

Impact of nutritional-CBT delivered by a mobile application in adults with type 2 diabetes

Nicole L. Guthrie, MS | Kevin J. Appelbaum, BSE | Martha L. Simmons, MD, PhD | Prapti Mehta, MD
David Rodbard, MD | David L. Katz, MD, MPH | Mark A. Berman, MD

Introduction

Despite advances in pharmacological treatment, half of U.S. patients with type 2 diabetes are not achieving glycemic control [1]. Even when adequate glycemic control is achieved via pharmacotherapy, a substantial residual risk to all-cause mortality still exists [2]. The behavioral determinants of type 2 diabetes, which remain largely unaddressed by usual medical treatment, are a significant contributor to both poor glycemic control and mortality risk [3,4].

The role of behaviors, including dietary pattern and exercise, in the development and progression of type 2 diabetes and other cardiometabolic conditions is well established [5,6]. These behavioral determinants are resistant to change because they are created and reinforced by strong social norms and culturally-held ideas. The use of behavioral therapy to directly target these behaviors is a fundamental aspect of diabetes care, but our health system is not organized to provide comprehensive behavioral therapy at the scale needed. While clinical guidelines consistently recommend healthcare providers facilitate behavioral changes, they often do not have the ability to provide or prescribe effective behavioral therapy to their patients [7,8].

Digital therapeutics (software designed for the treatment, prevention, or mitigation of disease) enable the delivery of behavioral therapy at scale to fill this critical gap in care. To be widely adopted, we believe an effective digital therapeutic needs to be prescribable by healthcare providers and reimbursed by payors like a traditional medication. This allows a digital therapeutic to leverage and bolster the trust established in a patient-provider relationship and to provide actionable data back to both provider and patient that advances care.

Nutritional Cognitive Behavioral Therapy

What is it and how can it be delivered digitally?

Nutritional Cognitive Behavioral Therapy (nutritional-CBT) is a novel form of behavioral therapy under development by Better Therapeutics for patients with type 2 diabetes and other cardiometabolic diseases. Nutritional-CBT is an adaptation of CBT that is designed specifically to address the cognitive patterns and mental structures that drive dietary patterns and associated lifestyle behaviors.

CBT is a treatment paradigm originally developed for the management of psychiatric conditions such as anxiety and obsessive-compulsive disorder. Traditional CBT aims to correct maladaptive behaviors (behavioral responses to a situation that are either non-productive or have adverse effects) by identifying and changing the core beliefs that produced them. It has since been successfully applied to a wide range of chronic conditions, including cardiometabolic diseases, and has been observed to be generally well-tolerated and to provide durable treatment effects, either alone or in combination with other therapies [9–12]. In current practice, CBT represents a family of therapies that have evolved over several decades and include modalities such as acceptance and commitment therapy, dialectical behavior therapy, and mindfulness-based cognitive therapy [13].

Nutritional-CBT builds on traditional CBT by systematically targeting the cognitive structures, behavioral routines, emotional patterns and coping skills that underlie culturally-specific eating behaviors. The content and delivery mechanisms of our nutritional-CBT were developed internally from first principles, leveraging experience from clinician- and health coach-patient interactions to distill common maladaptive thinking and beliefs pertaining to diet and lifestyle. It is designed as a digitally-delivered therapy so that it can be widely-disseminated to large patient populations, yet personalized to the individual patient using AI-driven feedback loops.

Measuring Impact

Over the past four years, we have been developing behavioral therapy through a software-based digital therapeutic (an “app”) paired with human support. Human support has consisted of remote health coaching delivered telephonically and care escalation to nurses and physicians, as needed. We studied the effectiveness of this program to improve glycemic control in a non-blinded, single-arm interventional study in 97 adults with type 2 diabetes. After 3 months, a mean improvement in hemoglobin A1c (HbA1c) of 1% (SD 1.4) was observed in participants with baseline HbA1c >7%. A full description of this study can be found in a peer reviewed article published in [JMIR Diabetes](#) [14].

Most recently, we translated the learnings gained from the use of the app with human support into a software-only app configuration delivering nutritional-CBT. Our hypothesis was that this software-only configuration would improve glycemic control but likely to a lower degree than a human + software configuration.

Did digitally-delivered nutritional-CBT impact glycemic control?

