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Use of Continuous Glucose Monitors in Type-1 Diabetes: An Analysis of Wave Form Versus Glycemic Values in the Improvement of Glucose Control and Fear of Hypoglycemia

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USE OF CONTINUOUS GLUCOSE MONITORS IN TYPE-1 DIABETES: AN ANALYSIS OF WAVEFORM VERSUS GLYCEMIC VALUES IN THE IMPROVEMENT OF GLUCOSE CONTROL AND FEAR OF HYPOGLYCEMIA

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ABSTRACT

USE OF CONTINUOUS GLUCOSE MONITORS IN TYPE-1 DIABETES: AN ANALYSIS OF WAVEFORM VERSUS GLYCEMIC VALUES IN THE IMPROVEMENT OF GLUCOSE CONTROL AND FEAR OF HYPOGLYCEMIA

by

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Type-1 diabetes is a disease of subtle complexities. Patients struggle to understand glucose patterns and their responses to insulin or food intake while maintaining hectic lifestyles. Minor misjudgments in treatments can result in disastrous consequences with significant hypo- or hyperglycemic excursions.

Despite improvements in technologies available for diabetes management including home monitoring of blood glucose, more predictable insulin therapies, and improved insulin delivery via insulin pump, the average HbA_{1c} has remained relatively unchanged. Poor diabetes control is recognized as contributing to long-term diabetes comorbidities including neuropathy, nephropathy, retinopathy, and micro- and macrovascular disease.

Real-time continuous glucose monitors, such as the Dexcom SEVEN PLUS™, offer a tool with potential to improve glucose pattern management. Their integrated alerts

for high and low glucose levels offer an early warning system in the prevention of glucose excursions. While these systems have been available since 2006, adoption into practice has been slow. There is little understanding of how they impact a person's glucose variability and fear of hypoglycemia.

This pilot study used a quasi-experimental design to assess reductions in HbA_{1c} and standard deviations of glucose variability across a 12-week randomized clinical trial. Secondary endpoints included an assessment of change in the level of fear of hypoglycemia, as measured by the Fear of Hypoglycemia Survey tool, and changes in Quality of Life measures, using the Ferrans' and Powers' Quality of Life in Diabetes tool. An open-ended question was conducted on the final visit to elicit the patient's perception of real-time continuous glucose monitors (rt-CGM).

Subjects for this trial were persons with Type-1 diabetes, naïve to rt-CGM. They were randomly assigned to either the control group with unmodified Dexcom SEVEN PLUS™ devices or rt-CGM devices which had been modified to obscure the glucose value but otherwise functioned normally. Subjects were followed through a 12 week trial with data downloads of their rt-CGM performed monthly, and HbA_{1c} testing conducted at enrollment and termination of the study. Findings indicated a reduction in HbA_{1c}, average glucose, and standard deviation of the glucose in both the control and the experimental groups. Fear of Hypoglycemia and Quality of Life indicators demonstrated similar improvements.

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To my father Dr. Charles E. Walker, you have always been a quiet guide to me, even when you thought I was not listening. Your continued support and belief in me throughout your own struggles has been overwhelming.

Finally I must acknowledge the unwavering support of my best friend and wife, Linda. We have faced many challenges together, including school – more than once! I would not be where and who I am today without you.

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INTRODUCTION

Diabetes Mellitus (DM) is a milieu of diseases frequently lumped together. Traditionally it has been categorized into two main diagnoses: Type-1 DM, which is characterized by insulinopenia and is ketosis-prone if not treated adequately with insulin replacement therapies, and Type-2 DM, which is traditionally adult-onset, characterized by physiologic insulin resistance, excessive hepatic glucose output, and dwindling but present insulin production (American Association of Clinical Endocrinologists, 2007). The prevalence of Type-2 DM is growing dramatically in the general population, in direct correlation with increasing obesity rates, while the incidence of Type-1 DM remains relatively stable (American Diabetes Association, 2010; AACE, 2007). Despite the increased incidence of Type-2 DM, there are currently no medical therapies that have been shown to extend the functional life of the insulin secreting beta-cell; therefore, Type-2 DM will eventually result in insulinopenia (Beaser, 2010). This study focuses on those individuals with Type-1 DM who require insulin therapies to maintain glucose control.

Prior to development of insulin therapies in 1922, diabetes was a terminal illness for those afflicted. Despite aggressive study into the disease and an understanding that there was a deficient "carbohydrate co-factor" (Joslin, 1916), there were no effective therapies. Forward thinking physicians recognized early that to survive DM, the patient must be actively involved (Joslin). Additionally, nursing was recognized as contributing

uniquely to the care of patients with DM and that hospitalization and physician interventions were frequently detrimental for the patient (Joslin).

The complexity in the therapies available for care of people with Type-1 diabetes has been increasing since the identification and production of insulin by Drs. Banting, Best, MacLeod and Collip in 1921. Recent developments, including insulin analogues in the 1990s and 2000s, have greatly improved care (Yki-Jarvinen, Dressler, & Ziemen, 2000; Ferguson, Strachan, Janes, & Frier, 2001), providing more stable and predictable insulin therapies than were previously available. Despite dramatic pharmacologic advances and improved understandings of glucose management, most patients still struggle with glucose control.

In the 1980s home glucose monitoring began to be widely available. This was initially met with concern on the part of physicians, who felt this could complicate diabetes care for patients, but was rapidly recognized as a valuable tool to improve control (Tattersall, 1979; Ikeda et al., 1978). In the ensuing decades, home testing of blood glucose, along with improved understanding of meal matching and carbohydrate counting, has improved the efficacy with which patients are able to self-manage their diabetes. Current standards of care recognize the value of Diabetes Self-Management Training (DSMT) and the need for patients to actively adjust their therapies to improve their glucose control (AACE, 2007; AADE 2010).

There are approximately 1.2 million people with Type-1 DM in the United States (Centers for Disease Control, 2011). Technologies for diabetes management have evolved dramatically over the last 20 years. Among these new technologies are insulin

pumps capable of delivering 0.025 unit increments of insulin (approximately 1/40th of 1 unit); they are capable of supporting multiple basal insulin patterns, and offer feedback and suggestions to improve insulin dosing and glucose control (Alsaleh, Smith, Keady & Taylor, 2010). Despite these advances, the majority of people with Type-1 DM manage their disease with multiple daily injections (MDI) and home fingerstick glucose testing, also referred to as self-monitored blood glucose (SMBG). As understandings of glucose fluctuations improved, it became apparent that while Self-Monitored Blood Glucose (SMBG) was helpful, it provided inadequate information regarding the normal variations of glucose levels.

In 1967 the journal Nature published an article discussing the phenomenon of measuring glucose concentrations by voltage changes across a membrane impregnated with glucosoxidase (Updike & Hicks, 1967). The article discussed the possibility of an implanted sensor, based on this conceptual model, which would measure glucose levels on a continuous basis. The concept of continuously available glucose level readings became the subject of great anticipation in diabetes care. Regrettably, it has taken 40 years for this concept to be realized.

In early 2000 Medtronic released a retrospective continuous glucose monitoring (r-CGM) system that allowed patients to wear a wire-connected biosensor that would record their glucose patterns retrospectively for 72 hours. The device was entirely blinded to patients and they had no idea what or even if the device was recording. Following the 72-hour period the patient would return to the clinic, the r-CGM device would be

downloaded and the data made available for the clinician's use in adjusting the patient's therapies (Currie, Poole, & Papo, 2009).

Retrospective sensing technology had several inherent weaknesses. First, the sensors would fail and the patient would be unaware it was not recording. Second, the patterns were reviewed only retrospectively, precluding any real-time adjustments to diabetes interventions. Third, the systems were not capable of providing a warning in the event of hypoglycemia, which has regrettably resulted in failure to potentially identify and avert documented fatalities (Tanenberg, Newton, & Drake, 2010). Finally, it was a cumbersome unit connected to the patient by a wire that was not waterproof, creating a significant lifestyle impact for the patient.

Figure 1. Medtronic CGM Gold™ Retrospective Monitor.

In 2006 this technology was dramatically advanced with the simultaneous release of the Medtronic Paradigm R/T™ system, consisting of an insulin pump with an integrated real-time glucose sensor, and the Dexcom STS™ real-time glucose sensing

system, the latter representing a “stand alone” real-time continuous glucose monitor (rt-CGM). This was followed shortly by the release of the Navigator by Abbott, also a “stand alone” real time CGM. These three systems represented the first forays into real-time glucose sensing developed for patient use. These devices now had the ability to alert patients of potential hypoglycemic and hyperglycemic events. For the first time, patients were able to have a degree of security that they could be alerted to high or low glucose levels and take corrective action prior to developing a more severe glycemic issue.

It is important to differentiate the nature of CGM use as to whether it is for the benefit of the clinician, or for the benefit of the patient. With the development of real-time feedback, diabetic patients can see their glucose levels in real time. The amount of information available to the patients has dramatically increased—a person can now see the direction in which the glucose level is heading, whether it is climbing or falling, and where the levels have been for the last few hours. As with the prior development of home glucose testing, many diabetes care professionals are unconvinced of the value of these systems (AACE, 2010). The arguments against their use remain fairly consistent with arguments about SMBG: the devices have issues with accuracy, certain medications interfere with their functioning, it is too much information for patients to have, and patients won’t know what to do with all of this information. In many ways, this is an echo of the initial arguments against home glucose testing, which has now become the standard in diabetes management.

Identification of the Problem

Despite the advances in technology and pharmacology, overall diabetes control in the United States remains poor. Glycosolated hemoglobin (HbA_{1c}) is that subsection of hemoglobin used clinically to measure average plasma glucose concentrations. It refers to the sub-unit "A" of hemoglobin, which combines with glucose, becoming glycosolated and forming "A1". The sub-unit "C" of this is measured for the commonly used HbA_{1c} test (Beaser, 2010). This test represents the current measured standard of glucose control in diabetes care. Current recommendations for targeted glucose control are HbA_{1c} of 6.5% or below (AACE, 2007). However, it is estimated that only 37% of patients with diabetes achieve a $HbA_{1c)}$ of less than 7% (AACE, 2007; Grant, Buse, & Meigs, 2005). The average HbA_{1c} on an insulin pump is 8.5% (Weissberg-Benchell, Antisdel-Lomaglio, & Seshadri, 2003). It is estimated that diabetes and its complications cost the US health system $174 billion in 2007 (CDC, 2011). While HbA1c remains the standard measure of care for diabetes control, it provides no insight into glucose variability (Danne, Lange, & Kordonuri, 2008).

Poorly controlled diabetes increases the risk of complications and the potential future costs to the health system (CDC, 2011; LeRoith & Smith, 2005). While technologies and pharmaceutical interventions have advanced, the anticipated dramatic improvement in glucose control has not occurred. Current estimates show that HbA_{1c} control remains relatively flat despite the aforementioned advances.

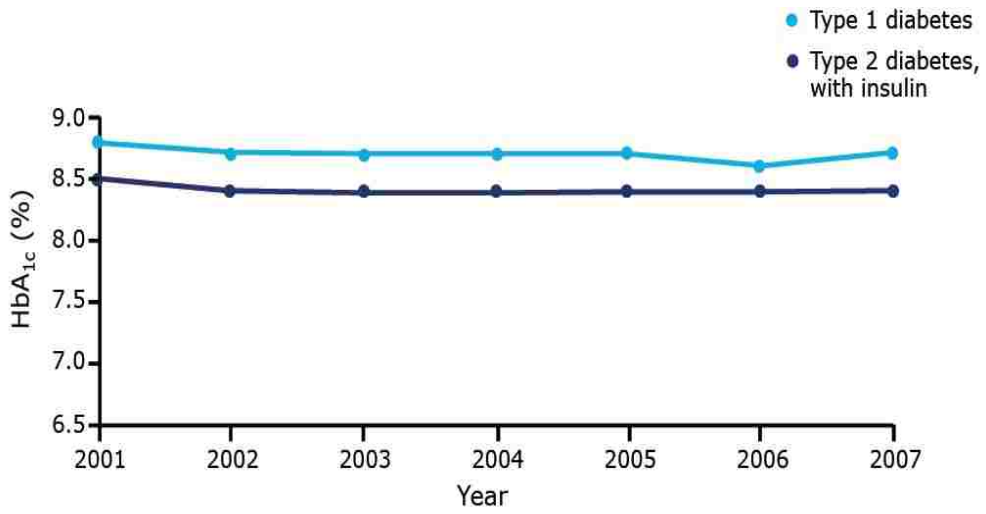


Figure 2. Average HbA_{1c} for Type-1 and Type-2 Diabetics. These data represent averaged data from 2001 to 2007. Adapted from Currie, Gale & Poole, 2010.

Aggressive therapies for Type-1 DM carry with them the risk of hypoglycemia (Cryer, 1999; Diabetes Control and Complications Trial Research Group, 1993). Many patients with Type-1 DM lose their awareness of impending hypoglycemic events due to autonomic nervous system changes related to diabetes complications (Cryer, 1999; AACE 2007; Graveling & Frier, 2010). This change in physiology, associated with a drop in counter-regulatory hormones, is often referred to as "Hypoglycemia Unawareness" or more accurately as "Impaired Awareness of Hypoglycemia" (Graveling & Frier). Given the risk of hypoglycemia, many patients under-treat their disease and allow their glucose levels to remain high. This "fear of hypoglycemia" carries with it a significant negative impact on diabetes control and the potential for long-term complications.

The benefits to patients utilizing rt-CGM to improve glucose control have been well established (AACE, 2010; Garg et al., 2006). While there is an increasing

acceptance of the home and personal use of rt-CGM devices, there remains a poor understanding of how patients are using these devices. The general belief has been that patients are benefitting from seeing their numerical value of blood glucose. However, many clinicians have questioned this, given that all glucose testing done in the home (SMBG) is subject to a margin of error of 10-30% when compared to laboratory standards, depending on the device being used (Kildegaard, Christensen, & Hejlesen, 2009). Depending on the device, margin of error with rt-CGM is 5-30% of Median Absolute Relative Difference (MARD), when compared to YSI laboratory standards for serum glucose (Garg et al.; Kildegaard et al.).

The introduction of additional layers of variance creates a potential compounding of measurement errors when rt-CGM is calibrated against SMBG (Apurv, Mahalingham, & Brauker, 2009). Recognizing this inherent inaccuracy in glucose measurement, one can hypothesize that perhaps patients are benefiting more from being able to see their glucose pattern rather than simply their glucose value.

Given the limited clinical experience we have with rt-CGM (less than 5 years at the time of this writing), this hypothesis warrants further exploration. An understanding of whether patients benefit from an awareness of trending (visualization of the glucose pattern and direction of change) or from being able to see the numerical value of their glucose has yet to be determined.

Use of home glucose monitoring via self-monitored blood glucose testing (SMBG) is now a standard of care in the management of diabetes (AACE, 2007; AADE 2010). It has become so commonplace that the inherent accuracy of these devices is not

questioned. Unfortunately, most home glucose testing devices are allowed an accuracy of ± 20% for blood glucose levels > 75mg/dl and ± 15mg/dl with glucose levels less than 75mg/dl (Kuo et al., 2011). The imprecision of glucose meters has been widely ignored despite the very real risks that remain.

The American Diabetes Association (ADA) standard for home glucose testing recommends glucometers be within 5% of laboratory standard, though this standard is usually not met (Brunner et al., 1998). This inherent inaccuracy of home glucose testing is rarely addressed, with most clinicians and patients assuming the home glucose meter is correct and "that is what the sugar is". The accuracy of real-time Continuous Glucose Monitors (rt-CGM) will be covered in the review of the literature.

Purpose of the Study

To improve the quality of care for people with Type-1 DM, a clearer understanding is needed of how patients are benefiting from CGM technologies. Acknowledging that fear of hypoglycemia remains a real and ongoing problem, it is reasonable to propose CGM devices will benefit patients in reducing that fear, and will improve glucose control.

The purpose of this study is to determine:

1. If there is a difference in glucose control, as measured by HbA_{1c}, when persons with Type-1 DM are able to visualize the numerical glucose value and its trending pattern, versus trending pattern alone.
2. If there is a difference in glucose control, as measured by variability (i.e., standard deviation) of glucose levels, when persons with Type-1

DM are able to visualize the numerical glucose value and its trending pattern versus trending pattern alone.

3. If use of rt-CGM devices reduce the fear of hypoglycemia as measured by the Hypoglycemia Fear Survey (Appendix B).

Significance of the Study

As previously noted, glycemic control in diabetes remains poor despite improvements in available technology and medications. Further insight into improving glucose control is critical. Poorly controlled glucose contributes to a variety of chronic illnesses including retinopathy, neuropathy, nephropathy and numerous micro- and macrovascular complications that increase healthcare costs. It has been estimated that a 2% reduction in the HbA_{1c} will result in a 40-60% reduction in these costly long term complications (Adler, 2008; DCCT, 1993; Shichiri, Kishikawa, Ohkubo, & Wake, 2000). Pattern management of glucose has the potential to reduce variability and would be expected to reduce the incidence and severity of these complications.

Emerging data are strongly suggestive that reductions in glucose variability may be more important than reduction in the glucose values overall (Danne, Lange, & Kordonouri, 2008). Reducing diabetes' long term complications and improving control with reductions in variability offers the potential of decreasing costs associated with this disease process. In 2007 direct and indirect costs associated with DM were estimated to be U.S. $174 billion (CDC, 2011).

Improved control of glucose will reduce costs for patients and the health care system, and will improve quality and length of life. Real-time CGM use has reached the

mainstream of diabetes care, but has done so with only a poor understanding of its benefits for patients; this capstone project will add to the needed understanding of rt-CGM for patients with Type-1 DM.

REVIEW OF THE LITERATURE

Introduction

Type-1 DM is a disease requiring a constant level of care. People with Type-1 DM must balance a variety of choices in food selections, glucose testing, and insulin dosing on a continuous basis. Failure to maintain the balance can provoke an unwanted hypoglycemic event. This event may respond quickly to intervention but often leaves the person feeling ill for several hours afterwards (Cryer, Davis, & Shamoon, 2003).

The risks associated with insufficient insulin include prolonged hyperglycemia and the subsequent physical injuries from the elevated glucose, or a potential diabetic ketoacidotic state requiring hospitalization. The physiologic injury from hyperglycemia occurs quickly and results in cumulative injury to the micro- and macrovascular systems (Cryer, 1999; AACE 2007). Most patients will have few complaints with mild hyperglycemia, despite the rapid accumulation of damage that is occurring.

For many people with Type-1 DM, there is a fine line between hyper- and hypoglycemia. When forced to make a rapid choice most people with Type-1 DM will allow their glucose to climb higher than is desired, rather than risk a potential uncontrolled hypoglycemic situation (Wild, et al., 2007). These choices become self-reinforcing over time when hypoglycemia unawareness progresses as part of the disease process. People with impaired awareness of hypoglycemia demonstrate resistance to intensive insulin therapy adjustments, in an effort to maintain glucose control and avoid the negative consequences of a hypoglycemic event (Smith et al., 2009; Wild et al.).

Nature of Diabetes

Diabetes remains a complex disease for patients and providers to manage. As with most chronic diseases, the patient's active involvement is a necessity. This was recognized in early management of the disease (Joslin, 1916). Aggressive management of glucose levels early in the course of diabetes can reduce the long term consequences; cardiovascular risk, as an example, is reduced by 50% when effective diabetes control is established early in the course of the disease (Adler, 2008; AACE 2007). Chronic non-communicable diseases, such as diabetes, contribute significantly to the increasing costs of health care in the United States (CDC 2011; Dancer & Courtney, 2010).

Expanding incidence and economic consequences.

Diabetes, primarily incidence of Type-2 DM (AACE, 2007), continues to grow at exponential rates in the United States, along with the parallel rise in obesity (Modak et al., 2000; Modak et al., 2001). This trend is shown in Figure 3.

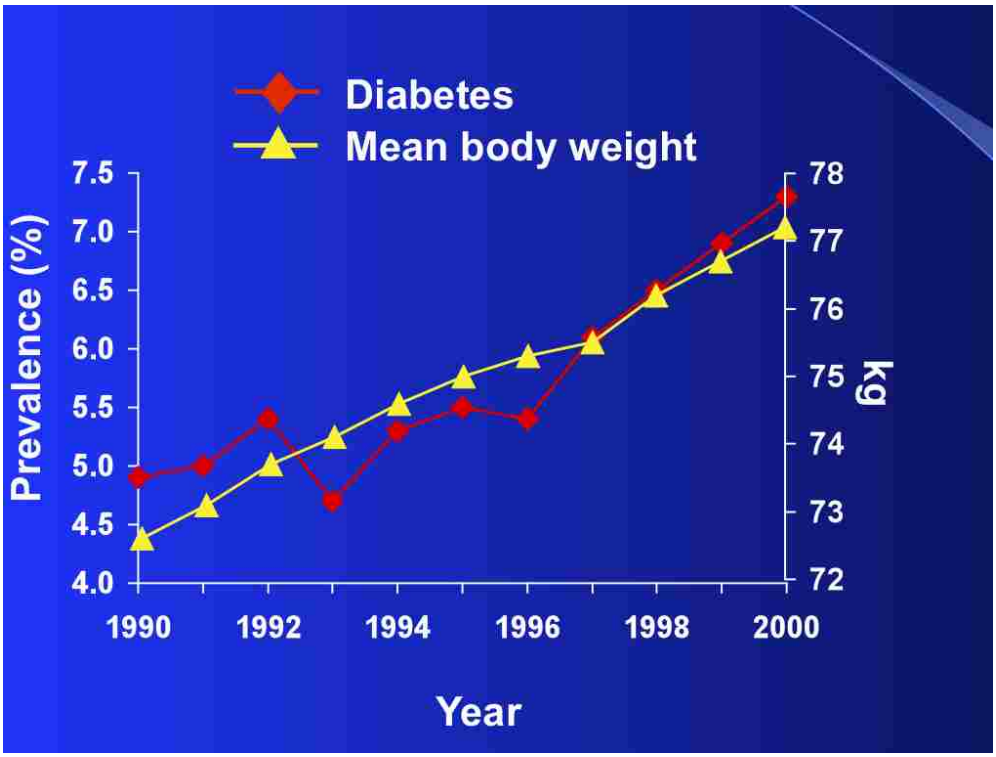


Figure 3. Relationship between diabetes and mean body weight. This figure is adapted from Mokdad et al., 2000 and 2001, and has been commonly used in diabetes care discussions.

