directly into the mobile app.

4.5. DISCUSSION

In this study, we found that patients with type 1 or type 2 diabetes who are in treatment with insulin may be able to reduce hypoglycemic frequency by using the Control:Diabetes mobile app. Individuals with more than 3 hypoglycemic episodes per week before entering the study, showed a reduction of hypoglycemic frequency between the first and the last week of the study, after using the app for 3 weeks. While the difference has not reached statistical significance, these preliminary results were underpowered to detect a difference of the observed magnitude (30% decrease in hypoglycemia). We also found participants may have improved their blood glucose prediction accuracy at the end of the study. These findings could be explained by an increasing awareness by the app users of their daily activities that could allow them to prevent

the excessive decreases of their blood glucose levels. This may have been achieved by the utilization of cognitive task analysis and operant conditioning that is facilitated by the app. In this way, the patients learn how their body reacts to various factors like food, exercise, medication, stress, etc., potentially allowing them to better control their blood glucose levels. This novel treatment approach based on the principles of educational psychology, if successful, could lay the foundation for an entirely new method of care of chronic illness.

There is a number of measures that can reduce the risk of hypoglycemia that are currently available to patients using insulin therapy and their healthcare providers. One is utilizing basal insulins with a less pronounced peak, such as glargine or degludec.[19-22] Another is using continuous glucose monitoring (CGM), including in conjunction with continuous subcutaneous insulin infusion (CSII).[23-25] Finally, relaxation of glycemic targets / reduction of intensity of anti-hyperglycemic treatment is a time-tested strategy. However, all of these approaches have their drawbacks. Using "peakless" basal insulins is more effective at reducing nocturnal than daytime hypoglycemia. Continuous glucose monitoring is expensive, especially when combined with CSII (insulin pumps), and therefore may not be available to everyone, especially as insurance deductibles in the U.S. continue to rise.[26-28] Increasing a patient's blood glucose levels trades short-term sequelae (hypoglycemia) for long-term ones (micro- and macrovascular complications). Consequently, effective and affordable methods for prevention of hypoglycemia are urgently needed.

Current standard of care of patients with diabetes has the healthcare provider making most or all of the treatment decisions. This process involves the provider collecting relevant information

from the patient and then issuing a recommendation to the patient on their medication, diet and exercise regimen. Typically, this only happens during face-to-face encounters between providers and patients, which are usually months apart due to the constraints on provider availability. In some care models communication may be remote (e.g. by video) and / or asynchronous (e.g. by email or fax). These models allow for more frequent communications but are not universally supported by payors. However, even in the best-case scenario, provider-patient communications are weeks to months apart, whereas the environmental factors that affect blood glucose levels can change hour-to-hour, and sometimes minute-to-minute. It is not and will never be feasible for a patient to contact their healthcare provider with that frequency. In order to truly optimize care of patients with diabetes it is necessary to have the patient make the tactical decisions about their medications, diet and exercise – a patient-centered approach uniquely enabled by the Control:Diabetes mobile app.

An interesting finding during the recruitment of this study is that 100% of patients who completed 3 weeks of continuously using the Control:Diabetes app were female. While there were four men who enrolled in the study, all of them stopped using the app before completing 3 weeks. In the United states, previous studies have shown that women are more likely to engage in diabetes self-management education (DSME) programs than men. Nevertheless, when included in these programs there has been no difference in glycemic control between males and females. DSME programs have shown improvement in clinical outcomes in the general population.[29] This opens the question on which kind of diabetes self-management education programs could be attractive to the male population in order to achieve better clinical outcomes in diabetes.

This analysis did not find a reduction in blood glucose after participants used the Control:Diabetes app for 3 weeks when comparing blood glucose measurements at the first and last week of the study. This could be explained by the fact that most of these patients were not only trying to achieve better glycemic targets by reducing their high blood glucose levels but also were trying to reduce hypoglycemic episodes associated with their treatment. Accomplishing an optimal glucose control is an uphill task that most people living with diabetes struggle to achieve, especially when diagnosed with type 1 diabetes, since most of the patients have to manage the competing risks of hyperglycemia and hypoglycemia.[30] It is important to remember that when trying to achieve appropriate glycemic targets, neither high or low levels of HbA1c are protecting factors of hypoglycemic frequency.[31] This sums to the hypothesis that even without achieving HbA1c targets, using the Control:Diabetes mobile app could decrease low blood sugar episodes.