To determine whether nutritional-CBT could improve glycemic control in patients with type 2 diabetes, we examined data from participants who used a software-only version of the digital therapeutic (the “app”). Participants were recruited online between September and November of 2019 for usability testing of the app and to provide feedback on content through online surveys. Interested individuals self-identified as having a diagnosis of type 2 diabetes of any duration, a blood glucose meter at home and a smartphone. We included in our analysis participants with a baseline 3-day average fasting blood glucose (FBG) > 152 mg/dL; a value corresponding to an hemoglobin HbA1c >7% [5]. 74 adult participants were identified for inclusion. As part of typical use over 90 days, participants were encouraged to self-monitor their fasting blood glucose daily with a home glucometer and to enter those values directly into the app. In addition to interactive nutritional-CBT content, weekly goal-setting was used to guide participants in replacing highly-processed foods with whole foods, and steadily increase the proportion of meals coming mostly from plants. Within the app, this is called eating more “plant-based meals.” A summary of the results were published in the [Journal of the Endocrine Society](#).

Number of participants	74
Age, years, mean (SD)	55.2 (7.0)
Body Mass Index, kg/m ² , mean (SD)	34.7 (7.9)
Glycemic medications reported, count, mean (SD)	2.2 (0.9)
Fasting blood glucose, 3-day average, mg/dL, mean (SD)	199.4 (45.1)
Estimated HbA1c, %, mean (SD)	8.7% (2.0)
Time since diabetes diagnosis, years, mean (SD)	10.6 (7.1)
Gender, % female (n)	72% (53)
Geographic location, U.S. states represented, count	32

Table 1: Participant Baseline Characteristics

We examined the change in self-reported FBG by looking at the difference between 3-day averages anchored by the first and last values reported. To examine whether participants who were not tracking FBG might negatively impact population outcomes, we performed an intent-to-treat (ITT) analysis by assuming no change in FBG for those who did not track after reporting a baseline.

Mean change in FBG was -22.9 mg/dl (SD 42.0) over an average of 69 days (SD 30.0), which corresponds to an estimated HbA1c change of -1%.

Participant Sub-group	Fasting Blood Glucose, mean (SD)			
	n	Baseline Average	Last Average	Change
All	74	199.4 (45.1)	176.5 (49.8)	-22.9 (42.0)*
Stable glycemic medications	65	197.7 (43.8)	176.0 (49.2)	-21.7 (40.2)*
Baseline HbA1c 7-11%	65	187.4 (32.6)	168.4 (45.1)	-19.0 (40.1)*

* Paired t-test comparing baseline average to most recent average, $p < 0.001$

Table 2: Changes in Fasting Blood Glucose

The digital therapeutic was used in a real-world setting while participants continued usual medical care. Participants were free to change medications as directed by their physician and were encouraged to adhere to prescribed medications and report any changes within the app. The impact of changes to glycemic medications while using the app was examined. At baseline, 93% (69/74) of participants reported using anti-hyperglycemic medications. Over the 90-days observed, 9 of the 69 participants reported a change (dose or count of meds); 2 reported a decrease and 7 an increase. Exclusion of these 9 participants from the analysis did not have a meaningful effect on the mean improvements in FBG observed.

To examine whether outliers might overly influence outcomes and to align with the inclusion criteria for an upcoming randomized controlled trial, we examined the mean change in FBG in participants with an estimated baseline HbA1c between 7 and 11%. In these 65 participants, the mean change in FBG was -19.0 mg/dL over a mean of 71 days (SD 27). Using their ending 3-day FBG average, 43% (28/65) of participants in this subset were now at goal (FBG < 152 mg/dL, estimated HbA1c < 7%), and 19% (12/65) met a much more aggressive goal for glycemic control (FBG < 130 mg/dL, estimated HbA1c < 6.5%).

What is driving the improvements seen in glycemic control?

The relationships between improvements in glycemic control and use of key nutritional-CBT features (therapy lessons, skills, and weekly goal setting) and self-reported diet and exercise behaviors were explored. Counts were summed for each participant and changes in FBG were examined for thirds of the entire population, from lowest to highest (tertiles) of feature or behavior type. In regression models, we controlled for baseline average FBG, years since diagnosis of diabetes and the duration of observation (the length of time between first and last value reported).

Of all variables explored, the use of nutritional-CBT content and the number of plant-based meals tracked demonstrated the strongest dose responses with improvements in FBG (Figures 1 & 2). In addition, a significant positive correlation was found between the use of the nutritional-CBT and change in dietary pattern ($p < 0.05$ using linear regression).