While the incidence of Type-1 diabetes remains approximately the same, representing 5-10% of all diabetes cases, improved diagnosis is now possible through antibody measurements and the ability to assess insulin production through C-peptide levels (AACE, 2007; ADA, 2010 Lohman et al., 2001). There is no evidence that costs attributed to diabetes and its co-morbidities, as stated by the CDC (2011), are decreasing, or even that annual increases are slowing.

Differentiating Type-1 and Type-2 diabetes mellitus.

There is a great deal of discussion among practitioners regarding the differentiation of Type-1 and Type-2 diabetes. For the purpose of this project, only

persons with Type-1 diabetes will be studied. Type-1 diabetes is characterized by an absolute insulin deficiency. Thought to be related to an autoimmune destruction of the pancreatic "Beta" ß-cells, typical Type-1 DM patient presentation is with the "polys" – polyuria, polydipsia and polyphagia, all symptomatic responses to the high glucose levels (AACE, 2007). There are a variety of Type-1 DM presentations, but often presentation is the classic rapid onset of ß-cell failure in adolescents and children, resulting in early insulinopenia, diabetic ketoacidosis, hospitalization, and potential death if not recognized and treated quickly.

While often regarded as a disease of the young, adults are equally likely to develop Type-1 diabetes. The destruction and failure of the β-cell in adults tends to be slower when compared to children or adolescents (AACE, 2007; Beaser et al., 2010; Lohman et al., 2001). This slower presentation can lead to some confusion on the part of the health care provider as the patient presents with characteristics of both classic Type-1 and Type-2 diabetes. This pattern has been named Latent Autoimmune Diabetes in Adults (LADA). It is possible to screen for the presence of autoimmune antibodies related to this destructive process, but the tests are known to have variable sensitivities despite a high specificity (AACE; Lohman, et al.). Age is not regarded as a limitation in this diagnosis and case reports of new onset auto-immune Type-1 diabetes have been reported in people in their 80's (Pozzilli & Di Mario, 2001). Despite our ability to detect these antibodies, there are no effective interventions to arrest or delay the progressive destruction of the β-cell.

Type-2 diabetes is often characterized as an adult-onset syndrome (AACE, 2007). This accounts for approximately 90% of all diabetes cases. Type-2 DM is associated with an underlying physiologic insulin resistance, often in the presence of obesity, in combination with decreasing insulin secretion and excessive hepatic glucose output. The majority of affected individuals are sedentary, obese, and present with a family history of the disease, suggesting a strong genetic link (AACE, 2007; Beaser, 2010). Type-2 DM is often seen as a triad presentation consisting of dyslipidemia, hypertension, and central obesity (AACE; Beaser).

Therapeutic realities and clinical limitations.

Diabetes management for most patients involves continuous adaptation to a disease in constant fluctuation. Patients use home glucose monitors, which have a significant variability in accuracy, to calculate insulin therapies; these calculated doses are injected to cover foods whose nutritional value is being estimated, during any given day with variable stressors and physical activity. The inherent complexities, uncertainties, and opportunities for error are endless. Insulin pumps have offered improvements in delivery options, and insulin pharmacodynamics have shown dramatic increases in consistency and reliability, but our methods of glucose testing and monitoring have remained essentially unchanged since the late 1970's.

Glucose Testing

Home glucose testing remains the standard of care for people with diabetes. Its value in helping patients improve their glucose control is well established (AACE, 2007;

AADE 2010). Home glucose testing is widely available, relatively inexpensive, and can be conducted without a prescription. Today, self-monitoring of blood glucose (SMBG) is a cornerstone of diabetes education (AADE, 2010). By encouraging patients to measure their glucose and take action based on that knowledge, we have expanded the ability of our patients to manage their own disease (Garg & Hirsch, 2010).

Home testing from past to present.

Previous models for home glucose control involved urine testing of glucose. This failed to achieve control due to the time delays in glucosuria, variability in the renal threshold for glucose release, and the lack of quantification to allow a patient to adjust their insulin therapies (Beaser, 2010; Berganstal & Gavin).

Self-monitored blood glucose (SMBG) is a standard of care for the treatment of diabetes (AACE, 2007; AADE 2010). Consensus statements agree that SMBG improves glucose control in patients with diabetes, and its value has been established (Bergenstal & Gavin, 2005). Numerous studies have demonstrated that people with Type-1 DM who test more than 3-4 times daily, on average, have a HbA_{1c} 0.7% less than those who do not (Blonde & Karter, 2005).

Standards and concepts.

While there is no fixed number of tests a person with Type-1 DM should conduct daily, general rules exist. Blood glucose should be tested before meals, before operating a vehicle, and before going to bed. If a person with Type-1 DM is feeling poorly and the reason is uncertain, glucose level should be tested. Additionally, dosing for insulin

therapies should be based on the glucose measurements taken at mealtime. A consensus statement supports the need for people with Type-1 DM to test their glucose at least 3-4 times a day (Bergenstal & Gavin, 2005). SMBG provides invaluable information for patients about their current glucose levels, their response to therapies or meals, and the need for further interventions (Beaser, 2010; Renard, 2005).

Comprehensive diabetes education programs include a focus on SMBG and education to assist patients in acting on SMBG information (AACE, 2007; AADE 2010). Providing patients with real insight and truly effective tools to manage their glucose levels requires a real-time measurement of the glucose level (Renard, 2005). Patients must be instructed in the use of SMBG and possess the ability to "troubleshoot" potential problems related to their glucose control (AADE; AACE).

Accuracy in home glucose testing.

SMBG suffers from a number of potential sources of error, including but not limited to testing strips that are temperature sensitive, potential contamination from soiled hands, calibration/coding errors, medication interference, and inaccuracies inherent in the technology. There are case reports of falsely high SMBG resulting from "sticky fingers" and problems with contaminated finger-stick samples (Kinmoth, 1981). Unfortunately many clinicians and patients are unaware of the accuracy issues associated with SMBG and blindly accept the value provided.

Despite inherent issues with accuracy, SMBG is a valuable tool for people with Type-1 DM. Providing information on current glucose levels assists in the management of insulin therapy and meal choices, which help normalize glucose levels (Renard, 2005).

Accepting its flaws, it is hard for a clinician today to imagine glucose management without this standard of care.

Figure 4 shows a container of glucose testing strips. Notice that the strips have an accepted accuracy range of 83-125 mg/dl when calibrated against laboratory standard 100mg/dl glucose solution.

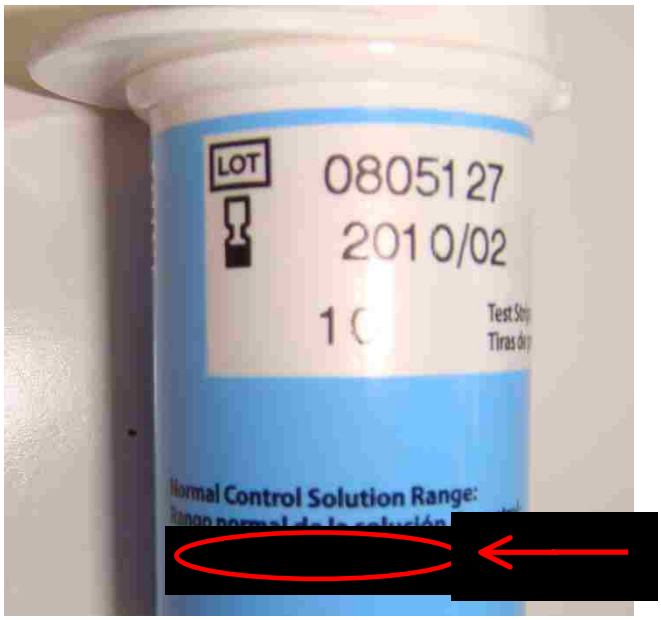


Figure 4. Glucose test strips control range. This figure is a photograph of a container of standard glucose testing strips showing the acceptable calibration range when tested with a laboratory standardized solution.

The FDA requires that home glucose testing meters conform to ISO 15197:2003 testing standards for accuracy (Kuo et al., 2011). These standards require a glucometer to be accurate 95% of the time ± 20% for blood glucose levels > 75mg/dl and ± 15mg/dl with glucose levels less than 75mg/dl (Kuo et al.). The imprecision of glucose meters has been widely accepted despite the very real risks that remain. The ADA standard for home glucose testing is that home use glucometers should be within 5% of laboratory standard,

and as noted previously many of these meters do not meet this standard (Brunner et al., 1998).

Standard Deviations in Glucose

Conceptual standards.

The continuous variability of glucose levels is an accepted reality. Joslin, Gray and Root (1922) recognized that glucose and insulin responses could vary dramatically within the same person following similar events. The need for improved testing methods for home use was addressed with the development of SMBG and its wide scale implementation (Berganstal & Gavin, 2005). Providing patients with the ability to test glucose levels and address high or low blood sugars has improved their ability to limit glycemic excursions (Beaser, 2010; Blonde & Karter, 2005). The decrease in variability has led to reduction in HbA_{1c} and a reduction in end organ damage from elevated glucose levels (AACE, 2007). While HbA_{1c} testing provides an 8-12 week retrospective average of glucose levels, it provides little information about the intraday variability that occurs (Beaser; Renard, 2005). Wide scale adoption of SMBG has improved the awareness of intraday variability and enhanced the person's ability to manage their diabetes.

Recognizing that glucose levels fluctuate, it has been suggested that SMBG testing should demonstrate a Standard Deviation (SD) of 1/3 mean glucose reading (Hirsch & Brownlee, 2005). The most common methods for assessing this is by downloading the memory of the patient's SMBG device and reviewing the available data. Variability in glucose levels is becoming an area of increasing concern as we gain

understanding of the rapid injury that occurs with elevated glucose and fluctuating glucose levels (Hirsch & Brownlee; Sieglaar, Holleman, Hoekstra, & DeVries, 2009).

The variable nature of glucose poses several concerns for patients and clinicians. While glucose can be stabilized in a controlled environment, patients deal with a continuously changing reality (Kildegaard et al., 2009). The long-term risks associated with variability in glucose levels is acknowledged; the importance of reducing variability by any means available is an ongoing goal of the diabetes care community (Kildegaard et al.).

Clinical realities.

Most patients who are actively involved in their diabetes care and using MDI or CSII (Continuous Subcutaneous Insulin Infusion, i.e., insulin pump) therapies are performing SMBG 4-6 times daily (AACE, 2007; Renard, 2005). Numerous studies have demonstrated that aggressive use of SMBG will improve glucose control, but the benefit-ratio with SMBG seems to flatten when the patients are testing 8-10 times a day (Davidson et al., 2004). Care for persons with diabetes and an estimated understanding of glucose control is based on the HbA_{1c}, test (Dailey, 2007). This test reflects overall averages and not the continuous cycle of variability in glucose levels (Dailey). It is possible to have a HbA_{1c} of 6.5%, the suggested glucose target by AACE (2007), with a blood sugar that is continuously variable from 60-300 mg/dl. While the HbA_{1c} remains the standard of measurement for glucose control, its effect of overall averaging of the glucose levels presents a limitation (Beaser, 2010). Additionally, as HbA_{1c} decreases, the

impact associated with the post-prandial variability increases, as the fasting glucose impact decreases. This is illustrated in the figure below.

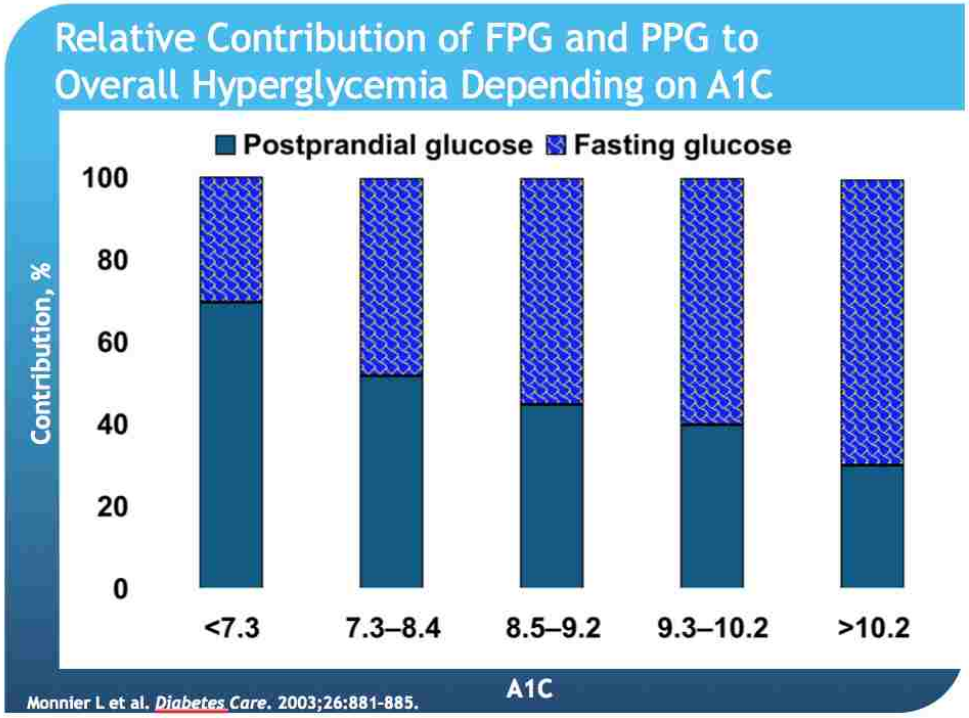


Figure 5. Relative Contribution of fasting and PPG to the HbA1c.This figure is commonly used in discussing diabetes care and is adapted from Monnier, Lapinski, & Colette, 2003.

Consequences for long-term outcomes.

Type-1 diabetes is a disease necessitating life-long management. The need for continuous stable control is evidenced by the rapid increase in risk associated with hyperglycemia. While frequent testing provides valuable information on glucose levels and need for therapy adjustments, patients are still struggling to improve control. Patients deal constantly with variations in their glucose levels and responses to interventions

based on the diversity of their lives. To improve long-term outcomes, we must be able to reduce glucose excursions and limit the variability in glucose levels, recognizing that these variations contribute rapidly to the micro- and macrovascular damage that is occurring (Hirsch & Brownlee, 2005; Sieglaar et al., 2009).

Hypoglycemia

The realities of hypoglycemia.

Hypoglycemia is the most common endocrine emergency that is encountered in the patient care setting. Hypoglycemia is recognized as the most significant factor limiting our ability to control diabetes and is the most frequent complication of insulin dependent diabetes care (Carroll, Burge, & Schade, 2003; Cryer, 1999). It is estimated that 25% of people who have had Type-1 DM for > 5 years demonstrate impaired hypoglycemic awareness (Graveling & Frier, 2010; Ferguson et al., 2001). The first reports of impaired hypoglycemic awareness occur in the literature in 1922 with the early use of insulin. It was noted that hypoglycemia could occur spontaneously and without warning, particularly in those who had been diabetic for some period of time (Joslin et al., 1922). On average people with Type-1 DM experience hypoglycemia 1 to 2 times a week; additionally it is estimated one third of them have a severe hypoglycemic occurrence annually (Strachan, 2007). Hypoglycemia is considered serious or severe when the assistance of another person is required to manage the event (Carrol et al., 2003; Strachan 2007).

Hypoglycemia is generally defined as serum glucose <50mg/dl with symptomatic complaints, and serum glucose <40mg/dl without symptomatic complaints (Carroll et al.,

2003). Symptoms associated with significant hypoglycemia include visual disturbances, decreased cognitive abilities, emotional lability and behavioral changes (AACE, 2007; Graveling & Frier, 2010). Recurring episodes of hypoglycemia have been shown to suppress physiologic awareness of future episodes, furthering the degree of impaired awareness (Carroll et al.; Graveling & Frier). As the awareness of hypoglycemia decreases, many patients develop fear/avoidance behaviors to decrease the risk of these events (Andebro, et al., 2010).

Strategies to decrease hypoglycemic events include increasing SMBG testing, meal planning, and strategic use of insulin, in combination with intensive diabetic counseling (AADE, 2010; AACE 2007). Improved stability and predictability of insulin analogues has offered reductions in hypoglycemia; insulin glargine (LANTUS™) was demonstrated to provoke fewer nocturnal hypoglycemic events when compared with the older, long acting Neutral-Protamine Hagedorn (NPH) insulin (Yki-Jarvinen et al., 2000). Modern short acting insulin analogues such as insulin lispro (HUMALOG™) have been demonstrated to have less hypoglycemia overall, including nocturnal hypoglycemia. This represents a significant improvement over the previous faster acting standard, human regular (R) insulin (Ferguson, et al., 2001).

Though newer insulin therapies have demonstrated a reduction in hypoglycemic events, hypoglycemia continues to occur with an unacceptable frequency. This is particularly true in pursuit of tight glycemic control. In seeking to reduce the occurrence of hypoglycemia (and more importantly, fear of hypoglycemia, discussed further in the next section), we must consider other interventions. We must allow patients more

flexibility in their lifestyle choices, while simultaneously improving their overall glucose control. This represents a major challenge in diabetes care.

Impact of hypoglycemia on patient fear-related behaviors.

Repeated hypoglycemic events and negative consequences can increase the anxiety and fear response, concurrent with avoidance behaviors (Andebro et al., 2010; Green et al., 2000). The impact of hypoglycemia-associated fear on patients' diabetes management behaviors is a documented phenomenon; patients intentionally under-treat glucose levels or decrease meal coverage in order to reduce the risk of a hypoglycemic event (Irvine, Cox, & Gonder-Frederick, 1994).

Impaired awareness of hypoglycemia (IAH) affects an estimated 25% of people with Type-1 DM (Carroll et al., 2003; Strachan, 2007). A decrease in autonomic nervous system response is believed to be a key component. With this decrease in autonomic response, people experiencing hypoglycemia lose the initial physiologic responses commonly seen, which include sweating, shaking, nervousness and hunger (Graveling & Frier, 2010). The fear of nocturnal hypoglycemia is underscored by the reality that nocturnal hypoglycemia accounts for 6% of deaths in Type-1 diabetics under the age of 40 (Sovik & Thordarson, 1999).

Increasing fear and hypoglycemia avoidance behaviors to are in large part due to prior negative experiences (Irvine, Cox, & Gonder-Frederick, 1992). Recurrent negative responses to hypoglycemia are self-reinforcing and lead to the development of these avoidance behaviors (Green et al., 2000; Irvine, et al.). These behaviors include

inappropriate eating, under dosing of insulin and alterations in normal daily activities to avoid a potential hypoglycemic event.

Prior models to reduce fear of hypoglycemia.

Recognizing that fear of hypoglycemia is contributing to poorly controlled diabetes, several training and education models have been proposed. Traditional models of diabetes education, while addressing the issues of hypoglycemia and its prevention, do so in less detail and intensity than specialized hypoglycemia education programs (AADE, 2010). Blood Glucose Awareness Training (BGAT) is one commonly cited model. BGAT is an eight-week intensive training program whereby people learn to identify their various responses to foods, stressors, insulin, and activity (Cox, et al., 2006). The BGAT program has been peer reviewed, subjected to test-retest and demonstrates reproducible benefits to patients. BGAT participants have demonstrated improved HbA_{1c} levels and reduced glycemic variability that has been sustained through 12 months of follow-up assessment. BGAT requires an eight-week commitment to class work and record keeping, where people learn to manage their disease process, individualize their responses, and plan for interventions. Patients who have completed this course have been able to demonstrate decreased hypoglycemic events and a lower level of fear associated with hypoglycemia at 12-month follow up, when compared to baseline.

A similar program, the Hypoglycemia Anticipation, Awareness and Treatment Training (HAATT) program has also been studied. This program differs from BGAT in that it focuses specifically on individuals experiencing repeated hypoglycemic events (Cox et al., 2006). The HAATT program consists of eight educational sessions with

follow up care targeting individual responses to therapies and interventions (Cox, et al., 2004). Follow up studies on HAATT have suggested the reductions in hypoglycemic events are sustained at 18 months post training (Cox et al.). Comparisons between BGAT and HAATT have shown them to be statistically equivalent with regards to hypoglycemic reductions (Cox et al.). The major weakness of these training programs is the required time commitment, which generally consists of several weeks of ongoing instruction.

Recognizing the need for improved access to aggressive glucose management programs has led to the development of the Blood Glucose Awareness Training at Home program (BGATH). This is a web-based interactive 8-week course (WWW.BGATHome.COM). Participants maintain individual profiles and progress through the training on-line. Research suggests this may be as effective as the traditional training methods; however, results varied based on successful program completion and subjects' time commitment (Cox et al., 2008).

While BGATHome was considered easy to use by its participants and demonstrated a statistically significant decrease in hypoglycemia, their data were limited by a small sample size (n=20). Subjects in the BGATHome trials were receiving ongoing feedback related to their participation in the trial, which certainly served to supplement the success of the program (Cox et al., 2008).

Continuous Glucose Monitoring

Continuous glucose monitoring (CGM) uses a biosensor inserted into the subcutaneous tissue to measure glucose levels on a continuous basis. This is traditionally differentiated into two types: Retrospective (or Professional), and Real-Time. In

retrospective monitoring, the patient is blinded to the data obtained by the CGM and it is worn for the benefit of the clinician. While wearing the device, the patient is given no information regarding high or low BS events, and is dependent on provider download and interpretation to use the data obtained (AACE, 2010). With real-time CGM (rt-CGM), the patient has access to glucose values on the face of the CGM device, and is able to view the pattern trending of their current glucose levels, with access to both the current glucose values and the trending of the last few hours (AACE, 2007).

Current technologies for CGM draw upon the original model of Updike and Hicks (1967). Glucose levels in bodily fluids are reflective of electrical activity created by the interaction of glucose, oxygen and glucose-oxidase as represented in Figure 6.

