PROTOCOL

A Cognitive Behavioral Therapy Intervention (FREE) to Reduce Fear of Hypoglycemia in Young Adults with Type 1 Diabetes

1. ABSTRACT

In persons with type 1 diabetes (T1DM), iatrogenic hypoglycemia is the major limiting factor in achieving optimal blood glucose control. All persons with T1DM are at risk for hypoglycemia (blood glucose level < 70 mg/dl), which is life-threatening and has serious physical symptoms and psychological sequelae that lead to profound fear of future hypoglycemic events. This fear results in greater glucose variability (the intra-day fluctuations in blood glucose), due to under- or overcompensation of food intake, insulin dosing, or physical activity, as well as anxiety, depression, and reduced quality of life. Greater glycemic variability (GV) is associated with a higher risk of hypoglycemia and diabetes complications. Young adults are particularly at risk because they report greater FOH and have poorer glycemic control. A major gap exists in how to manage FOH as a crucial component of diabetes self-care. Our overall objective is to reduce FOH and improve diabetes self-management, glycemic control, and variability in young adults with T1DM. We specifically aim to: (1) Determine the feasibility of an 8-week CBT-based intervention to reduce FOH and (2) obtain means and standard deviations of group differences from baseline to program completion on the outcomes of FOH, self-management, glycemic control and glycemic variability in young adults with T1DM who experience FOH. To achieve these aims, we propose a randomized control pilot trial in 10 young adults aged 18 to 30 years with T1DM. Participants will be screened for FOH levels. Eligible subjects will be randomized to the intervention (Fear Reduction Efficacy Evaluation [FREE]) program or attention control group. A 1-week run-in phase is planned, with baseline measures of FOH and 24-hour real-time continuous glucose monitoring recordings (RT-CGM) to calculate GV for both groups. The intervention group will participate in eight weekly one-hour sessions using a cognitive behavioral therapy (CBT) and exposure treatment for specific fears. RT-CGM and a daily FOH diary will be used as feedback cues. The control group will wear a 24-hour RT-CGM device during the same 8-week period and return for weekly RT-CGM site changes by study staff. At completion, FOH will be measured, and RT-CGM recordings will be analyzed to determine within-group and between-group differences. The findings from this proposed study will serve as the foundation for a larger clinical trial to reduce FOH and improve self-management, glycemic control, and variability. Meeting these goals will have important clinical implications to reduce diabetes complications and improve quality of life in young adults with T1DM.

2. RESEARCH PLAN

B. Specific Aims

The specific aims of this IRSP pilot study are:

1. Determine the feasibility of the 8-week fear reduction intervention FREE in young adults with T1DM who report FOH. Feasibility will be determined through analysis of recruitment, retention, and participant evaluation.

2. Obtain means and standard deviations of within-group and between-group differences from baseline to program completion (8th week) and post-program (12th week) on the outcomes of FOH, self-management, glycemic control (A1C), and GV. This data will be used for calculation of effect sizes for a future larger study.

C. Research Strategy

1. Significance

Why focus on FOH in young adults? Despite refinements in insulin therapy and advancements in glucose-sensing technology over the past several decades, fear of hypoglycemia (FOH) remains a critical deterrent to T1DM self-management, psychological well-being, and quality of life (QOL).[15] Fear is conceptualized as an emotion arising from a cognitive appraisal of a specific threat or danger.[20] Normal fear is adaptive, stimulating more vigilance and improved performance; whereas heightened fear leads to increased anxiety and may result in a delay to action or inappropriate action.[19,20,21] Anxiety may mimic the symptoms of

hypoglycemia and impair its detection, further complicating the problem.[5,22] At the extreme, fears can develop into anxiety disorders and phobias.[7,19,23] Young adults experience higher FOH levels than adolescents and middle-aged adults;[15] thus, it is critical to develop strategies to assist young adults in coping with FOH. Previous negative experiences of hypoglycemia influence health behaviors used in diabetes self-management, including insulin dosing, dietary patterns, and physical activity.[10,15,24-28] Insulin doses may be inappropriately reduced in anticipation of hypoglycemia, and diet may be modified to avoid hypoglycemia. Dietary modifications may include excessive eating, particularly more carbohydrates[11,29] or snacking at night.[27,30] These excessive modifications lead to increased GV.