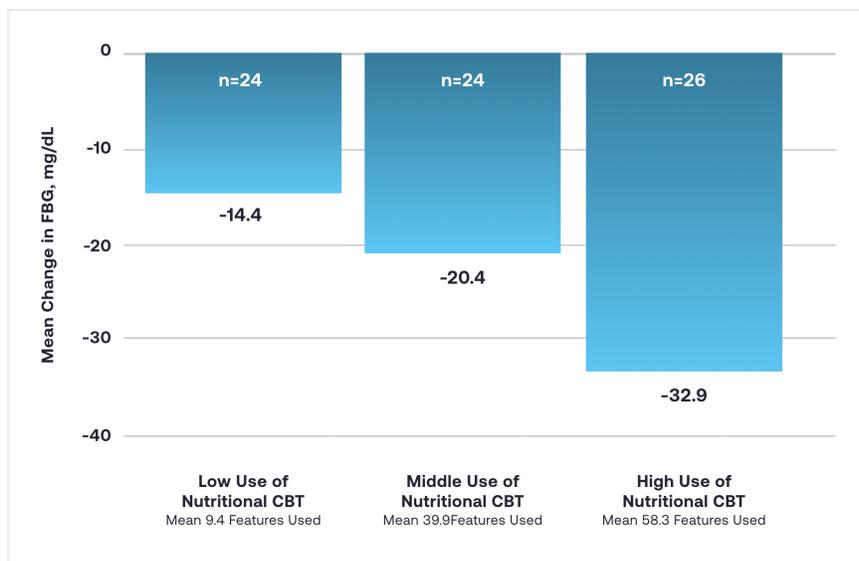


Figure 1: Fasting Blood Glucose Changes by Tertile of Nutritional-CBT Use

Mean sum of nutritional-CBT actions completed for tertiles low to high were 9.4, 29.9 and 58.3. Pairwise comparison of the least square means controlling for baseline FBG, years since diagnosis and duration of FBG tracking was used to compare FBG across tertiles: low vs high tertile $p=0.06$, middle vs high tertile $p=0.04$.



Figure 2: Fasting Blood Glucose Changes by Tertile of Plant-Based Meals Reported

Mean sum of plant-based meals reported for tertiles low to high were 17, 56 and 128. Pairwise comparison of the least square means controlling for baseline FBG, years since diagnosis and duration FBG tracked was used to compare FBG across tertiles: low vs high tertile $p=0.18$, middle vs high tertile $p=0.46$.

We observed a trend between increased minutes of exercise reported and improvements in FBG but the dose-response pattern was not as clear as seen with nutritional-CBT and changes in diet (Figure 3).

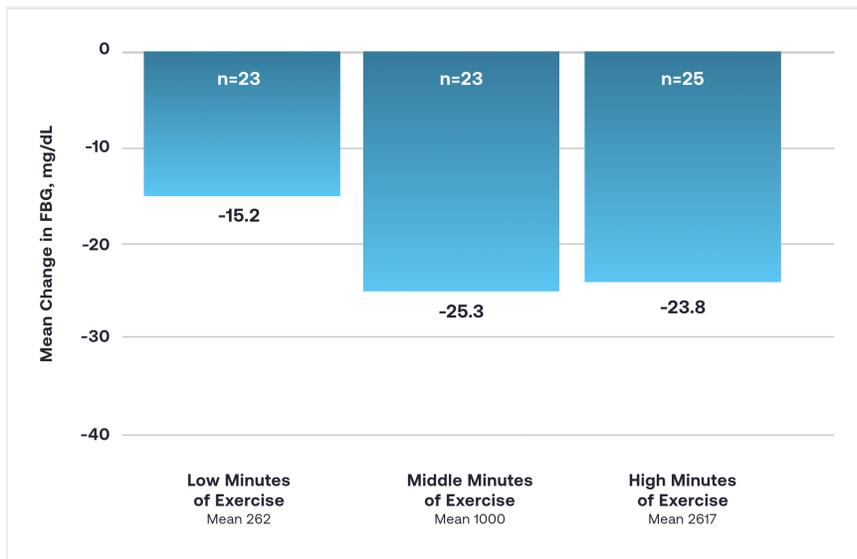


Figure 3: Change in FBG by Tertile of Minutes of Exercise

Mean minutes of total exercise over the 90 days reported for tertiles low to high were 262, 1,000 and 2,617. Pairwise comparison of the least square means controlling for baseline FBG, minutes of exercise in week 1, years since diagnosis and duration FBG tracked was used to compare FBG across tertiles: low vs high tertile $p=0.08$, middle vs high tertile $p=0.48$.

Weight loss can also lead to large improvements in glycemic control if participants lose 5-7% of body weight. We explored whether changes in weight were associated with improvements in glycemic control. An average weight loss of 1.7% (SD 2.2) over a mean of 61 days was found between 3-day averages for baseline and last weight values reported. In a linear regression model, percent weight loss was significantly correlated with improvements in FBG ($p=0.01$). A tertile analysis of nutritional-CBT use and changes in weight revealed that higher use was associated with larger improvements in weight (Figure 4). While more weight loss was achieved by those who made more use of nutritional-CBT, the degree of weight loss observed suggests that weight loss may not have been the major driver of glycemic changes.