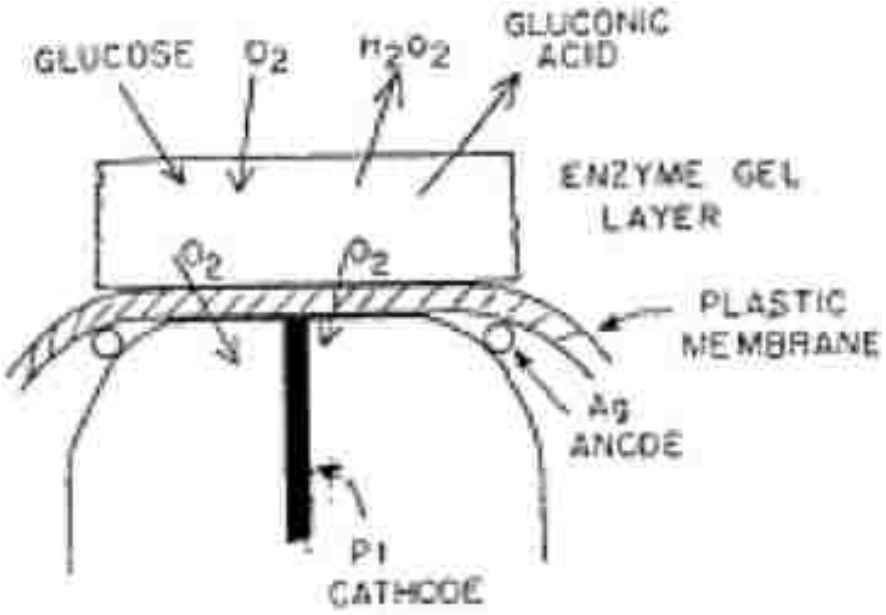


Figure 6. Glucose-Oxidase Sensor. This is the diagram of the original enzyme electrode design as described by Drs. Updike and Hicks in 1967.

In both types of data collection, devices can be downloaded and the data interpreted for the benefit of the patient and the clinician. Only the rt-CGM allows the patient to have constant feedback regarding the current direction in which their glucose is moving, an estimate of the speed at which it is changing, and a historical pattern indicating the direction of travel in the recent past.

Retrospective monitoring: A failed concept.

Detailed feedback on a patient's 24-hour glucose levels and patterns provides clinicians with key information to improve a patient's glucose control. Traditional methods have involved patients checking and logging their blood sugars every one to two hours, and then plotting and interpreting the patterns.

Retrospective monitoring allows clinicians to collect continuous glucose data on patients. This collection is a blinded process whereby the receiver unit for the sensor provides no visible glucose level or waveform. Retrospective CGM (r-CGM) technology is widely used in the clinical setting. Its major attractions for many providers is that it is easily set up, patient training is minimal, and most insurers will reimburse for the procedure as long as the device is worn for a minimum of 72 hours (AACE, 2010).

Studies utilizing r-CGM have demonstrated limited improvement in diabetes control (Currie, Poole, & Papo, 2009; Danne et al., 2008). While the majority of these studies have used small sample sizes, the concept incorporates several weaknesses. It is dependent on the patient keeping logbooks of activity, diet, and insulin dosing while wearing the device. The clinician then downloads the receiver unit, prints out the retrospective graphs, and interprets the data in an effort to improve glucose control. Each

colored line represents a 24-hour period from midnight to midnight on the x-axis, with the glucose levels on the y-axis. An example of this is shown in Figure 7.

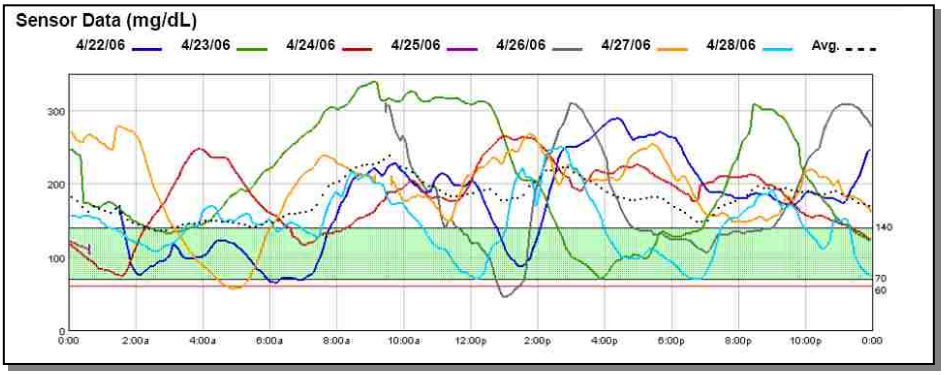


Figure 7. Medtronic CGM Printout. This is an example of the data obtained from the Medtronic retrospective CGM system as retrieved from the Medtronic Carelink Pro™ software.

Tanenberg et al. (2004) evaluated the effects of retrospective technologies in reducing hypoglycemic events. Outcome data suggested with retrospective adjustments, the amount of time spent in a hypoglycemic state was reduced; however, the number of hypoglycemic occurrences was not significantly improved. There was no evidence of improvement in hyperglycemia and long-term sustainability of glucose improvements was not supported.

Currie et al. (2009) conducted a review of the literature regarding retrospective CGM and patient benefits. Studies reviewed suggested that overall improvements in HbA_{1c} were modest (0.2%) when compared to control subjects. Additionally, while there was a reduction in time spent hypoglycemic, the number of hypoglycemic events did not change.

The use of retrospective data gathering should be limited to those instances when a subject must be blinded to the data being collected, such as a clinical trial.

Retrospective CGM is unable to address the inevitable variability that will occur in the daily activities of people with Type-1 DM. While initial short-term improvements can be demonstrated, they are unsustainable due to the fixed interval nature of retrospective data.

The use of blinded glucose data in clinical practice assumes the data are more valuable to the clinician than they are to the person with diabetes. This is a paternalistic view and deprives patients of valuable information that could benefit their disease control. The lack of high and low blood glucose alarms on retrospective systems has contributed to at least one documented case of fatal hypoglycemia (Tanenberg et al., 2010). While the development of retrospective systems was a necessary step in the evolution of CGM technology, it is difficult to justify their continued use when real-time technologies are readily available at comparable costs.

Real-Time Monitoring: The good and the bad.

It would seem logical that, in providing a person with Type-1 DM continuous information regarding their glucose, their control would improve. Most patients are using self-monitored blood glucose (SMBG) to control their diabetes with acceptable results (Garg & Hirsch, 2010). Along with the numerical glucose value, real-time CGM provides the additional ability to see where the blood glucose is trending (direction of change), as well as the velocity of that change. This offers significantly more information than traditional SMBG. Regardless of the number of fixed-point readings measured in a day, SMBG only provides that reading at a fixed point in time.

Juvenile Diabetes Research Foundation (JDRF) trials with rt-CGM have been unable to demonstrate a benefit in HbA_{1c} lowering for persons less than 25 years of age

(Tamborlane et al., 2008). This could be due to the inconsistency of rt-CGM use in this population. Older populations, those greater than 25 years of age, have shown better consistency in the use of the sensors. Consistent use of rt-CGM for 6-7 days a week has been correlated with significant and sustained improvements in HbA_{1c} (Tamborlane et al.).

Controlling diabetes is about maintaining euglycemia. Maintaining euglycemia as much of the time as possible reduces the physiologic injury that occurs with variable glucose levels (AACE, 2007). The use of rt-CGM helps patients reduce their HbA_{1c} by as much as 0.8% and maintain that control for more than one year (Chase, et al., 2010). This improvement has not been demonstrated with retrospective CGM (Currie, Poole, & Papo, 2009).

Insulin pumps (CSII) and rt-CGMs have been integrated in an effort to provide a combination product, potentially coupling the known reduction of hypoglycemia associated with insulin pumps, with the improvements in HbA_{1c} that have been documented with rt-CGM use. However, results of the combination products have been disappointing, with little indication that the integration is of benefit to patients (Rubin & Peyrot, 2010). The reasons for this are not clear, but may relate to the existing technologies and their inherent limitations.

Hirsch et al. (2008) conducted a comparative trial, between patients starting on an insulin pump and frequent SMBG, and those starting on an insulin pump with an integrated rt-CGM. There was no significant difference in the glucose control between those patients using the integrated pump and traditional, aggressive SMBG.

Though several companies have devices in development targeting this integrated pump-sensor model, the only integrated pump/rt-CGM product currently on the market is the Medtronic Paradigm R/T™ insulin pump and sensor combination (www.medtronic.com). The Medtronic Paradigm R/T™ sensor, with a significant worsening of accuracy when the glucose levels are below 80mg/dl, has a Clarke Error Grid "A" zone score of 60% in that glucose range (Medtronic, 2008). The accuracy issues associated with the Medtronic sensor and the poor adherence to long-term use of this product likely contribute to its lack of success in this highly anticipated field.

Accuracy and reliability.

The purpose of this paper is not to debate the merits or the accuracy of rt-CGM devices. All rt-CGM devices on the market perform within reasonable parameters and have FDA approval. For this study we will be using the Dexcom SEVEN PLUS™. The Dexcom system consists of three components:

1. Sensor, inserted subcutaneously into the abdominal fat.
2. Wireless transmitter.
3. Receiver with an integrated display screen, trending information, and high and low alerts.

Figure 8. Dexcom SEVEN PLUS™ system. This figure represents the three primary components of the Dexcom SEVEN PLUS™ system.

The most common method of measuring accuracy with glucose readings is the Clarke error grid. Originally developed for SMBG testing, the scale is also used to measure clinical accuracy. The Clarke error grid is designed to analyze the amount of error incurred in measuring SMBG against a laboratory standard, in this case a Yellow Springs Instruments (YSI) glucose measurement. An example of the grid is shown in Figure 9.

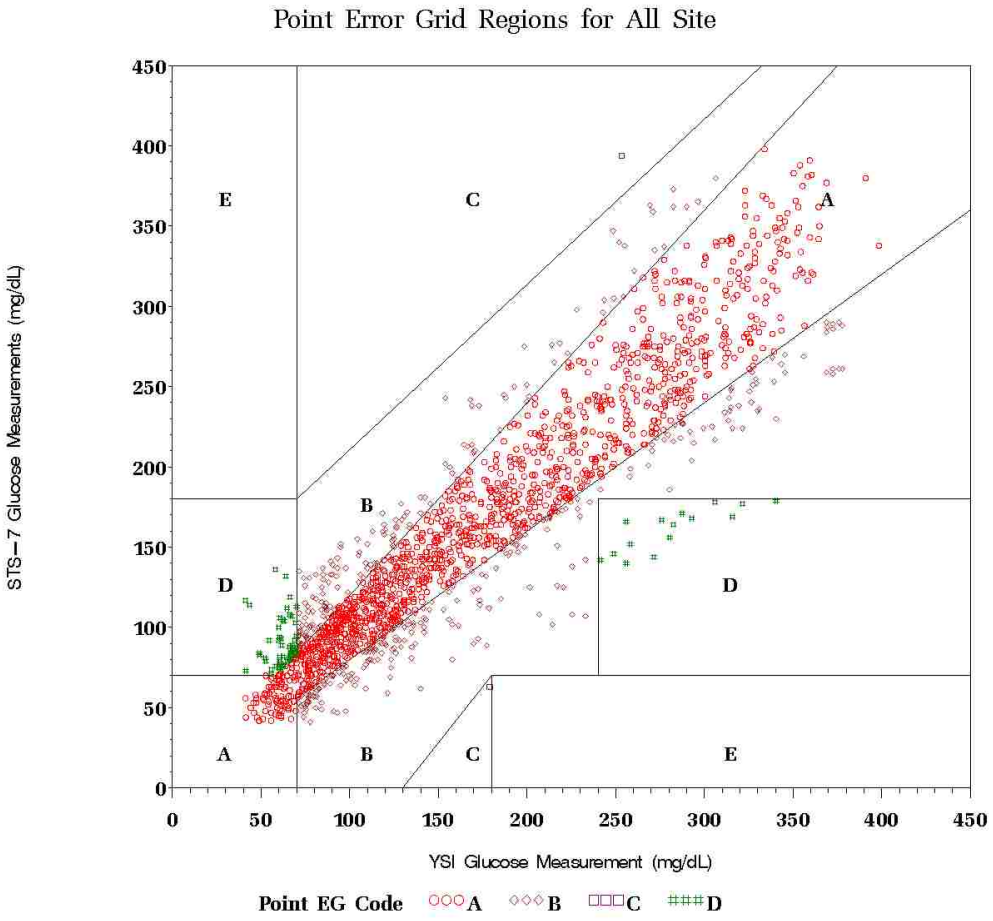


Figure 9. Clarke Error Grid for Dexcom SEVEN PLUS™. The Clark Error Grid represents the statistical scoring of the Dexcom SEVEN PLUS™ system when compared to laboratory standardized measurements. This figure is adapted from the Dexcom SEVEN PLUS™ user guide.

Glucose readings in grid zone:

1. “A” - considered clinically accurate for therapy adjustments.
2. “B” - considered sufficiently benign; would not adversely affect therapies
3. “C” - would lead to over-correction of normal glucose levels, potentially inducing a hypoglycemic event
4. “D” - would lead to failure to recognize and treat high or low glucose levels
5. “E” - would lead to inaccurate and dangerous treatment options.

The Dexcom SEVEN PLUS™ demonstrates the accuracy distribution shown in Table 1.

Table 1

Dexcom Seven Plus Clark Error Grid Accuracy

Zone	Percentage Matched Pairs
A	73.8%
B	22.1%
A+B	95.9%
C	0.2%
D	3.9%
E	0.0%

Note. This table is adapted from the Dexcom SEVEN PLUS™ Users Guide.

Recognizing the concern for hypoglycemia warning, the Dexcom SEVEN PLUS™ has a Clarke error grid rating of 84.2% (A+B) for glucose levels of 40-80mg/dl. The Clarke error grid contains a number of concerns when applied to rt-CGM. It was designed to assess point accuracy of SMBG devices and was never designed for systems in motion. As such, a better choice in assessing the accuracy of CGM devices against SMBG would be the Median Absolute Relative Difference percentile. Viewed in this context the Dexcom system has a Median ARD% of 15.8% for glucose levels of 40-80 mg/dl, 15.1% for glucose levels 80-180mg/dl, and 12.6% for glucose levels 180-300 mg/dl (Garg et al., 2009). Given acceptable accuracy of 95% of the time, ± 20% for blood glucose levels > 75mg/dl, and ± 15mg/dl with glucose levels < 75mg/dl by ISO 15197:2003 testing standards, the Dexcom systems are quite accurate (Kuo et al., 2011).

Given that all rt-CGM devices must be calibrated at intervals to maintain accuracy, an error factor is introduced when the instruments are calibrated with SMBG. The true accuracy of the device can be assessed when the rt-CGM is calibrated to YSI standards. In this circumstance the median-ARD% drops to 4.5% (Brauker, 2009).

Popular conception is that the Dexcom system measures interstitial blood glucose. Interstitial blood glucose lags 15-20 minutes behind serum glucose levels (Apurv, et al., 2009). The Dexcom SEVEN PLUS™ has a demonstrable lag time of less than 6 minutes when compared to serum glucose (Apurv et al.). In light of this obvious incongruity, current thinking is that the rt-CGM is actually measuring wound fluid surrounding the subcutaneous catheter. Wound fluid behaves more like capillary glucose and this would potentially explain the shorter lag time (Apurv et al.).

Evidence of benefit and professional support.

The American Academy of Clinical Endocrinologists (AACE, 2010) state the reduction of HbA_{1c} with the use of rt-CGM is a demonstrable benefit; a sustained decrease in HbA_{1c} has been demonstrated in patients who use CGM devices regularly (Chase et al., 2010). Clinical trials have also demonstrated a clear reduction in the occurrence and duration of hypoglycemia (AACE).

Early home trials using rt-CGM devices show that with minimal training on use of the device, patients demonstrated an improvement of their HbA_{1c} of 0.4% in 12 weeks; this was achieved with only the assistance of the rt-CGM (Garg et al., 2007). Patients using the system decreased their rate of hypoglycemic events compared to the control group, spent less time hyperglycemic, and more time within glucose target range of 60-150 mg/dl (Garg, et al.).

A minimal reduction in hypoglycemic events was demonstrated; patients spend less time hypoglycemic when they are using rt-CGM devices (Rubin & Peyrot, 2010). Statistical improvements in HbA_{1c} have been shown, with evidence of sustained control in those patients who use their sensors 6-7 days a week (AACE, 2010; Rubin & Peyrot).

Patients use rt-CGM effectively to quickly improve their diabetes control. Having access to the continuous feedback of their glucose levels and the ability to see the response to interventions in real time, results in rapid reduction of hyper- and hypoglycemic excursions. In Figure 9 below, we see rapid improvements in glucose control, with reductions in standard deviation and hypoglycemia. This figure demonstrates average glucose levels for three days of retrospective CGM use followed by

six days of rt-CGM use. Median glucose decreased 25% and Standard deviation 40% in six days (Garg et al., 2006).

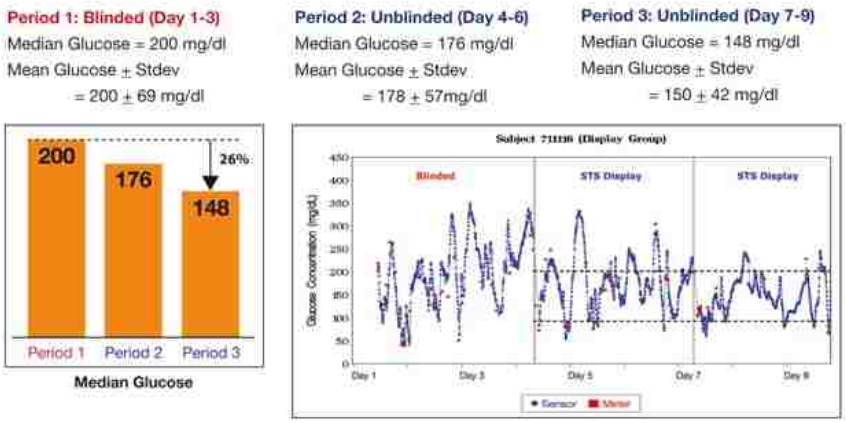


Figure 10. Six days of rt-CGM improves glucose control. This figure has been adapted from the work of Garg, et al., 2006.

Meta-analysis of rt-CGM.

Given the recent advances in rt-CGM technologies we are only now beginning to see meta-analyses of existing studies. These meta-analyses support existing data that significant reductions in HbA_{1c} are possible through the use of rt-CGM (Hoeks, Greven & deVolk, 2011; Pickup, Freeman & Sutton, 2011). Reductions in hypoglycemia occurrence and duration are similarly supported through meta-analysis (Gandhi et al., 2011). While the focus of this project has been on Type-1 DM, the benefits in improved glucose control and hypoglycemia reductions are seen in both Type-1 and Type-2 diabetes (Gandhi, et al.).

The meta-analysis conducted by Gandhi et al. (2011) raises some interesting concerns as these data included both rt-CGM and r-CGM, as well as use of an older

transcutaneous system which has been discontinued (G2 Glucowatch). While meta-analyses have shown support for the use of rt-CGM, there is an ongoing call for more data on the use of rt-CGM in children, pregnancy, and impaired awareness of hypoglycemia (Hoeks et al., 2011).

Understanding of patient utilization.

With the rt-CGM market release in early 2006, there was great anticipation that these devices would significantly improve the care of people with Type-1 DM (Rubin, Borgman & Sulik, 2011). Initial enthusiasm was quickly dampened because of difficulties related to third party reimbursement, technological limitations, and the learning curve for both providers and patients. Use of rt-CGM has been accelerating over the last few years as improved clinical results have been demonstrated and third party insurers begin covering costs of the device for personal and professional use.

Currently there are no algorithms to differentiate those patients who will do best with rt-CGM technologies. The consensus opinion on CGM (both real-time and retrospective) by the American Association of Clinical Endocrinologists (AACE, 2010) suggests that Type-1 diabetics with poorly controlled diabetes as evidenced by HbA_{1c} above target ranges, and those with excessive variability of glucose, will benefit from the use of the devices. People with Type-1 DM who have impaired hypoglycemic awareness will benefit from the alerts the CGM systems can provide regarding impending hypoglycemic events. Real-time CGM use, while not FDA indicated, is also supported for those Type-1 DM patients who are pregnant or engaged in pre-conception planning (AACE). Meta-analyses support the aforementioned conceptual models, but note that

significant reductions in HbA_{1c} have not been demonstrated in persons under the age of 25 years (Gandhi et al., 2011).

From a clinical standpoint, adoption of these devices has been slow. Much of what has been learned is trial and error, based on the experience of clinicians who have taken an interest in this technology. As we move diabetes care forward, the need for a more formalized understanding of rt-CGM use is a necessity. The transition from a tacit knowledge perspective to evidence based practice with rt-CGM will require an improved understanding of device use from the perspective of the person living with diabetes.

CONCEPTUAL FRAMEWORK

The conceptual framework used to guide this study is that of Human Becoming. This framework shall be based on the work of Dr. R. Parse and the science of Human Becoming (Parse, 1992; Parse, 1994; Parse, 2005). The Parse model has been actively applied to clinical settings where patients are involved in disease self-management. This section shall include a discussion of the theoretical model and a review of the literature with regards to its clinical applicability.

Human Becoming

Developing a universal theory in the provision of nursing care has been problematic (Cody, 2006). This reflects not the immaturity of nursing science, but the complex reality of human interaction (Landers, 2000). The coherence of a unifying paradigm in nursing must be sacrificed in order to reach out to the diversity of our profession. However, by embracing theoretical models to assist in the development of research and improve nursing-client interactions, there are several functional models to choose from.

Diabetes is a disease of self-management (AACE, 2007). Patients are educated, assisted and provided tools, but ultimately persons with diabetes are responsible for their own care. In considering a conceptual framework for this pilot trial, the underlying belief is that patients are ultimately benefitting from the information provided with rt-CGM technologies. While the initial development of CGM was intended to benefit providers,

the subsequent evolution has demonstrated their greater value to the patients who are living the experience of their Type-1 DM.

Nursing care occurs between individuals; the nurse and the patient interact, and by doing so form a shared vision (Parse, 1994). This creates an awareness that humans are unique systems and not easily quantifiable. As we assume a post-positivistic critical multiplism view of nursing, we acknowledge that we have our own biases, which impact our interpretations and interactions with others. Additionally we recognize the complexity of the human experience that cannot truly be understood solely through a quantitative model (Letourneau & Allen, 2006). In attempting to understand our patients' lived experiences, we recognize the value of esthetic knowing in the complexity of human interaction, including chronic disease management (Raymond, 2006). An understanding of human science must contain the recognition that there is simultaneous reality and value in the quantitative and the qualitative.