Our study had a number of strengths. The use of online recruiting it's cost-effective and permits reaching a wide audience without having in person visits. We were able to recruit patients from different states of the Unites Stated and Canada. Not having in-person visits while the patient is actively engaging in the study and using the Control:Diabetes mobile app, portraits the reality on how patients interact with this self-management technology in terms of frequency of use and the changes made to achieve their targets.

The study leveraged these strengths to add to the existing self-management approaches a novel technology method for patients to actively engage in the therapeutic decisions regarding

their disease. The preliminary findings show that Control:Diabetes mobile app may be able to reduce frequency of hypoglycemia – an important complication of diabetes. These findings could help patients with type 1 and type 2 diabetes who are treated with insulin, to feel empowered and in control of their disease.

4.5.1. Limitations

The findings of this study should be interpreted in light of its limitations. As of this moment the study in not powered appropriately to show significant differences between blood glucose levels, hypoglycemic frequency and prediction accuracy at the first and last week of the study, for this particular population. The study would need additional recruitment time to achieve a higher number of participants that would continuously use the Control:Diabetes app for 3 weeks. Not having a control group arm may limit the interpretation of the results, since is difficult to prove causal relations with a single arm study and we cannot prove the changes between the first and last week of the study were made by the use of the Control:Diabetes mobile app and not by chance. The app does not have an explicit goal for participants to either lower their blood glucose or reduce hypoglycemia, and that may have limited their response to the app. Reducing high blood glucose levels could be a goal more commonly associated with patients with type 2 diabetes while reducing hypoglycemic frequency could be more commonly associated with type 1 diabetes. Recruiting both patients with type 1 and type 2 diabetes may have limited the impact that could be achieved by the app in each population. Some of the participants may not have been able to identify reasons for discrepancies between their blood glucose level forecasts and actual measurements on their own, and therefore would not benefit from the app. Finally, this study recruited participants within social media diabetes support

groups from the United States and Canada were 100% of the participants were white females. Therefore, our findings may not be applicable to other populations, including men.

4.5.2. Future Directions

In view of the limitations discussed above, the preliminary findings provided by the present study need to be confirmed by the final analysis when recruitment and follow-up is completed. Other subsequent research studies could provide more definitive guidance to clinicians and patients. These future investigations should form of larger clinical trials that could test the efficacy of the exposure to the Control:Diabetes mobile app in glycemic control and hypoglycemic frequency. Subsequent studies could be divided in different treatment goals, either improve glycemic control by decreasing hyperglycemia or by decreasing hypoglycemia episodes, and by recruiting either patients with type 2 diabetes or type 1 diabetes, respectively. Ideally a larger randomized interventional study could be performed, testing the difference in self-management technology between the Control:Diabetes app and other available mobile apps. A marketing study regarding the recruitment materials should be performed to understand what could be more attractive to the male population. Also, a survey to the men who started this clinical trial but not completed 3 weeks of continuous use, should be performed to understand how to engage men in this type of self-management technology. Data presented in this study could help formulate the questions to be addressed by subsequent investigations and assist in their design.

4.6. CONLUSION

Our results suggest that after using the Control:Diabetes mobile app for 3 weeks, participants may be able to improve their accuracy in blood glucose prediction and reduce frequency of hypoglycemic episodes. These findings could empower patients with type 1 or type 2 diabetes in treatment with insulin, to take control of their disease by reducing insulin treatment complications (hypoglycemia), using a cost-effective and interactive method. Further randomized interventional investigations are needed to establish if the Control:Diabetes mobile app is an optimal self-management method to improve glycemic control by reducing high blood glucose and an appropriate tool as a co-adjuvant in the treatment of type 1 and type 2 diabetes.