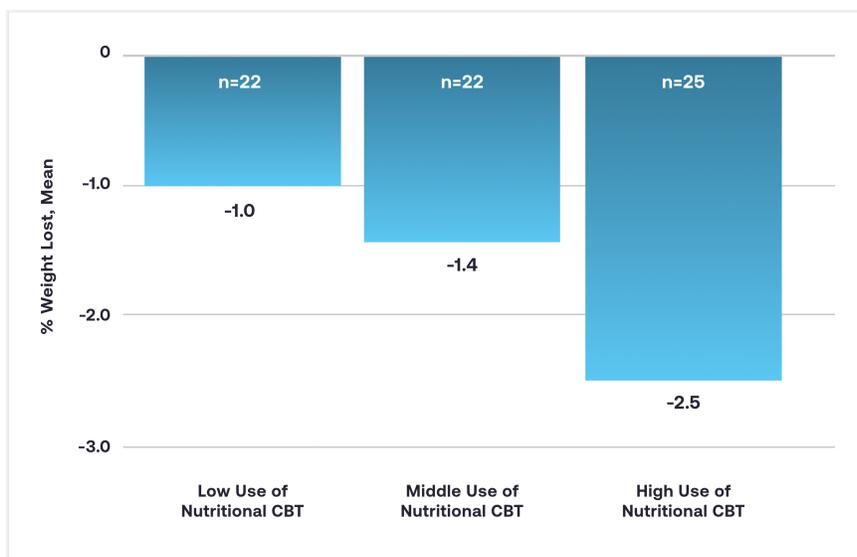


Figure 4: Percent Weight Loss by Tertile of Nutritional-CBT Use

Pairwise comparison of the least square means controlling for baseline FBG, years since diagnosis and duration FBG tracked was used to compare FBG across tertiles: low vs high tertile $p=0.02$, middle vs high tertile $p=0.09$.

Engagement

How much did participants use the app?

Usage data were examined to understand patterns of engagement, including frequency of use, time spent in each session of use and the duration of engagement. On average, participants used the app 4.5 days a week and spent 5 minutes in the app each day they used it. The duration of engagement was determined by the interval from the first day of use to the last day a participant either completed a nutritional-CBT task or entered a biometric value. 72% of the participants engaged with the program for 10 weeks or longer.

What did participants think about the app?

Participants were sent an online survey 10 weeks after starting their use of the app and 51% (38/74) completed the survey. The survey included questions about their experience using the app and the standardized Net Promoter Score (NPS) question - "How likely are you to recommend Better to a friend or family member with diabetes?" The calculated NPS was 58. A score of 0 to 30 is considered 'good', 30 to 70 is 'great' and over 70 is 'excellent'. The average score for the healthcare industry in a recent report was 27 [15].

Overall participant opinions were positive in response to questions about ease of use, relevance of content, and ability to meet or exceed expectations (Figure 5).