Dr. Parse's theory of human becoming is a phenomenological hermeneutic method. This theoretical framework focuses on the lived experience of the patient/subject (Parse, 2005). Type-1 diabetes is a chronic illness that requires a constant level of attention by the affected person; this theory is uniquely situated to evaluate that lived experience. Understanding this lived experience of chronic disease can improve our abilities to treat it. The Parse research process method includes three major components:

1. Dialogical engagement where the researcher lives true presence with the participant. This is characterized by the researcher moving in rhythm with patients, allowing them to define their

concerns and the nature of their reality with concerns to the researcher.

2. The extraction-synthesis where the language of the phenomenon being examined is moved from the participants into a scientific phenomenon. This allows patients to express, in their own terms, the significance of the phenomenon being studied and its impact on their reality.

3. The heuristic interpretation phase where structural transposition, integration and artistic expression occur. During this phase the lived experience of the subject is moved into the realm of understanding and science. This allows for further integration of the lived experience within the context of the phenomenon being studied. This is finalized with the artistic expression where the learning of the researcher is made known and available.

The Human Becoming model has been applied extensively in research with validation of its underlying concepts (Doucet & Bournes, 2007). It has been successfully applied in the investigation of the lived experience of chronic disease (Jonas-Simpson, 2001) and in patients with diabetes exploring consequences and choice (Mitchell & Lawton, 2000).

The Parse Human Becoming framework offers a Qualitative Descriptive Preproject-Process-Postproject method (QDPPP), which allows the evaluation of the subject's lived experience during the process of the investigation. This QDPPP is applied

by asking similar questions at the pre-, midprocess and post research points. The data are analyzed allowing insight not just into the question being asked, but also into the perception of the lived experience for the participant.

Utilizing QDPPP in this framework, patients with diabetes will be asked an open ended question about the nature of their experience with low blood sugar issues, and what they expect to get from using continuous glucose monitoring (CGM) technologies. Similarly, Quality of Life measures and Fear of Hypoglycemia will be assessed pre- and post-process during the trial. Diabetes is an intimately lived experience for most persons; by improving our insight into that experience we may be able to provide a better and more appropriate level of care.

Four major themes have been identified in the findings of human becoming studies (Doucet & Bournes, 2007). These four themes are well applied to understanding the lived experience of chronic disease, including diabetes.

1. Persistent struggling is persevering with urgent intensity. This concept includes strength and moving forward in the face of adversity. This is the essence of the lived experience.
2. Anticipating possibles is conceiving and visualizing what is not yet but may yet be. It contains the essence of hope and the perception of potentials. The possibles are the unique vision of the person living the experience.

3. Uplifting calmness is a buoyant serenity. Through this concept we understand the value of contentment and satisfaction. It includes the release of burden and the awareness of accomplishment.
4. Anguishing solemnity is coping with disease and change. This includes grieving for what may or may not be. It has been described as sorrowful and attentive bewilderment.

Through the application of the Human Becoming framework we can gain insight into the lived experience of our patients with diabetes. By focusing on the Persistent Struggling that occurs with chronic disease and the Anticipating Possible with regards to each patient's hopes in diabetes care, each patient will have the opportunity to improve his/her care.

Nurse practitioners, working with chronic disease, are often able to improve interactions based on reflective practice behavior (Johns, 2009). Reflective practice encourages nurses to look beyond the "high grounds" of facts being shared, and instead move into the "swampy low lands" of human interaction and patient care. This reflective process recognizes the value of bidirectional interaction. Human interactions are constantly in motion; this includes our concepts of health and the patient's concepts of health. Often these concepts are in conflict and moving in opposed directions.

By describing this ongoing pattern of occurrence, we can improve our understanding of health and goals through the lived experience of our patients. Through bi-directional dialoguing, insight into the lived experience of the individual and the impact of illness can be obtained. The embrace of tacit knowledge is vital in this

understanding (Johns, 2009; Raymond, 2006). Much of what occurs between providers and patients moves into realms that are difficult to quantify.

Human Becoming Leading-following

Dr. Parse's model has further evolved with the leading-following model (Parse, 2008). Whereas leadership is often viewed as a unidirectional activity, nurses recognize the necessity of its bidirectional nature. While the leader provides insight into direction, the patient must be a willing participant who embraces the shared vision that is crafted with the provider. In sharing this vision both the provider and patient are learning, and goals are seen as mutual.

The Leading-Following model holds that this is deliberately innovating with potent engaging. This conceptual model follows a belief in persistently pursuing excellence. Given the nature of human interaction, this is unpredictable and constantly changing due to the bidirectional creation process (Parse, 2008). The assumptions, essence, and processes of this model are outlined in Table 2.

Table 2

Human Becoming Leading Following Model

Assumptions	Essence	Processes
Meanings unfold with deliberate innovating	Deliberately innovating is committing to a vision with vigorous energizing	*Committing to a vision* is being passionately present with something of value *Vigorous energizing* is enlivening commingling
Changing patterns surface with potent engaging	Potent engaging is willingly risking in living with ambiguity	*Willingly risking* is daringly venturing forth *Living with ambiguity* is moving with the vague
Infinite possibilities emerge with persistently pursuing excellence	Persistently pursuing excellence is revering others with vigilant attending	*Revering others* is honoring uniqueness *Vigilant attending* is cautiously witnessing

Note. This table is adapted from Parse, 2008, p. 371.

Co-creating with patients allows for improved management of chronic disease states. Patients must be in charge of their disease; forming a shared vision encourages compliance with lifestyle changes and improved treatment. In selecting Dr. Parse's work as a theoretical model for this pilot study, this conceptual framework seeks to offer insight to improve patient care and draws upon the patient's lived experience.

Diabetes remains a disease of self-management and individual care. Allowing care to be tailored to each person's lived experience will result in improved patient engagement, diabetes control and better long-term outcomes. Following Parse's leading-following model, with the added tools of CGM, the patient can gain improved

understanding of their patterns, and the provider can improve their leadership role with greater engagement. While generalizations are possible and the development of interventional algorithms may improve care, each patient is ultimately responsible for how they manage their disease.

Parse's Human Becoming Leading-Following model uniquely embraces this. Understanding this bi-directional movement of information is critical to this process. This blending of nursing theory with clinical application of Continuous Glucose Monitors will provide additional information for both patients and providers.

METHODOLOGY

Background

Patients have had access to rt-CGM since 2006. There has been much discussion surrounding the use of these devices and the importance of always knowing what the blood glucose levels are. Many healthcare professionals working in the diabetes field believe that the trend analysis, by visualization of the waveform, may be more important than the awareness of the glucose level.

This pilot study explored this question by providing two groups of patients with Dexcom rt-CGM devices. The control group received standard rt-CGM devices, showing both trend and numerical glucose value. The experimental group received rt-CGM devices with their numerical glucose value obscured but were otherwise functioning normally.

Design, Setting, and Sample

A two-group quasi-experimental comparative design was used for this study. The setting was the subjects' homes or wherever they chose to monitor their glucose with their rt-CGM device. The sample (N = 10) was less than what had been originally planned for (N=20). However financial constraints limited the number of subjects enrolled. Subjects were recruited from the Desert Endocrinology private Endocrine practice in Henderson, Nevada and consisted of two groups of 5 subjects each. Subjects were enrolled using the inclusion criteria below. We were unable to meet the goal of N=20, which was estimated to provide sufficient power to detect statistical significance between the two populations' primary outcomes of HgbA1c and glucose level standard

deviations (SD). The power analysis by G*Power-3 (Faul et al., 2010) is shown in Figure 11.

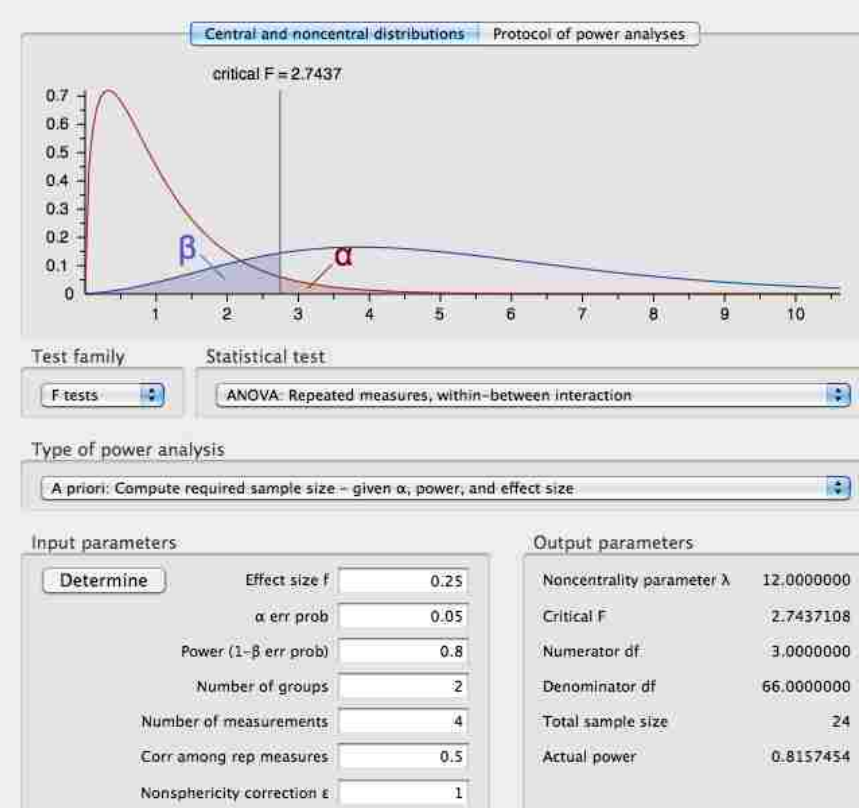


Figure 11. G*Power analysis of samples size estimated to reach statistical significance.

Inclusion criteria.

To participate in this study, subjects were required to meet the following criteria:

- 18-60 years old.
- Diagnosed with Type-1 DM and on insulin therapy for at least 6 months prior to the study.
- Receiving treatment of either continuous subcutaneous insulin infusion (CSII/pump) therapy or multiple daily injection (MDI) therapy.

- Naïve to rt-CGM; no prior experience with real-time CGM. Prior use of retrospective CGM analysis will not be exclusionary.
- Willing and able to understand and sign an informed consent in English.
- Willing to allow finger stick testing of glycosolated hemoglobin A1c (HbA_{1c}) to be done in the office at time of enrollment and completion of the study.

Exclusion criteria.

Subjects with any of the following criteria were excluded from this study:

- Age <18 or > 60 years old.
- Inability to understand and give informed consent in English.
- Current or past use of a real-time CGM device.
- Unwillingness to allow finger stick testing of HbA_{1c}.
- Type-2 DM.
- Chronic use of any acetaminophen containing product
- Not currently on MDI or CSII.
- Any contraindication in ability to complete this 12 week trial.

Instruments

Dexcom real-time Continuous Glucose Monitor.

The Dexcom SEVEN PLUS™ system is manufactured by Dexcom, Inc. of San Diego, California (www.dexcom.com). This is a real-time continuous glucose monitor that is designed to aid in the detection of hypo- and hyperglycemic events in persons 18-years and older. It is used to facilitate improvements in glucose control by providing

patients and providers with information regarding response to medications and adjustments in therapies, as well as providing alerts to potential hypo- and hyperglycemic excursions.

The Dexcom SEVEN PLUS™ system consists of three parts: a subcutaneous sensor functioning for seven days, a wireless transmitter, and a rechargeable receiver unit. This device has a wireless range of 6 feet from the transmitter to the receiver. The transmitter and sensor are waterproof for normal activities such as showering or bathing. Their use while swimming is discouraged. The receiver is not waterproof (Dexcom, 2010).

The Dexcom SEVEN PLUS™ allows a person using it to see the numerical value of his/her glucose, and review the glucose for the last hour, and the past 3, 6, 12, and 24 hour period as shown in Figure 12. Glucose readings are stored for approximately 30 days and can be downloaded via PC with Dexcom DM3 software.

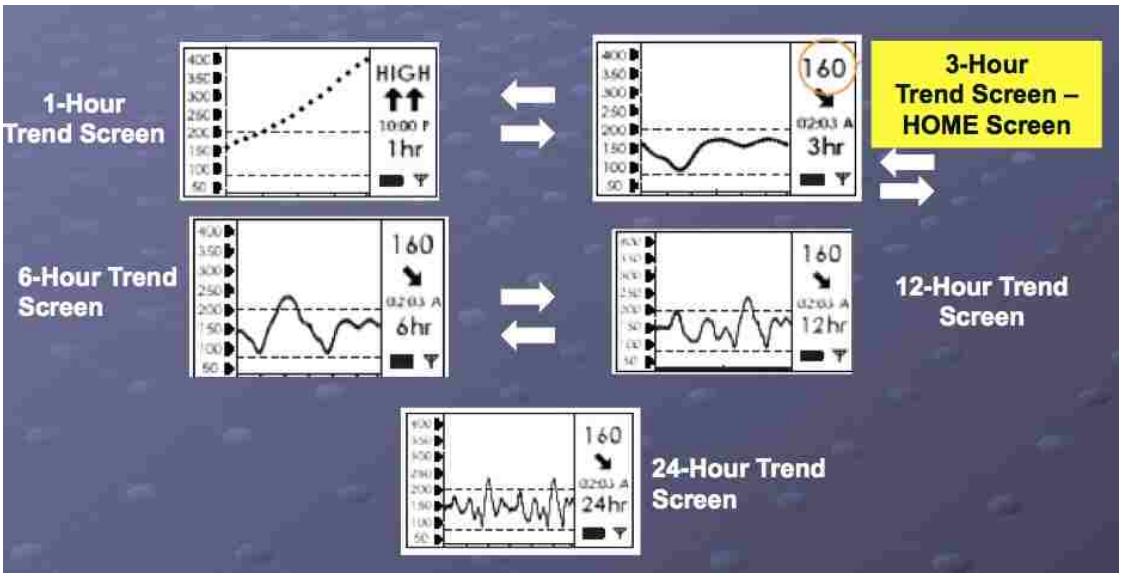


Figure 12. Dexcom SEVEN PLUS™ Screen Displays. This figure demonstrates the standard screens as

viewed on the Dexcom SEVEN PLUS™ system, allowing users to see their glucose level, rate of change, and recent pattern. This material is adapted from the Dexcom SEVEN PLUS™ User Guide.

The sensor and transmitter sample twice every second, recording the glucose value at the five-minute interval. No averaging of the glucose values occurs. The Dexcom SEVEN PLUS™ records 288 readings a day, providing valuable trending information on glucose levels. Rate and direction of change are also indicated with the Dexcom CGM, providing information on the current action of the patient's glucose. The Dexcom SEVEN PLUS™ requires that the patient enter a calibration point based on a SMBG every 12 hours.

An example of the Dexcom SEVEN PLUS™ printout is shown in Figure 13. The patient's glucose is visualized across the day. The X-axis is the time of day and the Y-axis is the glucose level expressed in mg/dl. Each colored line represents a 24-hour period, midnight to midnight.

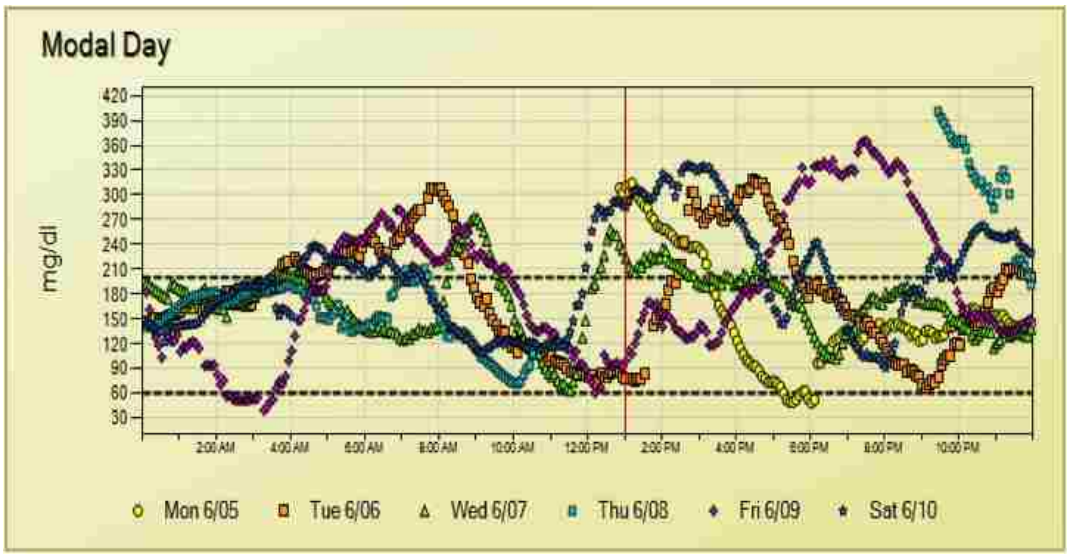


Figure 13. Dexcom DM3 Software Modal Day Printout. This figure comes from the collected data files of Tomas C. Walker.

Figure 14 represents an example of the data table obtained from the Dexcom DM3 software, corresponding to the same data file seen in the modal day charts shown in Figure 13. This chart provides information on the number of glucose readings, average, minimums, maximums, the SD, and quartile data. These data are both summed and broken down hourly.

Stat	Totals	12 am	1 am	2 am	3 am	4 am	5 am	6 am	7 am	8 am	9 am	10 am	11 am
# Readings	1271	59	58	60	57	60	60	59	59	60	60	46	34
Average	176.9	150.8	155.9	152.6	167.6	193.5	197.1	204.5	205.5	194.6	149.2	115.8	95
Minimum	39	103	70	51	39	148	135	124	126	104	71	74	63
Quartile 25	134	138	144.5	166	160	179.2	150.5	150.5	161.5	131.5	114.8	99.2	79.5
Median	169	149	168	174	189	192	214.5	209	203	216.5	135	115.5	87.5
Quartile 75	213	162.5	176	182	195	211.2	231.5	247	241	249.5	193.5	131.5	108.2
Maximum	401	191	187	190	223	238	256	282	307	293	256	178	187
SD	66.3	21.6	29.5	50.1	49.9	24.7	42.9	51.2	53.8	60.6	50.9	22.5	25.6
Est. SD	58.6	18.2	23.4	11.9	25.9	23.7	60	71.5	58.9	87.5	58.4	23.9	21.3
IQR	79	24.5	31.5	16	35	32	81	96.5	79.5	118	78.8	32.2	28.8
SE Mean	1.9	2.8	3.9	6.5	6.6	3.2	5.5	6.7	7	7.8	6.6	3.3	4.4
%CV	37.5	14.4	18.9	32.8	29.7	12.8	21.8	25	26.2	31.1	34.1	19.4	26.9

Stat	Totals	12 pm	1 pm	2 pm	3 pm	4 pm	5 pm	6 pm	7 pm	8 pm	9 pm	10 pm	11 pm
# Readings	1271	41	46	48	48	48	48	48	48	48	57	60	59
Average	176.9	154.1	194.6	207	194.9	197.8	184.7	184.8	195.4	177.2	188	182.3	170.3
Minimum	39	60	75	126	115	71	48	96	110	65	71	115	129
Quartile 25	134	83	151	176.8	150	160.2	112.8	118.5	137.8	118	131	144.2	137.5
Median	169	98	208	213.5	191.5	199	184.5	146	149.5	156	153	153	146
Quartile 75	213	234	252.2	239.8	229.2	251.5	263.2	223.2	217.5	208.8	224	182	202.5
Maximum	401	310	314	304	306	319	334	341	365	339	401	356	329
SD	66.3	87.6	67.8	50	57.4	78.6	93.9	89.6	90.9	84.3	93.1	69.2	46.6
Est. SD	58.6	111.9	75.1	46.7	58.7	67.6	111.6	77.7	59.1	67.3	68.9	28	48.2
IQR	79	151	101.2	63	79.2	91.2	150.5	104.8	79.8	90.8	93	37.8	65
SE Mean	1.9	13.7	10	7.2	8.3	11.3	13.6	12.9	13.1	12.2	12.3	8.9	6.1
%CV	37.5	56.8	34.9	24.2	29.4	39.7	50.8	48.5	46.5	47.6	49.5	38	27.4

Figure 14. Dexcom DM3 Software Statistical Table. This figure is adapted from the Dexcom DM3 Software and the collected data files of Tomas C. Walker.

Fear of hypoglycemia survey.

The Hypoglycemia Fear Survey (HFS) is a qualitative tool for assessing a patient's concerns related to hypoglycemia. Developed in 1987 and used extensively in diabetes research it has an established internal validity with a Cronbach's alpha (α) of 0.89 – 0.96, as well as an established record of reliability (Cox et al., 1987; Irvine et al., 1994). The HFS Survey tool (Appendix A) consists of a 33-question, Likert-type scale divided into two subsections: Behavior (HFS-B 15 questions) and Worry (HFS-W 18 questions). The HFS tool establishes an understanding of worry associated with hypoglycemia and the behaviors patients undertake in attempting to avoid these events. The HFS-W scale has been correlated with increased anxiety related to poor control of diabetes and unpredictability of hypoglycemic awareness. Fear reaction behaviors,

including insufficient use of insulin and excessive food intake, have been associated with high HFS-B scoring (Polonsky, et al., 1992).

There are few data associated with the use of rt-CGM and its impact on hypoglycemia fear. This tool will provide an opportunity to assess this potential benefit of rt-CGM use in decreasing fear of hypoglycemia. Retrospective CGM has not been studied in relationship to changes in hypoglycemia fear. Given the lack of real-time feedback, this survey is appropriate.

Quality of life index.

Quality of life issues are recognized as disproportionately impacting persons with diabetes. The need for constant attention and ongoing care assessments create continuous demands for persons with Type-1 DM. These demands are known to negatively impact perceptions of quality of life (Anderbro et al., 2010).

Ferrans and Powers have created a tool for assessing Quality of Life (QOL) issues in persons with chronic disease processes (Ferrans, 2011). This tool has been adapted for persons with diabetes. The Ferrans' and Powers' Quality of Life index-diabetes III version (QLI-D) is the result of this disease-specific tool development. The tool has been established to have internal and external validity and has subsequently been developed into other disease-specific assessment tools (DeSouza & Nairy, 2003).