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None.

4.7. TABLES AND FIGURES

Figure 1. Control:Diabetes mobile app

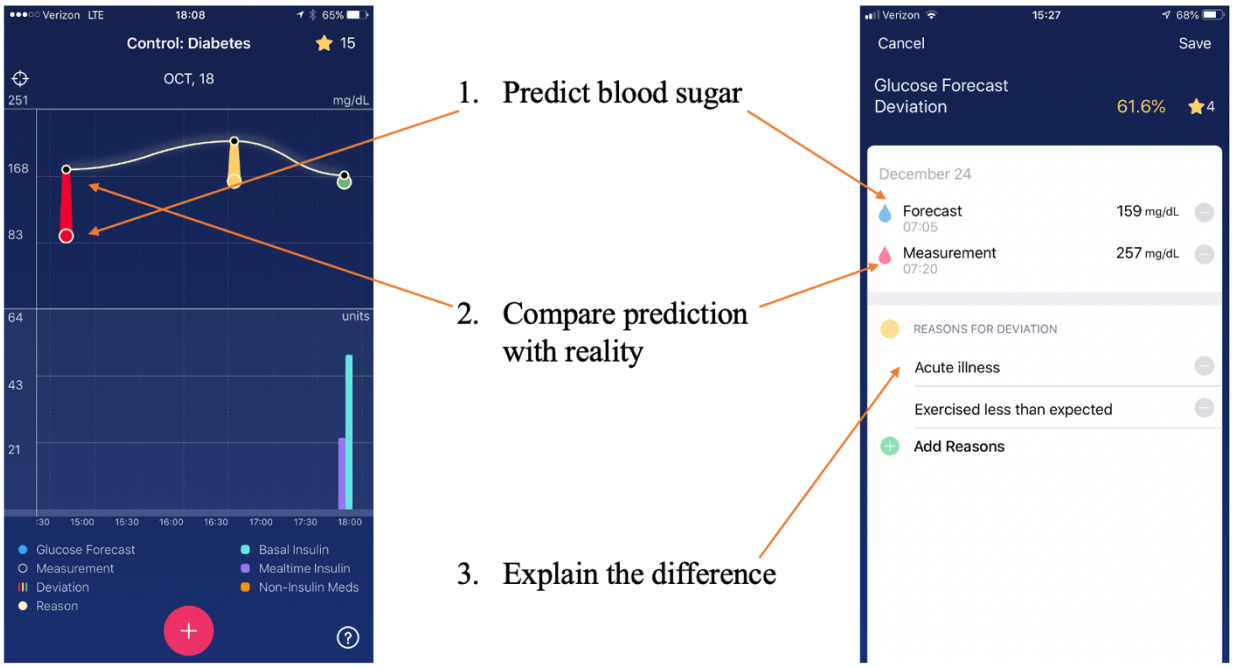

Figure 2. Recruitment

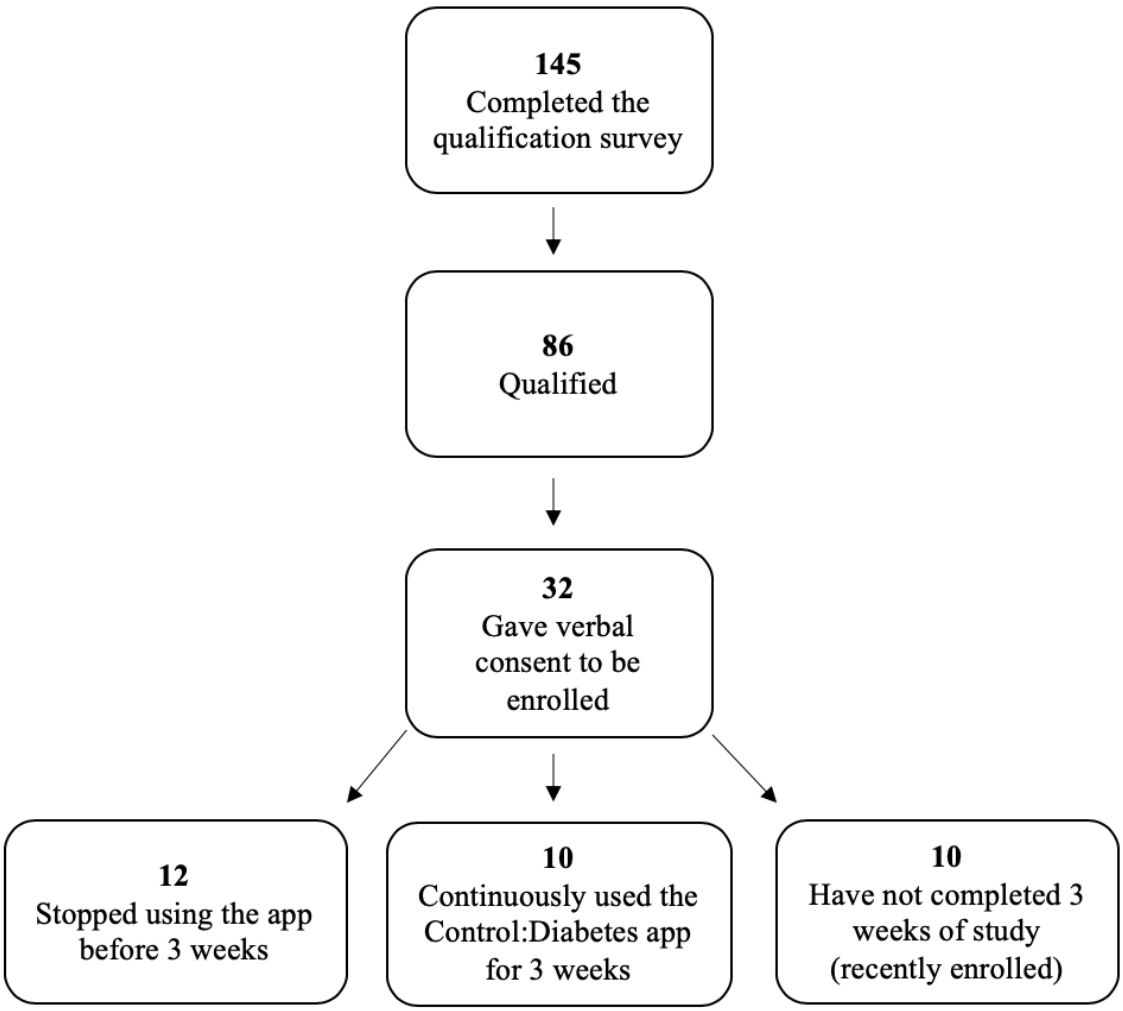

Table 1. Participant Characteristics

Variable	Study Participants
N	10
Demographics	
Age, mean (SD), y[a]	50 (9.3)
Female sex, No (%)	10 (100)
White race, No (%)	10 (100)
Country of residence	
United States, No (%)	9 (90)
Canada, No (%)	1(10)
Education	
Less than high school, No (%)	0
High school diploma, No (%)	0
Some college, No (%)	2 (20)
College degree, No (%)	4 (40)
Graduate degree, No (%)	4 (40)
Diabetes Characteristics	
Type 1 Diabetes, No (%)	8 (80)
Type 2 Diabetes, No (%)	2 (20)
Gestational Diabetes, No (%)	0
Years diagnosed, mean (SD)	25 (10.8)
Baseline HbA1c, mean (SD)	7.5 (1.3)
Hypoglycemia episodes 2 weeks prior, mean (SD)	3.4 (2.9)
Treatment Characteristics	
One daily insulin injection, No (%)	0
Multiple daily insulin Injections, No (%)	3 (30)
Insulin pump, No (%)	7 (70)
Comorbidities, No (%)	4 (40)
Retinopathy, No (%)	3 (30)
Neuropathy, No (%)	2 (20)
Nephropathy, No (%)	2 (20)
Hearth Attack, No (%)	2 (20)
Stroke, No (%)	0