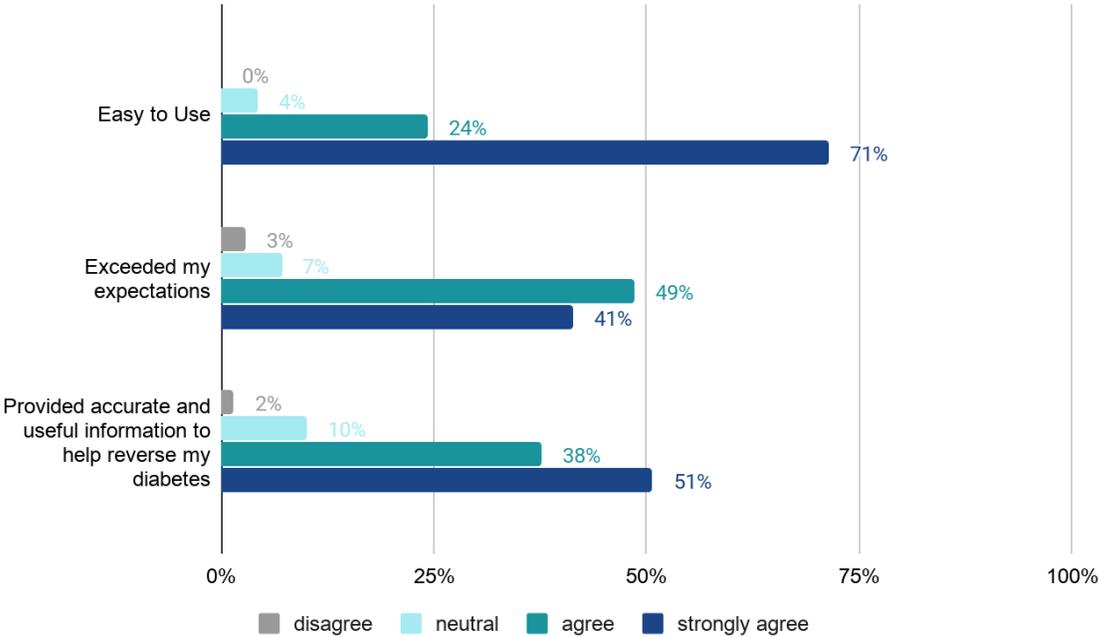


Figure 5: Participant Opinions of the App from Week 12 Survey

Discussion

Our digital therapeutic delivering nutritional-CBT resulted in clinically meaningful improvement in glycemic control [16,17]. The mean decrease in FBG of -22.9 mg/dL corresponds to approximately a 1% reduction in HbA1c. An HbA1c reduction of 1% has been associated with a 21% decrease in diabetes related mortality and a 40% reduction in microvascular complications in the UK Prospective Diabetes Study with long-term followup [18]. We believe this indicates that our software-only digital therapeutic offers potential as a standalone treatment and is ready for further study in a pivotal trial.

We have observed a significant dose response between the degree of engagement in nutritional-CBT and improvements in glycemic control among adults with type 2 diabetes. This is encouraging because it indicates that digitally-delivered behavioral therapy using only software has the potential to treat disease at scale.

Reductions in blood glucose were more significant and occurred faster than we had expected. Our investigational treatment is designed to allow patients to make behavioral changes at a gradual pace. In this context, blood sugar control was achieved more rapidly than expected, with 38% of participants achieving a fasting blood glucose level less than 152 mg/dL (corresponding to an HbA1c < 7%, which is commonly regarded as the goal for HbA1c for most patients with type 2 diabetes) and 16% achieving a fasting blood glucose less than 130 mg/dL (corresponding, on average to an HbA1c < 6.5%, a much more aggressive goal for HbA1c) after an average of 69 days. We hypothesize that longer duration of use may result in even greater improvements and plan to study this hypothesis in a randomized controlled trial.

Improvements in blood glucose occurred in participants from across the country and with long standing diabetes. While it is commonly assumed that only newly diagnosed patients will benefit from behavioral therapy, we were encouraged to see a strong efficacy signal in patients who were on average diagnosed with diabetes more than 10 years ago. We had excellent geographic diversity with participants from 32 states, including those with increasing prevalence of diabetes (e.g., Florida, Indiana and North Carolina) [19].

How is this work relevant in light of the COVID-19 pandemic?

We are now in the midst of a crisis placing exceptional demands on the healthcare system to respond to the spread of this disease, and calls for every American to do their part in flattening the curve, so that the system is not overwhelmed. According to the Centers for Disease Control (CDC), older individuals, especially those with diabetes and heart disease, are at higher risk of serious complications from COVID-19 [20].

Validated digital therapeutics can play an important role by being rapidly deployed into large populations to improve health, remotely monitor disease biometrics and self-reported symptoms,

and escalate care as needed for triage and medical direction. This may be an effective way to protect the most vulnerable high-risk patients and keep them out of hospitals, emergency rooms and primary care clinics, alleviating burden on the system and associated costs.

As healthcare resources become severely stressed in the months ahead, it will be especially important to develop remote means to support and improve the health of patients with diabetes and other cardiometabolic conditions. This work highlights the potential for using digital therapeutics, once validated, to advance the care of these patients without increasing demand on the health system.

What are the limitations?

The main limitations of this analysis are the lack of a control group and the reliance on self-reported values. A randomized and controlled trial is needed to more definitively evaluate efficacy and safety.

What are the next steps?

A 6-month randomized controlled trial will be conducted to assess the safety and efficacy of the digital therapeutic in addition to standard of care, compared to standard of care alone, in adults with type 2 diabetes. Data from the study will form the basis of our premarket submission to the US Food and Drug Administration (FDA). Concurrent with this research, we will be piloting our nutritional-CBT in a broad set of cardiometabolic diseases, such as hypertension, hypercholesterolemia and non-alcoholic steatohepatitis.

Conclusion

Data from pilot studies in participants with type 2 diabetes provides support for a pivotal clinical trial and represents a significant step forward on our path to create prescription digital therapeutics.

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