The QLI-D tool is well validated and has demonstrated consistency when assessing the QOL issues associated with diabetes (DeSouza & Nairy, 2003). Cronbach's alpha-α scoring has been validated at 0.94 and 0.97 in prior testing (DeSouza & Nairy; Ozer & Efe, 2006). Additionally, 27 studies have found the Quality of Life Index

sensitive when detecting change in perceptions of quality of life issues in pre- and post-test comparison (Ferrans, 2011).

For this pilot study we used the Diabetes specific, QOL Index – Diabetes III version assessment tool (QLI-D). Subjects were given a QLI-D assessment at the time of enrollment and again at completion of the study. Scoring on the QLI-D survey was conducted according to the guidelines published with the DM-QOL tool and using the spreadsheet analysis tool provided by the authors.

The QLI-D tool consists of 66 items divided into two sub-sections measuring 33 similar items, based on importance to the individual, and the individual's satisfaction with each item. The 33 items cover a base of 4 domains: health/function, social/economic, psychological/spiritual, and family (Appendix B).

Primary Outcomes

Primary endpoints were:

1. Measured changes in the HbA_{1c} from baseline (week Minus-1) and at completion (Week +11).
2. Changes in the standard deviation of the glucose, as measured by the Dexcom CGM device, between baseline (week Minus-1), Week +4, Week +8 and at completion (Week +11). Standard deviation will be the calculated averages furnished by the Dexcom DM3 CGM software.

Secondary Outcomes

Secondary endpoints were:

1. Changes in the level of fear related to hypoglycemia (Appendix A). The Hypoglycemia Fear Survey (HFS) was given at baseline (week Minus-1) and at completion (Week +11).
2. Changes in Quality of Life related to diabetes, as measured by the Ferrans' and Powers' Quality of Life – diabetes III version assessment tool (Appendix B). This was given at baseline (week Minus-1) and at completion (Week +11).
2. At the final visit, subjects were asked an open-ended question, allowing expression of how they most benefitted from the use of the CGM device (Appendix C).

Protection of Human Subjects/IRB

Approval for this study was obtained from the UNLV Institutional Review Board for the Protection of Human Subjects.

Procedure

Baseline/Week Minus 1:

Potential subjects were given an explanation of this pilot trial in accordance with informed consent procedures. Those agreeing to volunteer were asked to sign an informed consent document. Following informed consent, baseline HbA_{1c} was measured in the office using CLIA-waived instrumentation based on finger stick whole blood measurements. Subjects also completed baseline Fear of Hypoglycemia and Quality of Life Assessments.

Subjects were randomly assigned to groups by the withdrawal of red or blue marbles from a cloth bag. Five blue marbles were assigned to the unmodified units and five red marbles were assigned to the numerically blinded units. The modified units had the glucose value obscured but were otherwise completely functional. During the initial Week Minus-1 period all subjects were blinded to the data, allowing subjects to serve as their own controls.

Week 0:

Subjects returned for follow up. The Dexcom CGM units were un-blinded and returned to the subjects. This began the monitoring phase of the study. Subjects had the CGM units available to them for the next 11 weeks. Subjects were provided the investigator's contact information in the event of problems with their CGM units. Normal medical care and interventions were allowed. No additional diabetes education or counseling was conducted during the monitoring phase of the trial.

Week +4:

Subjects in both arms returned for regular downloading of their devices, after which the devices were returned to the subjects for ongoing use. Additional sensors were supplied to the subjects at this time.

Week +8:

Subjects in both arms returned for regular downloading of their devices, after which the devices were returned to the subjects for ongoing use. Additional sensors were supplied to the subjects at this time.

Week +11:

Subjects in both arms returned for their final data download. Study completion HbA_{1c} was performed in the office using CLIA-waived instrumentation based on finger stick whole blood measurements. Subjects also completed post-study Fear of Hypoglycemia and Quality of Life Assessments. Dexcom rt-CGM devices in both arms were returned to factory original condition, memory cleared, and given to the patients to keep for personal use.

Data analysis

Descriptive statistics (frequencies, mean, SD) are used to describe the sample's demographics and characteristics (see Appendix D – Demographic Information Form). Mean HbA1, average glucose levels, and standard deviations of glucose were analyzed by Repeated Measure ANOVA at Week -1, Week +4, Week +8, and Week +11. Analysis of the Hypoglycemic Fear Survey was conducted via Repeated Measure ANOVA.

The Ferrans' and Powers' Quality of Life Index was scored using a tool supplied by the authors. This tool provided graphing output as well as statistical scoring in the changes detected in Quality of Life measures.

Data Management Plan

Subject glucose data were collected from the rt-CGM devices using Dexcom DM3 Software package (www.dexcom.com). Patient data files were labeled using a subject identifier that was stored separately from the subject demographic data. Subject identifier consisted of first and last initials and birth year. Glucose level data were analyzed using the Dexcom DM3 CGM software and SPSS/PASW software.

Quality of Life data were analyzed using the Excel spreadsheet tool provided by Ferrans and Powers, as well as SPSS/PASW. Data will be maintained as separate files securely stored at Desert Endocrinology Clinical Research Center and with Dr. Carolyn Yucha at the University of Nevada, Las Vegas. After 5 years electronic data will be deleted per 7-pass wipe, and physical documentation will be shredded.

Study Dates:

First Subject enrollment: 02 November 2011

Completion of last patient last visit: 03 Feb 2012

FINDINGS

Data were analyzed using the Statistical Package for the Social Sciences (SPSS 20.0, 2011). Primary end points measured included the changes in HbA_{1c} levels from baseline enrollment (Week -1) to study completion (Week +11). Additionally, primary end points evaluated changes in standard deviation of the glucose and the average glucose, from enrollment, to completion with data gathered at Week +4 and Week +8 during data downloads.

Sample Description

Ten persons with Type-1 diabetes were enrolled in this trial study, beginning with the first patient's first visit on 2 November 2011, and enrollment of the last subject on 18 November 2011. All subjects provided written informed consent prior to initiation of the study. The final subject's final visit and closure of the study occurred on 3 February 2012.

Subjects were naïve to the use of real time continuous glucose monitoring (rt-CGM). Previous use of retrospective (diagnostic) CGM was not considered exclusionary. The sample consisted of 4 male (40%) and 6 female (60%) subjects with an average age of 42.6 ± 9.6 years. Patients on multiple daily injection therapy (MDI) composed the majority of the sample, representing 60% (6 subjects); 40% (4 subjects) used continuous subcutaneous insulin infusion/pump therapy (CSII). The sample population had an average Body Mass Index (BMI) of 26 ± 2.1. Duration of Type-1 diabetes in study

subjects ranged from 2 to 40 years, with average duration of 20.0 ± 13.6 years. Baseline HbA_{1c} was 7.46 ± 1.27%.

After informed consent was obtained, subjects were randomized to either the experimental or the control group. Baseline HbA_{1c} for the control group was a mean of 7.24 ± 1.05%. The control sample consisted of 3 males and 2 females. Mean HbA_{1c} for the experimental group was 7.68 ± 1.56%. The experimental sample consisted of 4 females and 1 male.

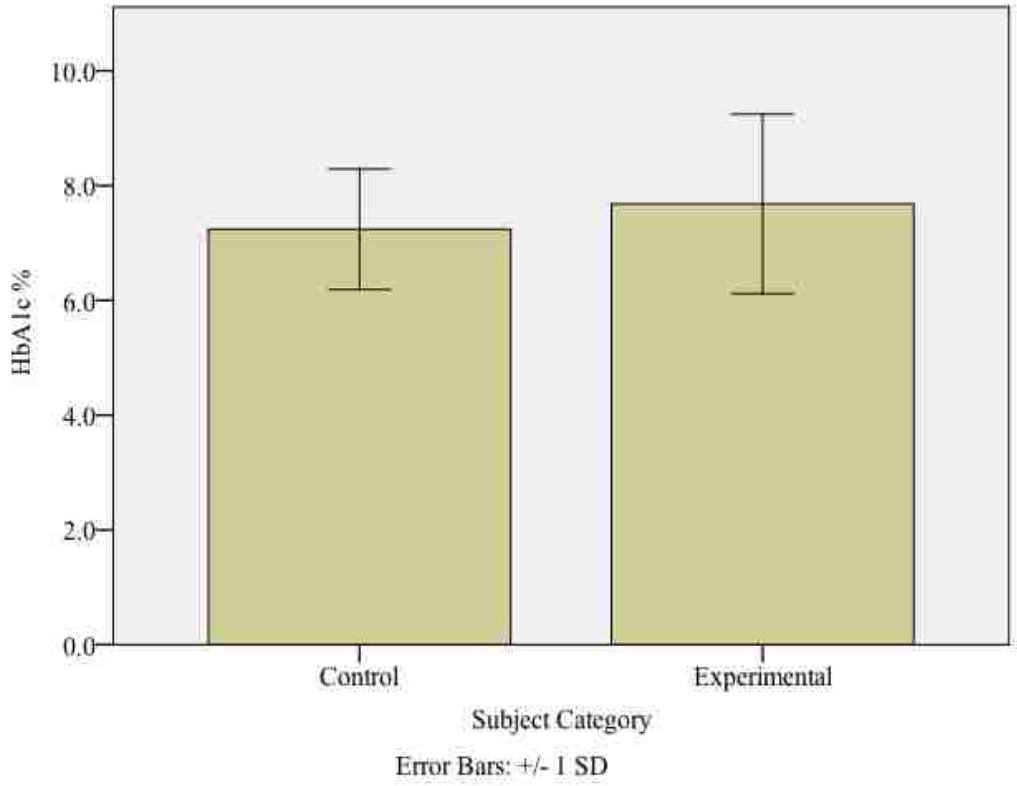


Figure 15. Baseline HbA1c for the Control and Experimental groups.

All subjects underwent an initial data collection period during which their rt-CGM device was blinded and functioning in a retrospective mode. This initial run-in

period provided baseline data of the patients' glucose patterns prior to initiation of the trial, allowing the subjects to serve as their own controls. Following the run-in period, the CGM was un-blinded and returned to the subject for continued use and data collection. The only restriction was on the experimental units, which were blinded to the numerical glucose value. Subjects with experimental rt-CGM devices were able to visualize their glucose patterns, including directional arrows with rate of change information. High and low glucose alerts functioned normally. Patients were requested to use the device full-time but no value or restriction was placed on this request. There was no statistical difference (p = .251) in duration of use between the two groups of subjects.

Table 3

Days of rt-CGM use following blinded data collection period

Subject	n	M ± SD
Control	5	78.2 ± 3.2
Experimental	5	75.2 ± 4.3

Note. All subjects underwent a blinded data collection period of at least 5 days.

All subjects were provided sensors for the duration of the trial. Sensors were distributed at monthly intervals, allowing for downloading of data and prevention of information loss in the event of loss or damage to the rt-CGM device. There was no loss or damage of devices during this trial. One experimental subject withdrew at Week +1 due to a skin allergy associated with sensor adhesive. The withdrawn subject's data were

not included for analysis. This subject was replaced with an alternate, preserving the original target of ten subjects.

Primary Outcomes

Question 1. Measured changes in the HbA1c.

The mean HbA_{1c} and standard deviations are shown in the table below. HbA_{1c} was measured at the initiation of the trial and on the subjects' final day in the trial. Given the retrospective time-dependent nature of HbA_{1c} testing, this was measured only twice, at baseline enrollment and completion of the trial.

Table 4

Subject Baseline and Completion of HbA_{1c} % ± SD by Category

	Baseline	Completion
Control (n = 5)	7.24 ± 1.05	7.18 ± 1.31
Experimental (n = 5)	7.68 ± 1.56	6.18 ± 1.13

Note. All HbA1c testing by Bayer A1C NOW, CLIA waived kits.

The control subjects' average HbA_{1c} reduction was 0.06% ± 0.61%, but this was not statistically significant. This ranged from a decrease of 1.1% to an increase of 0.5%. Of the 5 control subjects, one exhibited no change in HbA_{1c}, 3 subjects had minor increases in HbA_{1c} ranging from 0.1 – 0.5%, and one experienced a decrease in HbA_{1c} of 1.1%.

The experimental group demonstrated a mean reduction in HbA_{1c} of 1.5 ± 0.9% which reached statistical significance ($p < .05$). Decreases in HbA_{1c} in the experimental group ranged from 0.1 – 2.7%. None of the experimental subjects experienced an increase in HbA_{1c}.

RM ANOVA revealed no significant difference in the HbA_{1c} reduction between the experimental and control groups ($p = .725$). Posthoc power analysis demonstrated insufficient power to detect such a difference. Despite the obvious difference in the plots, this failed to achieve significance most likely due to the small sample size.

Table 5

HbA1c Comparison between Groups

Source	SS	df	MS	F	*p*-value
Between Subjects					
Control/Exp.	.392	1	.392	.133	.725
Error	23.63	8	2.95		
Within Subjects					
Time	3.04	1	3.04	9.12	.017
Time*group	2.59	1	2.59	7.77	.024
Error	2.66	8	.333		

Note. Analysis by RM ANOVA

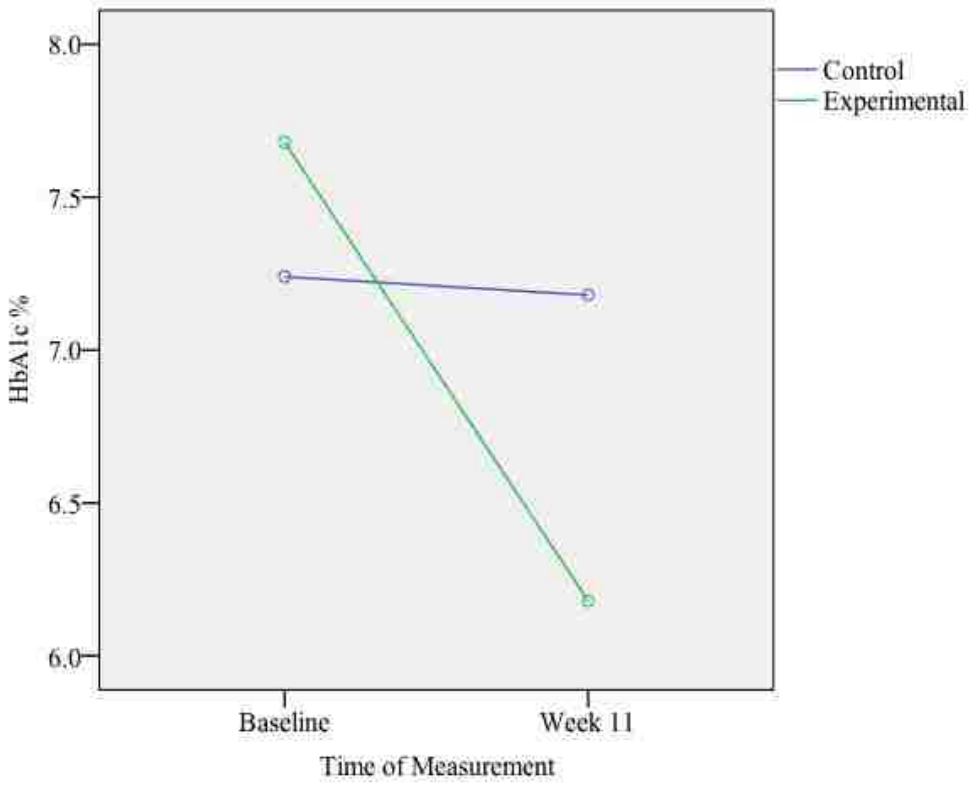


Figure 16. Plotted change in HbA1c by category.

The HbA_{1c} is considered to be an average of the subject's glucose level over the past 12 weeks. The mean glucose level is compared here at baseline week +4, week +8, and study completion. Mean glucose levels were calculated with the Dexcom DM3 software package (www.dexcom.com).

RM ANOVA revealed no significant difference in the mean glucose levels across the four measured data points between the groups (p = .521). There was significant variability demonstrated between and within groups for mean glucose levels.

Table 6

Change in Mean Glucose ± SD from Baseline to Completion by Subject Group

	Baseline	Week 4	Week 8	Week 11
Control (n = 5)	179 ± 29	179±32	158±32	169 ± 20
Experimental (n = 5)	157 ± 46	168±51	163±39	143 ± 28

Note. All glucose measurements presented in mg/dl.

Table 7

Comparison of Average Glucose between Groups

Source	SS	df	MS	F	*p*-value
Between Subjects					
Control/Exp.	1822.50	1	1822.50	.45	.521
Error	32414	8	4051.75		
Within Subjects					
Time	1830.20	3	610.06	1.52	.233
Time*group	1314.5	3	438.16	1.09	.369
Error	9582.8	24	399.28		

Note: Testing by RM ANOVA.

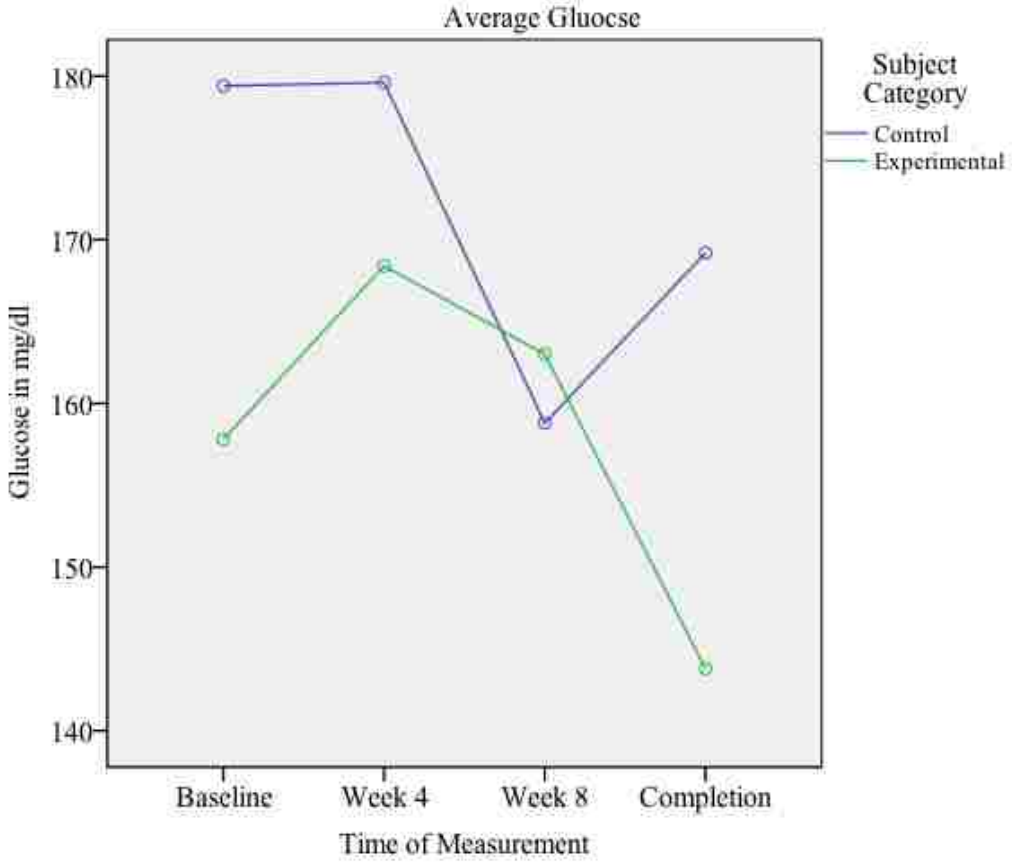


Figure 17. This figure presents the average glucose levels measured at baseline, Week +4, Week +8 and completion.

During the trial period there was no effort made to restrict the subjects' therapy modifications or other medical care. However, to the best of our knowledge, no subject underwent any significant medical intervention during the trial period.

Question 2. Changes in the standard deviation of the glucose.

Changes in glucose standard deviations were measured by the Dexcom CGM device, at baseline, week +4, week+8 and study completion. Changes in glucose standard deviation were evaluated for differences in glucose variability between the control and experimental group.

Subjects in the control group achieved a statistically significant drop in standard deviation ($p < .05$), while the decrease achieved in the experimental group did not reach significance. This might be attributed to the experimental groups' initial lower standard deviation. RM ANOVA revealed no significant difference between the groups ($p = .232$) despite the $p < .05$ achieved within the control group. While the drop in glucose standard deviation is encouraging, and warrants further investigation as to whether statistically significant improvements in reductions of standard deviation (inferred as glucose variability) could be achieved in a larger sample size.

Table 8

SD Glucose from Baseline to Completion by Subject Group

	Baseline	Week 4	Week 8	Week 11
Control (n = 5)	82±15	64±9	59±7	63±12
Experimental (n = 5)	61±14	62±13	58±22	52±10

Note. All glucose measurements presented in mg/dl.

Table 9

Comparison of Glucose Standard Deviation between Groups

Source	SS	df	MS	F	*p*-value
Between Subjects					
Control/Exp.	731.02	1	731.02	1.67	.232
Error	3494.20	8	436.77		
Within Subjects					
Time	1278.67	3	426.22	3.82	.023
Time*group	642.87	3	214.2	1.92	.153
Error	2678.2	24	111.59		

Note. Analysis by RM ANOVA.