Table 2. Difference between first and last week after using the Control:Diabetes mobile app (Wilcoxon Rank Test)

Variable	First study week	Last study week	p-value
Median blood glucose, gm/dL	149	143	0.35
Median difference between forecasted and actual blood glucose measurement, mg/dL	44.5	37.5	0.26

4.8. REFERENCES

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4.9. SUMMARY OF CONCLUSIONS

We conducted a retrospective observational analysis to determine patients' characteristics that could be predictive of glycemic control after declining insulin therapy when was first recommended by their physicians. Our results suggest that there are specific patient characteristics and therapeutic actions that could predict the clinical outcome of this population, by leading them to either, a better or a worse glycemic control.

Lifestyle changes was strongly associated with improving glycemic control. The effect of lifestyle counseling and behavioral changes on blood glucose levels is supported by both clinical trials and real-world evidence. Current guidelines recommend lifestyle management as a fundamental aspect of diabetes care, including diabetes self-management education and support (DSMES), medical nutrition therapy (MNT), physical activity, smoking cessation counseling, and psychosocial care.

Medication non-adherence and the discontinuation of non-insulin medication were associated with worsening glycemic control. Non-insulin diabetes medications were most commonly discontinued because they were being replaced with insulin or due to side effects, most commonly due to worsening of their renal function, which could have contributed to the poor glycemic control of the HbA1c non- decreased group. The causal relationship between the discontinuation of non-insulin diabetes medications and glycemic deterioration could have been bi-directional. Also, non-adherence to diabetes therapy was identified as a significant contributor to poor blood glucose lowering effect in this study as it is a well-established factor associated with suboptimal glycemic control by current guidelines.

These findings could help guide clinicians to optimize a patient-centered approach to individuals who declined insulin therapy in order to achieve glycemic targets.

Then we initiated a single arm clinical trial to test whether patients with diabetes on insulin treatment could reduce hyper- and / or hypoglycemia after using the Control:Diabetes mobile app for 3 weeks, by reducing blood glucose levels and hypoglycemia frequency. Our preliminary results suggest that after 3 weeks of using the Control:Diabetes mobile, participants may be able to reduce frequency of hypoglycemic episodes by also improving their accuracy in blood glucose prediction.

The study findings are explained by the utilization of the educational psychology strategies facilitated by the app, including cognitive task analysis and operant conditioning. The repeated self-feedback teaches users to adjust their daily activities and allows them to prevent the excessive decreases of their blood glucose levels. The Control:Diabetes mobile app users learn how food, exercise, medications, stress, illness, and other factors could impact their blood glucose levels and how much when multiple factors are present.

These findings could empower patients with type 1 or type 2 diabetes in treatment with insulin, to take control of their disease using a cost-effective and interactive method. The study leveraged these results to add a novel technology method for patients to actively engage in the therapeutic decisions regarding their disease.

4.10. DISCUSSION AND PERSPECTIVES

Results from both projects suggest that lifestyle self-management should be always included as part of the therapeutic approach in patients with Diabetes Mellitus. Current guidelines recommend diabetes self-management education and support (DSMES) as a fundamental aspect of diabetes care. DSMES approaches could improve glycemic control and reduce complications even after severe progression of the disease, as suggested by both research projects.

Specific cost-effective self-management strategies that are also compelling to the patient are not usually available. To optimize care of patients with diabetes it is necessary to empower the patient to make the tactical decisions about their medications, diet and exercise on a daily basis.

In patients with type 2 diabetes who decline their physician recommendation of initiating insulin therapy, further prospective interventional investigations are needed to establish the optimal treatment strategies and outline a provider-patient discussion approach that ensures that these individuals make fully informed choices while optimizing clinical outcomes.

In both patients with type 1 and type 2 diabetes who are currently in treatment with insulin, further randomized interventional investigations are needed to establish if the Control:Diabetes mobile app is an optimal self-management method to improve glycemic control by reducing high blood glucose and hypoglycemic frequency, and an appropriate tool as a co-adjuvant in the treatment of their disease.