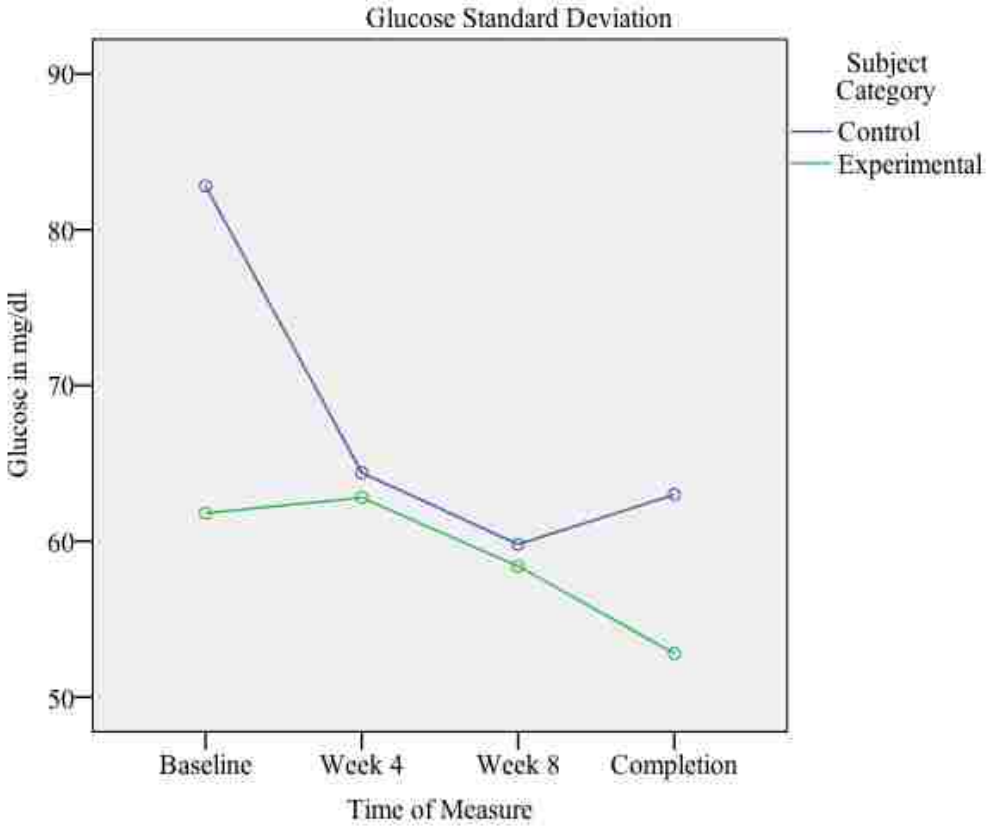


Figure 18. This figure presents the change in the Standard Deviation of the glucose from baseline to completion.

Secondary Outcomes

Two secondary endpoints were considered during this pilot trial:

1. Changes in the level of fear related to hypoglycemia as measured by the Hypoglycemia Fear Survey (HFS) (Appendix A). Subjects completed the HFS at baseline (enrollment) and at completion of the trial during the final visit.
2. Changes in the quality of life, as measured by the Ferrans' and Powers' Quality of Life (diabetes version) Survey, at baseline and study completion (Appendix B).

All subjects completed both sets of surveys.

Secondary Outcome - Question 1.

The HFS scale contains 33 questions scored as a total score, consisting of two sub-scales: Worry (15 questions) and Behavior (18 questions). These subscales attempt to determine the level of worry subjects experience regarding hypoglycemia, and its impact on their behavior in avoiding hypoglycemia.

Subjects in both the control group and experimental group reported reductions in their total HFS scoring as well as both subscales. RM ANOVA testing revealed these reductions were statistically significant within the groups ($p < .05$). Despite the clear changes in the plot comparison (Figure 19), differences between the groups did not achieve statistical significance ($p = .547$).

Table 10

Change in Hypoglycemia Fear Survey (HFS) Total Scoring

	Baseline	Completion
Control (n = 5)	47 ± 32.9	38.6 ± 23.5
Experimental (n = 5)	41.6 ± 26.6	24.6 ± 16.4

Table 11

Hypoglycemia Fear Survey Scoring (Total) Comparison

Source	*SS*	*df*	*MS*	*F*	*p-value*
Between Subjects					
Control/Exp.	470.45	1	470.45	.396	.547
Error	9496.00	8	1187.00		
Within Subjects					
Time	806.45	1	806.45	6.81	.031
Time*group	92.45	1	92.45	.789	.400
Error	937.60	8	117.20		

Note. Analysis by RM ANOVA.

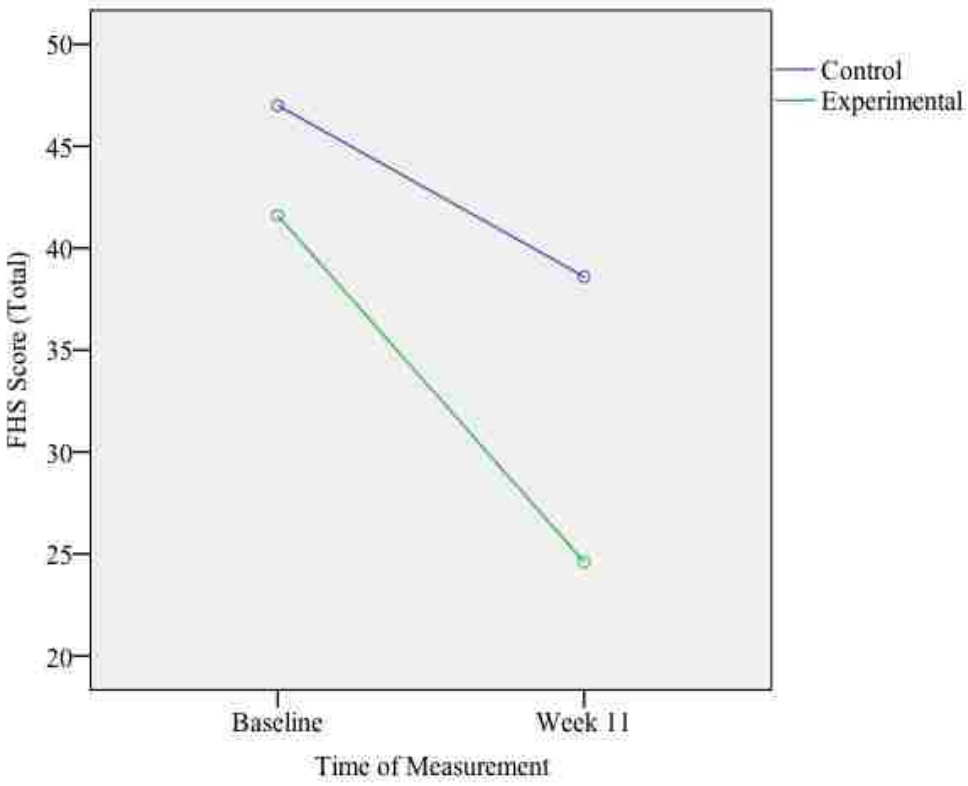


Figure 19. Hypoglycemia Fear Survey Scoring (Total) from Baseline to Completion.

In the interests of clarity, the Behavior and Worry subscales are presented separately.

Table 12

Change in Hypoglycemia Fear Survey, Behavior Sub-Scale

	Baseline	Completion
Control (n = 5)	17.8 ± 8.7	14.2 ± 4.9
Experimental (n = 5)	16.2 ± 7.7	11.5 ± 5.2

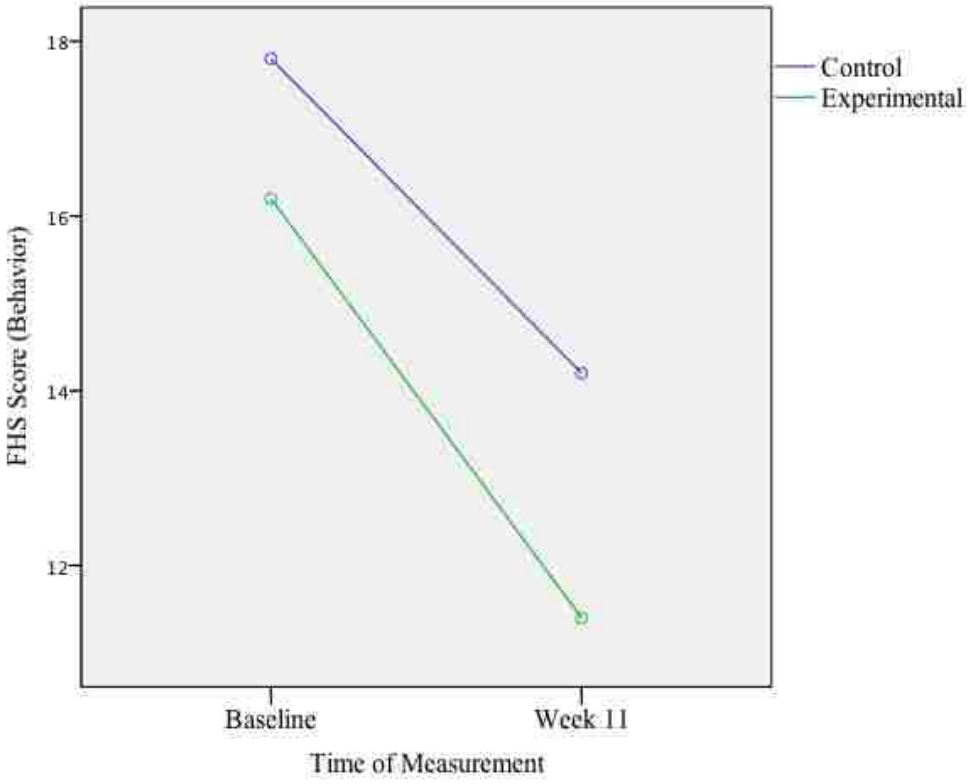


Figure 20. HFS Scoring: Change in Behavior measures sub-scale.

Table 13

Change in Hypoglycemia Fear Survey, Worry Sub-Scale

	Baseline	Completion
Control (n = 5)	29.2 ± 24.6	24.2 ± 20.2
Experimental (n = 5)	25.4 ± 20.2	13.2 ± 12.5

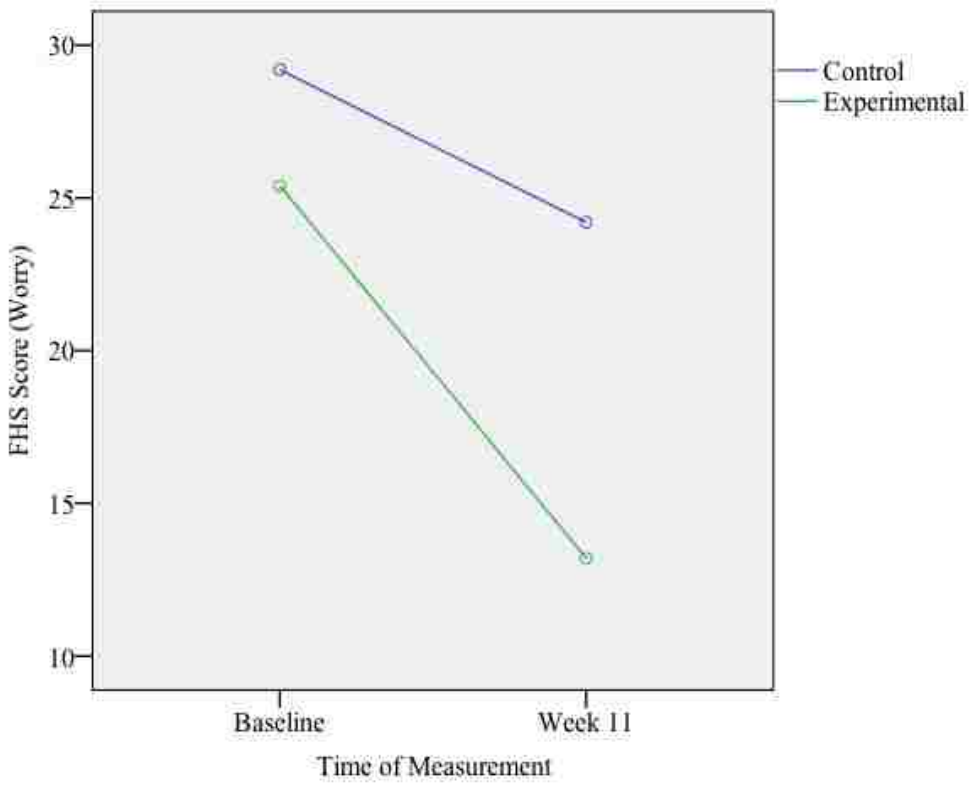


Figure 21. HFS Scoring: Change in Worry measures sub-scale.

Repeated measures of variance (RM ANOVA) were used to assess the HFS Total, Behavior, and Worry scores across the study, from baseline to completion. A statistically significant drop was seen from baselines to completion for total scoring (p = .031), worry (p = .034) and behavior sub-scales (p = .044). Significance was not demonstrated between the Control and Experimental groups for Behavior (p = .595) and Worry (p = .558) subscales.

While the trending is evident in favor of the experimental group, sample limitations prevent us from establishing statistical significance. Despite these limitations, data demonstrates a reduction in subjects' Fear of Hypoglycemia scores, both overall and within the sub-groups of Worry and Behavior.

Secondary Outcome - Question 2.

The Ferrans' and Powers' Quality of Life Survey tool is recognized for its value in assessing subjective quality of life, and measuring the impact of chronic disease. For this trial we utilized the Diabetes Version-3, which has previously established reliabilities with a Cronbach's alpha α of .94 -.97 (DeSouza & Nairy, 2003; Ozer & Efe, 2006).

This tool consists of two sections, each containing 34 questions, measuring the importance of selected variables as rated by the subjects. The QOL scoring tool tabulates scores based on quality of life, health, psychological, spiritual, and family relationship factors. These scores are presented as a numerical value for evaluation of change. Quality of Life data were collected at baseline and at termination of the study.

Table 14

Change in Quality of Life (Total) from Baseline to Completion

	Baseline	Completion
Control (n = 5)	23.1 ± 2.7	25.6 ± 3.9
Experimental (n = 5)	21.4 ± 5.6	24.6 ± 3.2

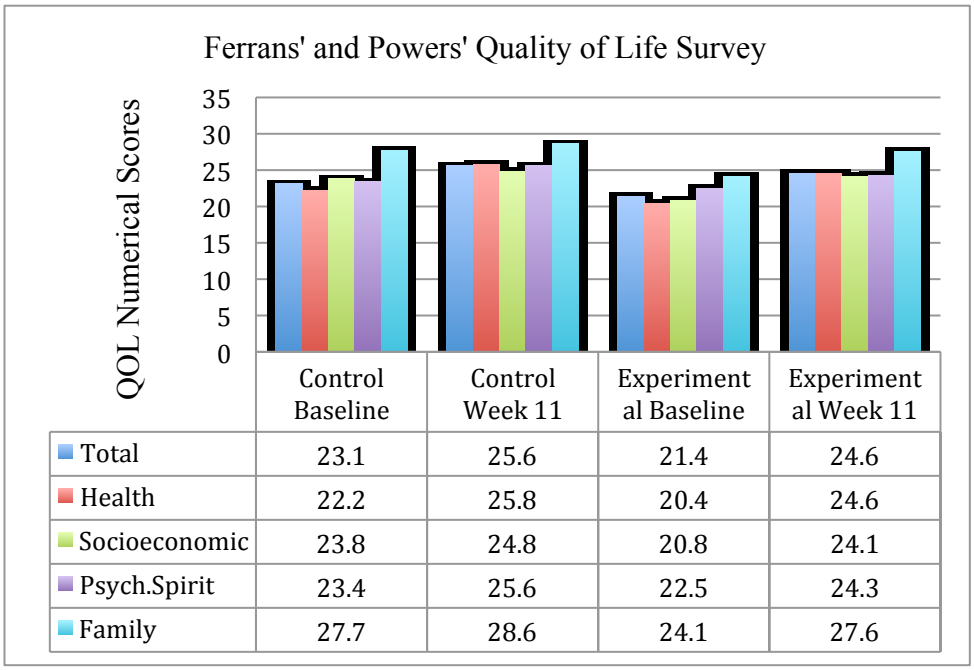
Note. Ferrans' and Powers' scoring is calculated with tools available at http://www.uic.edu/orgs/qli/

Table 15

Between Groups Comparison of Quality of Life (total)

Source	SS	df	MS	F	*p*-value
Between Subjects					
Control/Exp.	9.94	1	9.94	.327	.583
Error	243.26	8	30.40		
Within Subjects					
time	40.95	1	40.95	17.33	.003
Time*group	.641	1	.641	.271	.617
Error	18.90	8	2.36		

Note. Analysis by RM-ANOVA.



	Control Baseline	Control Week 11	Experimental Baseline	Experimental Week 11
Total	23.1	25.6	21.4	24.6
Health	22.2	25.8	20.4	24.6
Socioeconomic	23.8	24.8	20.8	24.1
Psych.Spirit	23.4	25.6	22.5	24.3
Family	27.7	28.6	24.1	27.6

Figure 22. Quality of Life, all scores. Scoring was improved in both the control and the experimental groups. Improvements were noted in all sub-scores of the scale from baseline to study completion at Week +11. Statistical significance is achieved for the QOL total scoring from baseline to study completion. Additionally a $p < .05$ was achieved for both the Health and Family subscales.

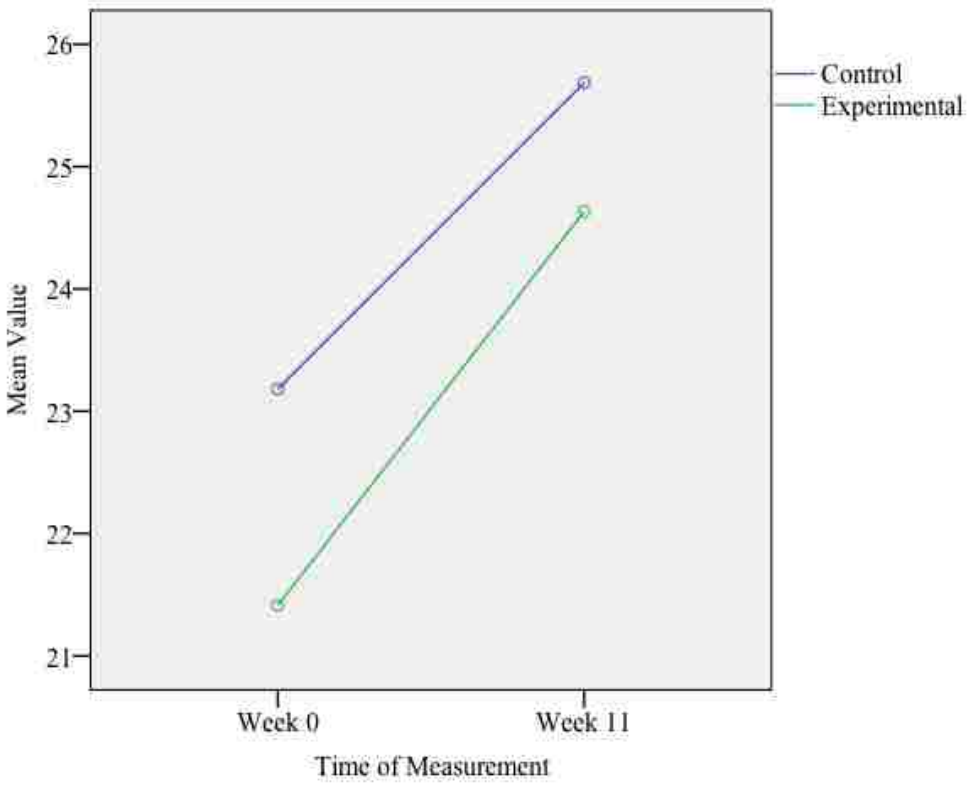


Figure 23. QOL Scoring totals, as a plot.

The QOL Total, Health, and Family scores demonstrated an improvement that reached a $p < .05$. The Socioeconomic and Psychological/Spiritual measures, though demonstrating improvements, did not achieve a $p < .05$. A larger sample may allow for these two subscales to reach statistical significance. The greatest improvement occurred in the perceived quality of Health category, as noted in the table below.

Table 16

Pooled effect Within Subjects (N = 10), Quality of Life.

	F	*p*
Total	17.3	.003
Health	21.7	.002
Socioeconomic	2.9	.125
Psych/Spiritual	4.0	.078
Family	8.5	.019

RM ANOVA testing fails to demonstrate significance between the groups on QOL total measures ($p = .583$). The QOL measurements were virtually parallel, suggesting that patients using the rt-CGM benefitted equally from improved awareness of their glucose patterns, with or without the numerical value (See Figure 24). Both subject categories demonstrated virtually identical changes in their QOL-Total and QOL-Health scoring from baseline to completion.

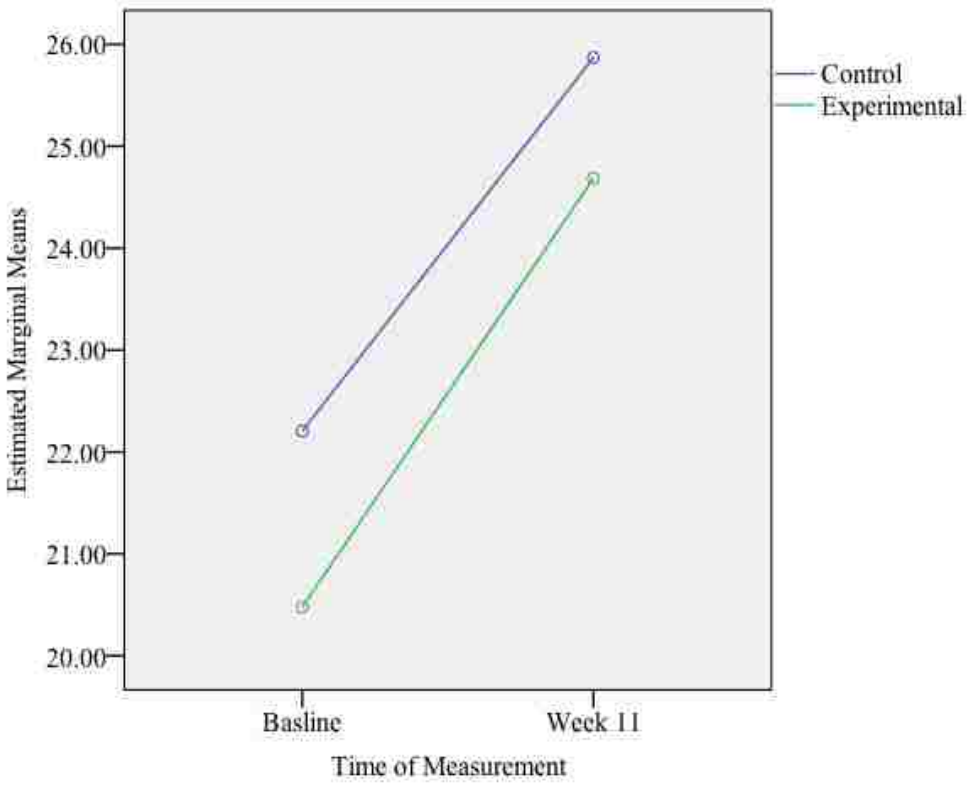


Figure 24. Quality of Life Total Scoring, baseline to completion.

DISCUSSION

This chapter will include a discussion of the study findings, a review of the limitations of this pilot study, and suggestions for future research. Additionally, data unrelated to the study questions will be reviewed, to stimulate further interest on the topic of rt-CGM and subject utilization.

Discussion and Interpretation

Primary outcomes discussion question 1.

The first research question "Changes in HbA_{1c} from baseline to study termination" focused on an examination of the difference between the control and the experimental group. It is recognized that rt-CGM has been demonstrated to improve glucose control as documented by decreases in HbA_{1c} (Garg et al., 2007; Pickup, Freeman, & Sutton, 2011).

There was no statistically significant difference in average HbA_{1c} reduction between the control and experimental groups, as demonstrated by RM ANOVA analysis. However, sample size was very small. Initial predictive analysis had suggested that N = 24 would be the minimum number of subjects needed to reach significance.

In this pilot study, the subjects in the experimental group demonstrated an average HbA_{1c} reduction of $1.5 \pm 0.9\%$ compared to control group subjects, who had a mean reduction of $0.06 \pm 0.61\%$. It is possible that a larger sample size would have demonstrated a significant difference in the control groups' reduction of HbA_{1c}.

Prior studies have suggested that personal use of rt-CGM can result in notable reductions in the HbA1c. Meta-analyses have suggested that the reduction in HbA_{1c} can be greater than 0.9% for persons who use rt-CGM more than 6 days a week (Pickup et al, 2011; Ghandi et al, 2011). However, this reduction calculation was based on patients having a baseline HbA_{1c} of 10%, suggesting that patients with poor control are benefitting the most (Ghandi et al.).

Garg et al. (2007) have reported an average reduction of 0.4% ± 0.5% in HbA_{1c} with rt-CGM use when contrasted against the control group, in persons who had reasonable glucose control (HbA1c ~ 7.4%). Raccah et al. (2009) reported that patients using sensor-augmented insulin pumps, with a baseline HbA1c of 9.1% ± 1.28%, demonstrated a reduction of >1.1% in their $HbA_{1c.}$ The subjects in the Raccah et al. study were being transitioned from MDI therapy to insulin pumps, whereas our subjects were continued on their existing therapies from time of enrollment. Insulin pump therapy initiation is associated with a mean reduction in the HbA_{1c} of 0.95% when subjected to meta-analysis (Weissberg-Benchell et al., 2003).

Previous experience that patients with poorest control would benefit the most is supported by our study. Experimental Subject 11 demonstrated a reduction in her baseline HbA_{1c} of 9.8%, to 7.1% over the course of this study. As an aggregate group, our study subjects (N = 10) demonstrated a mean HbA_{1c} reduction of .78%. This is consistent with other trials reporting improvements with the use of rt-CGM and achieving a $p <. 05$.

Table 17

Change in HbA_{1c} for the pooled sample (N = 10)

	N	M	df	Sig. (2-tailed)
Δ HbA_{1c}	10	.780	9	.048

This study was not solely interested in improvement in HbA_{1c} for those patients using rt-CGM, but also evaluated whether subject access to the glucose numerical value impacted outcomes. Despite the small sample size, subjects in the experimental group had a greater reduction in HbA_{1c} when compared to those in the control group.

We have been unable to find a similar comparison in the available literature, further supporting the contribution of this study. Conversations with those in industry, fellow researchers, and thought leaders in the field did not indicate the existence of any other studies in which rt-CGM was studied without the numerical glucose value. Comparisons to retrospective CGM (r-CGM) are not appropriate as our experimental and control groups had access to functional rt-CGM devices.

While use of an insulin pump--as opposed to multiple daily injections--is recognized as a more intensive insulin therapy, our population did not demonstrate a significant difference ($p = 0.477$) in reduction of their HbA_{1c} between those who utilized a pump compared to those on MDI. Likewise, duration of diabetes did not affect outcomes. This finding is consistent with other rt-CGM trials demonstrating that both

insulin pump users and multiple daily injection users appear to benefit equally from rt-CGM (Garg et al., 2011).

RM ANOVA revealed no significant difference between insulin pump (CSII) and MDI therapy subjects for changes in their HbA_{1c}, Fear of Hypoglycemia and QOL measures ($p > .05$). The trending noted on the figure below suggests that a larger sample may have found a significant difference between the groups however meta-analysis supports similar benefits seen in both MDI and CSII users (Pickup et al., 2011).

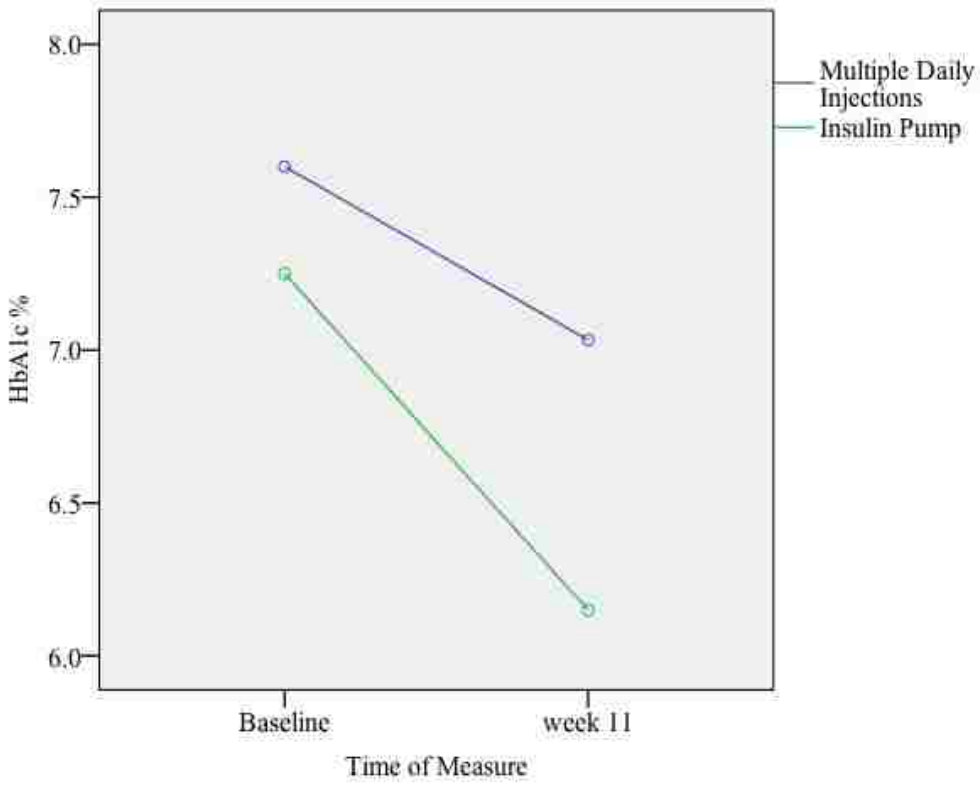


Figure 25. Comparison of HbA_{1c} change between types of insulin therapies.

Based on this small trial, findings suggest that subjects who did not have access to the numerical value of their glucose did better in controlling their glucose levels and

reducing variability, than those who were using unmodified units. This improvement could be related to several issues.

Subjects in the control group may have possessed the propensity of many persons with Type-1 diabetes to fixate on the "number" of their glucose. In contrast, the experimental group had only their trending lines and directional arrows on which to rely. The most significant improvements occurred in experimental subjects 1 and 6 who each reduced their HbA_{1c} by more than 2.0% during the trial, without access to their numerical glucose values.

The current recommended HbA1c level is 6.5% or lower per AACE (2007) guidelines. Experimental subject 1 was on MDI therapy and had a HbA_{1c} reduction from 9.8% to 7.1%, while experimental subject 6 was on insulin pump therapy and saw a similar HbA_{1c} reduction from 7.2% to 5.1%. These improvements are higher than has been reported in the literature, but anecdotal reports of similar improvements are common.

Primary outcomes discussion question 2.

This question sought to understand potential differences in the reduction of the standard deviation of the glucose between the control and experimental groups. Variability of glucose is recognized as contributing to long-term diabetes complications (Hirsch, 2005). There is increasing interest in tools for diabetes care, which can reduce glucose variability. For this trial we chose standard deviations of the glucose measured at baseline, during the blinded run-in, Week +4, Week +8 and during the final week of the trial.

Repeated-measures ANOVA on glucose variability demonstrated a within groups reduction in glucose variability ($F = 3.82$, $p = .023$). It is currently recommended that standard deviations of glucose be maintained at less than 30% of overall glucose average (Hirsch, 2005). Neither the control nor the experimental group reached this target, but both groups demonstrated reductions in their glucose standard deviations (Table 18).

Differences between groups achieved $p = .05$ (Table 9), suggesting that this small sample achieved significance favoring those patients in the control group. This would argue in favor of providing subjects with the numerical value of their glucose. The potential impact of the small sample size should be considered.

Table 18

Mean Glucose and SD as a Percentage of Total Glucose

		Baseline	Completion
Control (n = 5)	M Glucose	179 ± 29	169 ± 20
	SD Glucose	82 ± 15	63 ± 12
	%	45.8	37.2
Experimental (n = 5)	M Glucose	157 ± 46	143 ± 28
	SD Glucose	21.4 ± 5.6	24.6 ± 3.2
	%	38.8	36.6

Note. All glucose values in mg/dl.

Several factors impacted our measurements of glucose variability, including that, for many of the subjects, week +4 and week +8 coincided with the major holiday weeks of Thanksgiving and Christmas. It is likely this had a negative impact on the glucose variability. If we view the entirety of the data available to us, we see significant variability in the glucose standard deviations across the trial period (Table 19).

Table 19

Mean Glucose Variability ± SD at Measured Points

	Baseline	Week +4	Week +8	Completion
Control (n = 5)	82.8 ± 15.7	64.4 ± 9.7	59.8 ± 7.9	63.0 ± 12.1
Experimental (n = 5)	61.8 ± 14.5	62.8 ± 13.2	58.4 ± 22.1	52.8 ± 10.5

Note. All glucose values are presented in mg/dl.

Posthoc power determination demonstrated the power was insufficient to detect a statistically significant difference. This may be related to the variability of the data as seen in Figure 17 by the unexpected drop in average glucose as week +8 in the control group and the unexpected rise in the average glucose at week +4 in the experimental group. Funding for this study limited the number of subjects who could enroll; additional subjects might have led to a statistically significant difference between the two groups.

HbA_{1c} testing is recognized as missing much of the variability and complexity associated with diabetes. Assessing the glucose variability allows us to see the fluctuations in our subjects' blood sugar levels. Hoeks, Greven & de Volk (2010) have suggested that glucose variability, as measured by Standard Deviation of the glucose, be considered when assessing glucose improvements. Similar reductions in glucose variability have been noted by Garg et al. (2011) and in the meta-analysis of rt-CGM effectiveness (Pickup, Freeman & Sutton, 2011). As in our study, Garg et al. (2011) collected data on their patients during a blinded run-in period, allowing the patients to be used as their own controls. Thus each subject's changes in glucose variability could be assessed against their own baseline.

Measures of glucose variability have not been consistently studied as Standard Deviation of glucose, but have been measured as percent of time spent in control each day, with control defined as a glucose of 80-150 mg/dl; time spent hypo- or hyperglycemic is also defined as a percent of the day (Yoo, et al., 2008). For the purposes of this study we analyzed the calculated value of the glucose variability as Standard Deviations (Figure 18; Table 7). Our subjects experienced declines in their glucose standard deviations in both the control and the experimental groups.

The changes in average glucose between groups failed to achieve a $p < .05$ (Table 9). This suggests that the reductions in average glucose were not impacted by the presence of the glucose numerical value. Sample size was however small and a larger sample may have achieved statistical significance.

Secondary Outcomes

Secondary outcomes discussion question 1.

The first secondary outcome assessed the effect of rt-CGM on the fear of hypoglycemia, using a validated tool for this evaluation. While the fear of hypoglycemia is well recognized as being one of the major limitations in the effective treatment of diabetes, there is no support in the literature for use of rt-CGM to reduce this known barrier (Wild, et al., 2007). Efforts in addressing fear of hypoglycemia have primarily focused on blood glucose awareness training and cognitive-behavioral therapies (Cox et al., 2006; Wild, et al.). This pilot study is a beginning in building the needed data on rt-CGM's potential to significantly reduce the fear of hypoglycemia, thus decreasing this major treatment barrier.

Both the control group and the experimental group demonstrated reductions in overall fear of hypoglycemia. Reductions were seen as well in both the Behavior and Worry subscales. Subjects in both groups reported using their rt-CGM alarms to alert them of potential hypoglycemic events.

The HFS has an established internal validity Cronbach's alpha (α) of 0.89 – 0.96 (Cox et al., 1987; Irvine et al., 1994). Our pilot study demonstrated a Cronbach's α of 0.883 at baseline and 0.851 at the completion visit supporting the internal validity of this tool.

Table 20

HFS Cronbach's Alpha

	Baseline	Completion
HFS Total	.883	.851

Between groups effects did not demonstrate a $p < .05$ when evaluated between subjects. Reductions in hypoglycemia fear, total and both subscales, were noted in both groups. The presence of the numerical glucose value did not have a demonstrable impact on that.

Improving patient confidence in self-management of diabetes and reduction of worry are clearly benefits of rt-CGM. The ability to see the glucose level, as well as its direction and rate of change, was beneficial to the patient regardless of their ability to visualize the numerical value. While sample size was suboptimal statistical significance was achieved and the trending is quite evident that use of rt-CGM reduced the fear of hypoglycemia and had a mediating effect on worry and behaviors related to hypoglycemia unawareness. In a longer trial it is anticipated this will be demonstrated to be a sustained effect.

The effect of rt-CGM on fear of hypoglycemia has had limited reporting in the literature. One short-term trial in which subjects wore devices for less than one week reported a change in the HFS scoring (Davey, Stevens, Jones & Fournier, 2011). During a 12-month trial assessing nocturnal hypoglycemia with rt-CGM, it was noted that the HFS survey was not useful in predicting patients having the most nocturnal hypoglycemia.

However this study was not powered to draw any conclusions on the impact of rt-CGM on HFS scoring (JDRF Continuous Glucose Monitoring Group, 2010).

Existing knowledge of rt-CGM's effect on the fear of hypoglycemia is limited. This study contributes to the knowledge base and suggests that rt-CGM may be an underutilized tool in reducing what is widely recognized as the most significant barrier to controlling diabetes--the fear of hypoglycemia.

Secondary outcomes discussion question 2.

The impact of rt-CGM on quality of life measures was evaluated with additional secondary outcomes. This was assessed using the validated Ferrans' and Powers' Quality of Life Index, Diabetes Version 3. The impact of diabetes and other chronic diseases on quality of life is well established (DeSouza & Nairy, 2006). Chronic illnesses such as type-1 diabetes require ongoing attention; anything improving patient comfort and sense of control of their disease would likely improve perceived quality of life.

All subjects completed their QOL measures at baseline and study completion. There was no significant difference between the control group and the experimental group. When comparing their baseline and final datasets, both the experimental and control groups achieved $p < .05$ in their total QOL score, and their QOL-Health and Family sub-scoring.

Socioeconomic and Psychological/Spiritual QOL sub-scores were the least impacted in this trial. This raises several thoughts in consideration. Given the small sample size it became apparent that several of the subjects were coping with financial difficulties during this economic downturn, including loss of jobs, associated family

stresses, and emotional demands. While rt-CGM has offered benefits in their health awareness and reductions in their fear of hypoglycemia, and their QOL measures demonstrate this, there was little evidence of Psychological/Spiritual or Socioeconomic impacts

Others have shown that increasing patient knowledge of their glucose levels and providing an improved sense of control has benefitted QOL perceptions in diabetes (Ozer & Efe, 2006). Improved awareness of glucose levels with the ability to visualize rate and direction of change, offers a distinct informational advantage to persons dealing with this chronic disease. Devices such as the Dexcom SEVEN PLUS™ rt-CGM offer a direct application for patients in addressing these concerns. In a longer and larger trial we may have been able to elicit a better understanding of quality of life impacts.

Similar to the HFS data, the QOL data did not achieve a statistically significant difference between groups when subjected to RM ANOVA. This supports pooling the data for this measure.

Table 21

Baseline QOL Scoring

QOL	Scale Mean if Item Deleted	Scale Variance if Item Deleted	Corrected Item-Total Correlation	Squared Multiple Correlation	Cronbach's Alpha if Item Deleted
TOTAL	92.6390	280.618	.992	.996	.932
Health	93.5950	256.845	.929	.988	.943
Socio	92.6030	268.698	.903	.955	.947
Psy/Spirit	91.9540	302.827	.866	.927	.953
Family	88.9570	317.434	.770	.777	.967

Note. Quality of Life scoring at baseline demonstrated an internal consistency of .959.

Internal consistency for the Ferrans' and Powers' QOL – Diabetes Version III has been previously reported with a Cronbach's alpha-α scoring at 0.94 and 0.97 in prior testing (DeSouza & Nairy, 2003; Ozer & Efe, 2006). This pilot study demonstrated a Cronbach's alpha-α 0.959 on consistency testing at baseline. At completion of the trial a Cronbach's alpha-α 0.877 was noted (Table 22).

Table 22

Completion QOL Scoring

QOL	Scale Mean if Item Deleted	Scale Variance if Item Deleted	Corrected Item-Total Correlation	Squared Multiple Correlation	Cronbach's Alpha if Item Deleted
Total	102.9400	148.244	.979	1.000	.790
Health	102.8220	120.054	.795	.999	.851
Socio	103.6250	190.020	.457	.983	.902
Psy/Spirit	103.0730	141.908	.887	.996	.804
Family	99.9400	200.310	.635	.934	.881

Note: QOL at Completion Cronbach's alpha-α 0.877.

Quality of life issues in chronic disease remain problematic. Controlling diseases such as diabetes require a level of constant vigilance. Reducing fear and worry would offer additional improvements in quality of life for those individuals living with Type-1 diabetes. As the number one issue in controlling diabetes, controlling the fear of hypoglycemia requires the use of all available tools (Anderbro et al., 2010). Realtime-

CGM offers the unprecedented ability to reduce the fear of hypoglycemia by raising awareness of blood glucose, and more importantly, the glucose patterns of change.

Secondary outcomes discussion question 3.

For our final secondary outcome measure we asked our subjects to provide input on the perceived value of rt-CGM. While clinicians have focused on the improvements in glycemic levels and reduced variability, patients have provided little input on their perception of rt-CGM value. At the final visit, patients were given the query "Diabetes is a disease of individual care and characteristics. As such, your experience with this disease is unique. We would like you to express any thoughts you have on the Dexcom Continuous Glucose Monitor you have been using. Please give us your thoughts about using the CGM and how you feel it may have benefitted you most."

No attempt was made to quantify these data. The responses are transcribed verbatim by subject number:

Control Subject #01

"I have enjoyed being able to know what my blood sugar is and being able to do something about it, without having to always use my glucometer to do so. I don't know that I am in any better control, but I feel like I have had fewer really high blood sugars using the CGM than before having it."

Control Subject #02

"Bugs me too much with lows"

Control Subject #03

"It has helped me to be more aware of the need to check my glucose levels more often, the need to restrict my diet more, to exercise more…I was very frustrated with the

discrepency *(sic)* between the numerical readings on the monitor and the actual levels from the finger stick readings. I found I wanted to correct high readings immediately rather than test to confirm actual blood glucose. It was annoying carrying the monitor. Only once did it warn me of a hypoglycemic event when I wasn't aware of it. Typically it showed higher with an → direction when it was dropping."

Control Subject #04

"The CGM use has been useful to my control of night blood sugar levels and while working out. I was able to stablize (*sic*) my night blood sugar levels especially in this last week of use. I do an hour of cardio on an eliptical (*sic*) machine daily. The CGM helped me to know when to suspend my pump during this time.

I found the CGM was not always very accurate. Several times I felt hypoglycemic, but the monitor read 158 or so. When I checked my blood sugar, it was actually like 55. This happened about 8 times during the study."

Control Subject #05

"The Dexcom has helped me to catch my lows and not run as low so often. It has helped me figure out how my body reacts to different foods. The Dexcom has given me more freedom to exercise and catch my lows before it gets really low."

Experimental Subject #01

"The main benefit I experienced was the ability to monitor my sugars 24/7. I know that is why my A1-C was significantly improved. I was able to see for myself how foods or exercise affected my body and the way it processes internally."

Experimental Subject #02

"1. Become more aware of how I feel when my blood sugar is low or high.
2. Was able to help my low's (*sic*) by getting something to eat before going really low.
3. Didn't want to put off my checking of my sugar level. Easier to want to check my sugar and correct if needed."

Experimental Subject #04

"Dexcom CGM is very useful in obtaining a better result of A1C level. It is a good tool to use for a better control of blood sugar daily."

Experimental Subject #05

"It has helped me to see patterns I did not know exsisted (*sic*). It was able to help me make adjustments to my pump settings that keep my BG at a more even level. It helped me predict future BG levels more accuratly (*sic*) than before."

Experimental Subject #06

"The best part for me was the arrow. It would let me know that even if I was beeping low now I was on my way up so not to over sugar. And if I was still pointing down I need to pay attention. The constant graph also helped because I could quickly compare how I felt to where I actually was and better learn to identify how my hi's (*sic*) and lows felt. It made me stay even and in controll (*sic*) with less roller coaster of levels. It also made my husband feel better about my safety when he couldn't reach me."

Reviewing the subjects' comments highlights the wide variety in reported experiences. Not surprisingly, there are comments about inaccuracies of the rt-CGM when compared to their home glucose meter. While most valued the hypoglycemia alerts, it is interesting that one subject found them to be a drawback. Additionally, while the subjects began to recognize the limitations of the device, they still perceived the value of this technology and experienced improvement in their glucose control.

From the control group, several subjects commented to the author their frustration that the numerical glucose value of the rt-CGM and their home glucose monitor did not always correlate closely. This supports our earlier assertion that patients are placing an undeserved faith in the accuracy of their home glucose testing. When queried, subjects acknowledged they did not know the tolerated variances of their glucometers, but felt that they were "always accurate".

None of the experimental subjects commented on this due to their inability to see the glucose values. It is arguable that with the removal of the glucose value the subjects were more likely to be aware of their glucose trending, and conduct SMBG at appropriate times. The tone of the subjective responses was also clearly different with the control patients concerned about accuracy and alerts, while the experimental patients noted an increase in awareness of patterns and direction of change.

Unrelated Data of Interest

While not a direct measure of this study, the impact of insulin pump use is an area of interest. Exploration of the data reveals that subjects with insulin pumps had a dramatic improvement in their HbA1c when compared to those subjects on traditional multiple daily injection (MDI) therapy.

Table 23

Mean HbA_{1c} ± SD % at Baseline and Completion by Therapy

Insulin Therapy	Baseline	Completion
MDI (n = 6)	7.6 ± 1.4	7.03 ± 0.45
CSII (n = 4)	7.25 ± 1.22	6.15 ± 1.9

Note. MDI = Multiple Daily Injection therapy. CSII = Continuous Subcutaneous Insulin Infusion Therapy, also referred to as insulin pumps.

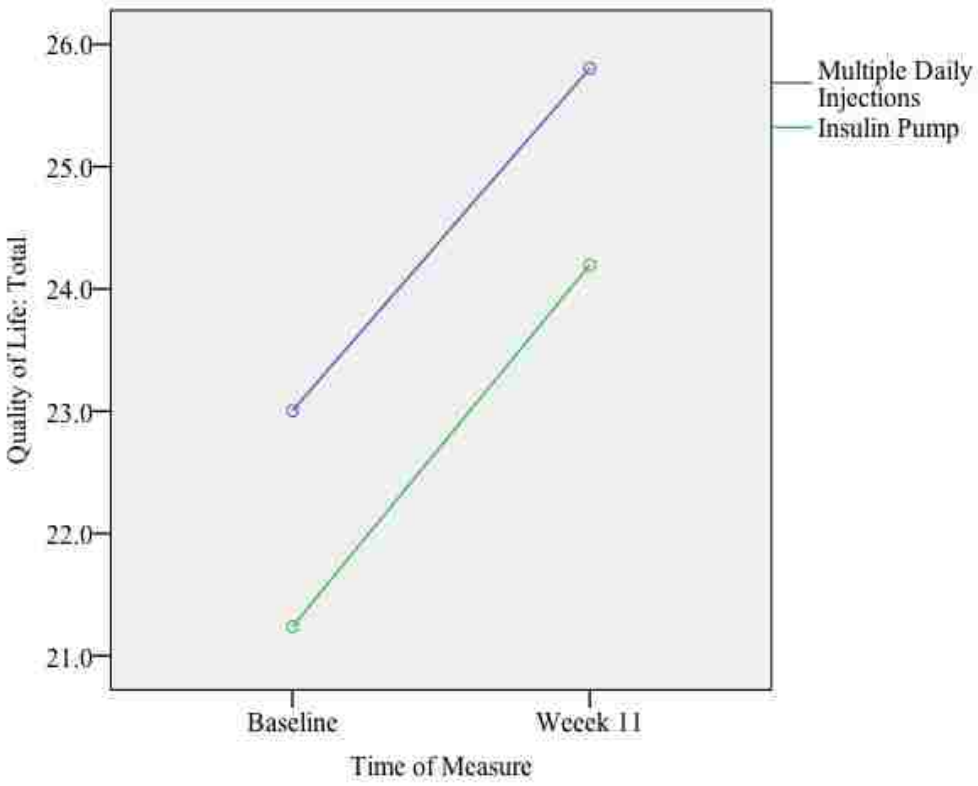


Figure 26. Change in the QOL by type of insulin therapy.

Control Subject #03 was on an insulin pump and demonstrated a slight worsening of her glycemic control so this should not be taken as an absolute. The quality of life issues measured between insulin pump and MDI demonstrated a virtual parallel improvement, while the reduction in Fear of Hypoglycemia was more profound in those patients on insulin pump therapy.

While these trends in this pilot study are interesting, no conclusions should be drawn from this because of the small sample size.

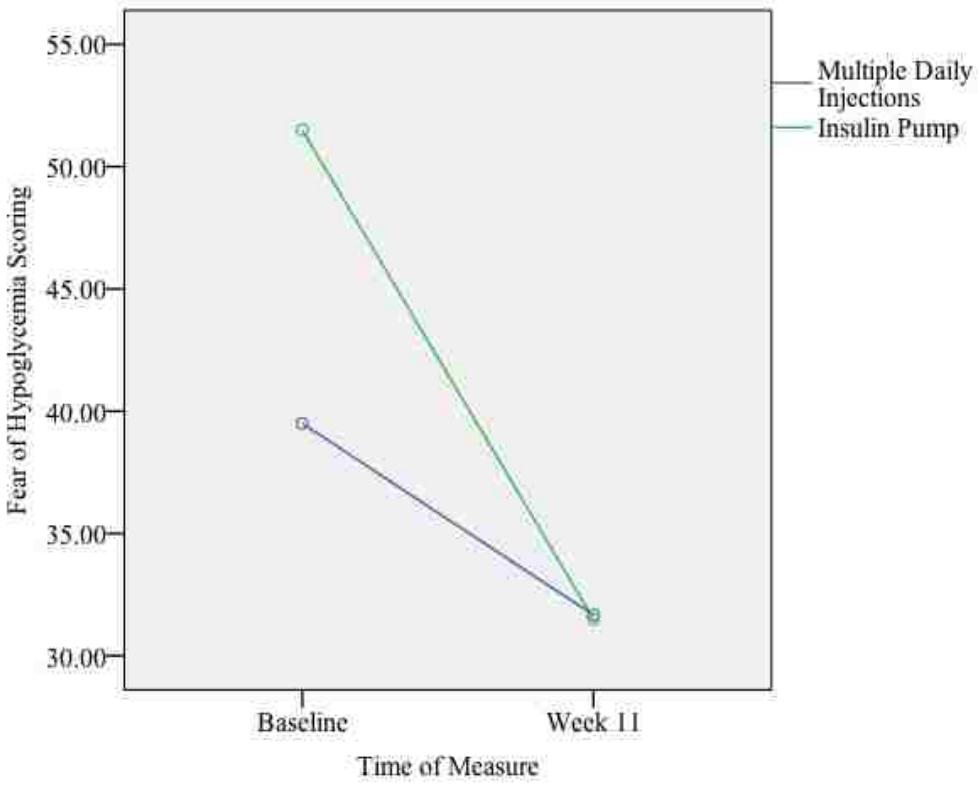


Figure 27. Fear of hypoglycemia scoring compared by type of insulin therapy.

Given that insulin pump therapy is known to reduce the fear of hypoglycemia, this raises further questions as to why those patients had a greater reduction in their fear of hypoglycemia. Additional studies to increase understanding of this relationship are warranted.

Outcomes Considerations

The pooled sample (N = 10) has demonstrated a reduction in HbA_{1c} of 0.78 ± 1.08% (p = .048). While we acknowledge this is within the expected response range reported in the literature, it is worth considering what this represents in the larger picture of diabetes care and complication risk. The DCCT trial established that improved glucose

control in Type-1 Diabetes was associated with a reduction in the risk of micro- and macrovacular complications (DCCT, 1993). Persons with Type-1 Diabetes will use eight times the amount of inpatient services and six times the amount of outpatient services when compared to their non-diabetic counterparts (American Diabetes Association, 2007).

Prior studies have demonstrated that a 1% reduction in the HbA_{1c} will result in a 35% reduction in the risk of nephropathy and other microvascular complications (Yoder, Dixon, Barnette, & Beardsley, 2012). Extrapolating those data we can argue that a 0.78% reduction in the HbA_{1c} would result in a 27% reduction in microvascular disease occurrences. The costs of nephropathy could be reduced by $39 billion annually with a 20% reduction in the progression of renal disease (Nichols, Vupputuri & Lau, H., 2011). This reduction in HbA_{1c} would also reduce cardiovascular risk.

Data from the EDIC trial have demonstrated that tight glucose control early in Type-1 diabetes has a legacy effect, resulting in decreased long-term complications for persons with Type-1 Diabetes (Epidemiology of Diabetes Interventions and Complications Research Group, 2002). Given these strong indicators of sustained benefit from even modest HbA_{1c} reduction, it is apparent that rt-CGM is an underappreciated resource. Coupled with the increased interest in reducing glycemic variability due to its role in microvascular complications, the expanded role for rt-CGM is a necessity (Hirsch & Brownlee, 2005).

Empowering patients to manage their own disease process is a cornerstone of the chronic care model and of particular interest in diabetes care (Frei et al., 2010). Real-time

CGM increases the user's awareness of their glucose level, direction of change and behavior in ways that were never possible before this technology. Incorporation of these technologies into the standards of care will be necessary as we seek to limit the complications of Type-1 Diabetes.

LIMITATIONS

This pilot study had a number of limitations. The sample size (N = 10) presented the greatest challenge as the initial sample size calculation suggested a minimum number of 24 subjects would be required to achieve statistical significance. Nevertheless, significant changes were noted in HbA_{1c}, hypoglycemic fear reductions, improvements in QOL issues and reductions in the standard deviation of glucose.

A second limitation was the short duration of the trial. While 12 weeks is adequate to demonstrate a change in HbA_{1c}, other measures, such as Quality of Life indicators, are known to change at a slower pace as persons adapt to new therapies. No time scale has been established for the changes in the Hypoglycemia Fear Survey, but short duration interventions with rt-CGM have proven ineffective (Davey et al., 2010).

No efforts were made to control for different therapy modalities – insulin pump or multiple daily injection therapies. It has been suggested that insulin pumps improve patients' satisfaction with their disease control in Type-1 diabetes, though this is controversial (Barnard, Lloyd & Skinner, 2007). Though this could have been a confounding factor, only 4 of the 10 subjects were using insulin pump therapy and similar improvements for fear of hypoglycemia and quality of life indicators were seen in those on MDI. RM ANOVA testing on Quality of Life issues between those subjects on MDI and CSII in this trial did not demonstrate $p < .05$, suggesting this was not a factor.

All of the participating subjects returned to the clinic every 4 weeks to receive additional sensors. While this was done to allow for data retrieval from their rt-CGM

device, it also introduced a potential Hawthorne effect as their contact with the researcher was increased.

CONCLUSIONS AND FUTURE RESEARCH

While failing to achieve statistical significance due to limited sample size, this study does suggest that the benefits of rt-CGM are more complex than mere reductions in HbA_{1c}. Notably, the Quality of Life total scores and sub-score of Health both showed improvements during the 12 week trial. The pooled study subjects had an overall reduction in HbA1c of 0.78 which is consistent with other published research. Reduction in the standard deviation of the glucose was seen in both the control group and the experimental group, and finally, reductions in the HFS were present but were limited by the sample size.

This is consistent with prior research that has demonstrated improvements in glucose control when patients are given unrestricted access to rt-CGM devices (Garg, et al., 2007). Reductions in fear of hypoglycemia and improvements in quality of life markers all indicate that rt-CGM has a far-reaching impact on patients who use them, extending benefits beyond improvements in glucose. While the technologies remain too new for us to establish their benefits in reducing long-term complications of Type-1 diabetes, the data are intriguing for their potential.

The data demonstrating improvements in glucose control challenge the necessity of providing a numerical glucose value on the rt-CGM device. Subjects in the experimental group with the modified units did better on HbA1c improvement when compared to the control group. Between subject testing failed to demonstrate statistically significant differences, between those in the control or the experimental group, further

our belief that the numerical value of the glucose on the rt-CGM is of questionable value. . While this achieved a $p = .05$ the small sample size challenges its importance.

In the final query, comments received supported the subjects' satisfaction with and use of directional and rate-of-change arrows, and the visualized waveform. Comments regarding the numerical values consisted of a familiar litany that subjects were unhappy when readings did not match their expectation of being identical to their home glucose meter. This study successfully challenges the concept that patients need to know their glucose value; rather it appears they will do equally well or better if they are only given the glucose trending and directional information.

Similar improvements in quality of life and reductions in the fear of hypoglycemia were noted in both arms of the trial. Both groups saw reductions in worry and fear-related behaviors with concomitant improvements in quality of life measures. There were no between group differences noted on the testing, suggesting that the numerical glucose value had no significant impact on these factors.

Future research needs to be conducted on this conceptual model. A larger sample including 40+ subjects would allow for statistical significance; a minimum of 20 MDI and 20 CSII patients would present an ideal population. This pilot study supports our challenge that the numerical value on rt-CGM is of questionable value and may actually be detrimental. The subjects did equally well or better without the visible value. Patients continue to have unrealistic expectations that their home glucose meter and their rt-CGM should be in precise agreement at all times. Additional training of people using rt-CGM

should focus on increasing understanding of the inaccuracies associated with all glucose testing, including rt-CGM and self-monitored blood glucose.

A longer duration trial of 6-12 months would provide additional information on the impact of rt-CGM on Quality of Life and Fear of Hypoglycemia measures. While all of these showed improvements in this small trial, a longer-duration trial may provide us with better insight and challenge the question of whether these improvements may be transitory. Broader demographic information regarding the patient's educational and socioeconomic status may provide additional information worthy of exploration.

In conclusion, despite failure to achieve statistical significance, the overall trending information is consistent with our initial hypothesis. Persons with Type-1 diabetes who use rt-CGM devices will do better regardless of whether they have access to the numerical value. Additionally, benefits of rt-CGM extend into the subjects' quality of life, and demonstrate subtle but real changes in behavior and worry related to hypoglycemia. Supporting persons with chronic disease will be an ongoing challenge for the future of healthcare; effective use of available tools will be crucial to our success.

APPENDIX A. HYPOGLYCEMIA FEAR SURVEY

Adult Low Blood Sugar Survey
(University of Virginia)

I. Behavior: Below is a list of things people with diabetes sometimes do in order to avoid low blood sugar and its consequences. Circle one of the numbers to the right that best describes what you have done during the last 6 months in your daily routine to AVOID low blood sugar and its consequences. (Please do not skip any!).

To avoid low blood sugar and how it affects me, I ...	Never	Rarely	Sometime	Often-times	Almost Always
1. Ate large snacks.	0	1	2	3	4
2. Tried to keep my blood sugar above 150.	0	1	2	3	4
3. Reduced my insulin when my blood sugar was low.	0	1	2	3	4
4. Measured my blood sugar six or more times a day.	0	1	2	3	4
5. Made sure I had someone with me when I go out.	0	1	2	3	4
6. Limited my out of town travel.	0	1	2	3	4
7. Limited my driving (car, truck or bicycle).	0	1	2	3	4
8. Avoided visiting friends.	0	1	2	3	4
9. Stayed at home more than I liked.	0	1	2	3	4
10. Limited my exercise/physical activity.	0	1	2	3	4
11. Made sure there were other people around.	0	1	2	3	4
12. Avoided sex.	0	1	2	3	4
13. Kept my blood sugar higher than usual in social situations.	0	1	2	3	4
14. Kept my blood sugar higher than usual when doing important tasks.	0	1	2	3	4
15. Had people check on me several times during the day or night.	0	1	2	3	4

II. Worry: Below is a list of concerns people with diabetes sometimes have about low blood sugar. Please read each item carefully (do not skip any). Circle one of the numbers to the right that best describes how often in the last 6 months you WORRIED about each item because of low blood sugar.

	Never	Rarely	Some-times	Often-times	Almost Always
Because my blood sugar could go low, I worried about...					
16. Not recognizing/realizing I was having low blood sugar.	0	1	2	3	4
17. Not having food,fruit, or juice available.	0	1	2	3	4
18. Passing out in public.	0	1	2	3	4
19. Embarrassing myself or my friends in a social situation.	0	1	2	3	4
20. Having a hypoglycemic episode while alone.	0	1	2	3	4
21. Appearing stupid or drunk.	0	1	2	3	4
22. Losing control.	0	1	2	3	4
23. No one being around to help me during a hypoglycemic episode.	0	1	2	3	4
24. Having a hypoglycemic episode while driving.	0	1	2	3	4
25. Making a mistake or having an accident.	0	1	2	3	4
26. Getting a bad evaluation or being criticized.	0	1	2	3	4
27. Difficulty thinking clearly when responsible for others.	0	1	2	3	
28. Feeling lightheaded or dizzy.	0	1	2	3	4
29. Accidently injuring myself or others.	0	1	2	3	4
30. Permanent injury or damage to my health or body.	0	1	2	3	4
31. Low blood sugar interfering with important things I was doing.	0	1	2	3	4
32. Becoming hypoglycemic during sleep.	0	1	2	3	4
33. Getting emotionally upset and difficult to deal with.	0	1	2	3	4

APPENDIX B. FERRANS' AND POWERS' QUALITY OF LIFE SURVEY

Ferrans and Powers
QUALITY OF LIFE INDEX©
DIABETES VERSION – III

PART 1. For each of the following, please choose the answer that best describes how *satisfied* you are with that area of your life. Please mark your answer by circling the number. There are no right or wrong answers.

HOW *SATISFIED* ARE YOU WITH:	Very Dissatisfied	Moderately Dissatisfied	Slightly Dissatisfied	Slightly Satisfied	Moderately Satisfied	Very Satisfied
1. Your health?	1	2	3	4	5	6
2. Your health care?	1	2	3	4	5	6
3. The amount of energy you have for everyday activities?	1	2	3	4	5	6
4. Your ability to take care of yourself without help?	1	2	3	4	5	6
5. Your ability to control your blood sugar?	1	2	3	4	5	6
6. The changes you have had to make in your life because of diabetes (such as diet, exercise, taking insulin or diabetes pill, checking blood sugar)?	1	2	3	4	5	6
7. The amount of control you have over your life?	1	2	3	4	5	6
8. Your chances of living as long as you would like?	1	2	3	4	5	6
9. Your family's health?	1	2	3	4	5	6
10. Your children?	1	2	3	4	5	6
11. Your family's happiness?	1	2	3	4	5	6
12. Your sex life?	1	2	3	4	5	6
13. Your spouse, lover, or partner?	1	2	3	4	5	6
14. Your friends?	1	2	3	4	5	6
15. The emotional support you get from your family?	1	2	3	4	5	6
16. The emotional support you get from people other than your family?	1	2	3	4	5	6
17. Your ability to take care of family responsibilities?	1	2	3	4	5	6
18. How useful you are to others?	1	2	3	4	5	6
19. The amount of worries in your life?	1	2	3	4	5	6
20. Your neighborhood?	1	2	3	4	5	6
21. Your home, apartment, or place where you live?	1	2	3	4	5	6
22. Your job (if employed)?	1	2	3	4	5	6
23. Not having a job (if unemployed, retired, or disabled)?	1	2	3	4	5	6

24. Your education?	1 2 3 4 5 6
25. How well you can take care of your financial needs?	1 2 3 4 5 6
26. The things you do for fun?	1 2 3 4 5 6
27. Your chances for a happy future?	1 2 3 4 5 6
28. Your peace of mind?	1 2 3 4 5 6
29. Your faith in God?	1 2 3 4 5 6
30. Your achievement of personal goals?	1 2 3 4 5 6
31. Your happiness in general?	1 2 3 4 5 6
32. Your life in general?	1 2 3 4 5 6
33. Your personal appearance?	1 2 3 4 5 6
34. Yourself in general?	1 2 3 4 5 6

PART 2.

For each of the following, please choose the answer that best describes how *important* that area of your life is to you. Please mark your answer by circling the number. There are no right or wrong answers

HOW *IMPORTANT* TO YOU IS:

1. Your health?	1 2 3 4 5 6
2. Your health care?	1 2 3 4 5 6
3. Having enough energy for everyday activities?	1 2 3 4 5 6
4. Taking care of yourself without help?	1 2 3 4 5 6
5. Controlling your blood sugar?	1 2 3 4 5 6
6. The changes you have had to make in your life because of diabetes (such as diet, exercise, taking insulin or diabetes pill, checking blood sugar)?	1 2 3 4 5 6
7. Having control over your life?	1 2 3 4 5 6
8. Living as long as you would like?	1 2 3 4 5 6
9. Your family's health?	1 2 3 4 5 6
10. Your children?	1 2 3 4 5 6
11. Your family's happiness?	1 2 3 4 5 6
12. Your sex life?	1 2 3 4 5 6
13. Your spouse, lover, or partner?	1 2 3 4 5 6
14. Your friends?	1 2 3 4 5 6
15. The emotional support you get from your family?	1 2 3 4 5 6
16. The emotional support you get from people other than your family?	1 2 3 4 5 6
17. Taking care of family responsibilities?	1 2 3 4 5 6
18. Being useful to others?	1 2 3 4 5 6
19. Having no worries?	1 2 3 4 5 6
20. Your neighborhood?	1 2 3 4 5 6
21. Your home, apartment, or place where you live?	1 2 3 4 5 6
22. Your job (if employed)?	1 2 3 4 5 6
23. Having a job (if unemployed, retired, or disabled)?	1 2 3 4 5 6
24. Your education?	1 2 3 4 5 6
25. Being able to take care of your financial needs?	1 2 3 4 5 6
26. Doing things for fun?	1 2 3 4 5 6
27. Having a happy future?	1 2 3 4 5 6
28. Peace of mind?	1 2 3 4 5 6
29. Your faith in God?	1 2 3 4 5 6
30. Achieving your personal goals?	1 2 3 4 5 6
31. Your happiness in general?	1 2 3 4 5 6
32. Being satisfied with life?	1 2 3 4 5 6
33. Your personal appearance?	1 2 3 4 5 6
34. Are you to yourself?	1 2 3 4 5 6

APPENDIX C. AN OPEN ENDED QUESTION

An Open-Ended Question:

Diabetes is a disease of individual care and characteristics. As such your experience with this disease is unique. We would like you to express any thoughts you have on the Dexcom Continuous Glucose Monitor (CGM) you have been using. Please give us your thoughts about using the CGM and how you feel it may have benefitted you most.

APPENDIX D. DEMOGRAPHICS FORM

Date _____

Name _____

☐ Male ☐ Female Date of Birth _____ Age: _____

Address: _____

City _____ State _____ Zip _____

Home Phone _____ Cell/Pager _____

Email _____

Height: _____feet _____ in Weight: _____ ☐ lbs ☐ kg

Do you have any allergies to medications? ☐ Yes ☐ No

If yes, please list: _____

Age when you were diagnosed with Type-1 Diabetes: _____ years old

Please list any other
medical conditions: _____

Emergency Contact: _____

Relationship _____

Address: _____

City _____State _____ Zip _____

Phone _____Alternate phone _____

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DOCTORAL PROJECT

USE OF CONTINUOUS GLUCOSE MONITORS IN TYPE-1 DIABETES: AN ANALYSIS OF WAVEFORM VERSUS GLYCEMIC VALUES IN THE IMPROVEMENT OF GLUCOSE CONTROL AND FEAR OF HYPOGLYCEMIA