Over the past three decades, a number of newer technologies have been designed to help patients with diabetes manage their treatment regimens, including continuous glucose monitoring (CGM) systems, insulin pumps, sensor-augmented pump therapy with threshold suspend features, and insulin bolus calculators. While these devices have improved glucose control (i.e., A1C), improved glucose control has not consistently translated into reduced FOH.[31-37]

What has been used to address FOH? Diabetes education programs typically discuss FOH but have not developed strategies to manage it.[4] Education, motivational interviewing, and cognitive behavioral therapy (CBT) interventions have been developed to improve glucose control,[38-40] but no program has been established to specifically address FOH. Improved glucose management has had variable effects on FOH.[4,39-45] Outcomes have demonstrated that, as glucose levels are lowered, worry levels have not consistently decreased,[38] and any improvements that have occurred have not been sustainable.[4] We hypothesize that the lack of consistent and sustainable reductions in FOH has occurred because the focus of these programs has been on glycemic control, not on FOH. Any strategy that focuses on managing glucose to near-normal levels must include methods to cope with the fear that lower blood glucose levels could lead to hypoglycemia. FOH management must be a part of diabetes care.[46] *A fear reduction program, informed by the proposed study, may provide a more comprehensive approach to diabetes care that reduces anxiety and improves glycemic control and variability.*

Why is glycemic variability (GV) important? Lower hemoglobin A1C levels are associated with a reduction in microvascular complications.[47] Although A1C provides a biomarker for average blood glucose over a 2- to 3-month period, it does not capture daily blood glucose level fluctuations that occur. Evidence supports the role that GV (daily fluctuation) plays in the generation of oxidative stress,[14] endothelial dysfunction,[48] and diabetes complications in T1DM.[49] High degrees of GV are associated with more frequent episodes of hypoglycemia[12] and fluctuations between glucose extremes (i.e., hypo- to hyperglycemic levels), which may occur with overtreatment of a hypoglycemic episode. *GV is directly influenced by self-management behavior[50] and is amenable to change with appropriate intervention.*

Why use a cognitive behavioral approach (FREE) to reduce FOH? Increased FOH creates anxiety, which may impair awareness of internal and external blood glucose cues and leave individuals less prepared to take action.[19] Heightened fear may develop due to previous negative hypoglycemic thoughts, feelings, and experiences that create a conditioned negative response to future fear triggers.[19,51] An approach that uses cognitive behavioral techniques such as cognitive restructuring, exposure to feared stimuli, and regular monitoring of symptoms has been effective in other populations.[52] In the proposed study, the FREE program will incorporate CBT to reframe the fear experience and reduce the adverse emotional response. Exposure therapy will be used to reduce anxiety through habituation to previously anxiety-provoking situations.[53] Feedback using RT-CGM readings and review of a fear diary will be used as cues to reinforce learning. The goal is not to replace standard diabetes therapy, but improve diabetes self-management through fear reduction. Our premise is that negative thoughts, feelings, or experiences of hypoglycemia increase FOH. This compromises diabetes self-management and increases GV. Our program is designed to reduce FOH and improve diabetes self-management, which will lead to improved glycemic control and variability. (Figure 1).

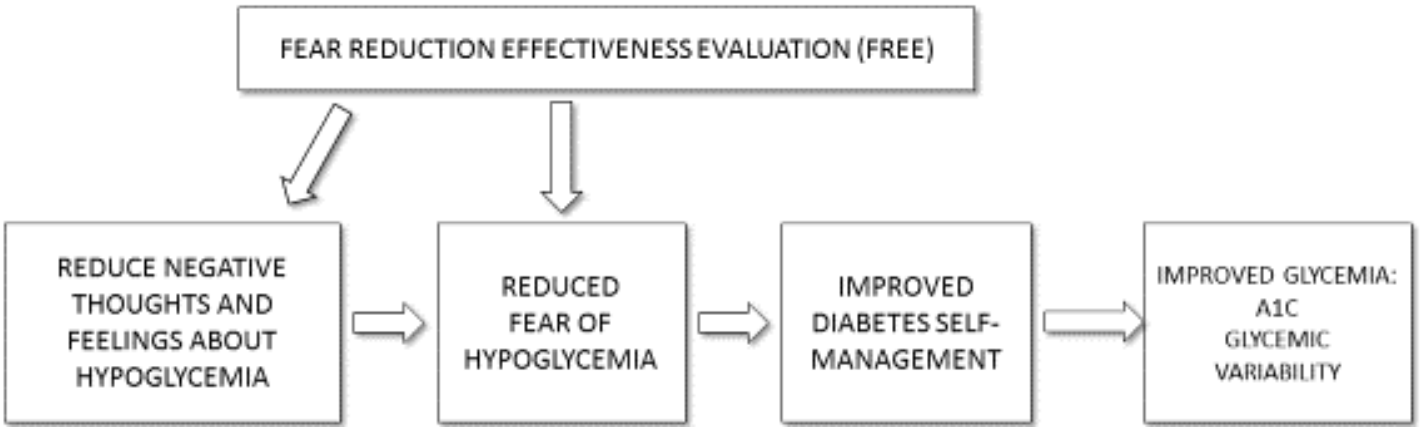

Figure 1. Components of FREE program

2. Innovation

With most diabetes self-management research focused on blood glucose management,[38-40] a FOH reduction intervention represents a novel approach to addressing the role of hypoglycemic fear in glycemic control and variability. Most individuals with T1DM struggle with hypo- and hyperglycemia and develop a profound fear from these experiences. FOH does not resolve with education alone,[4] and the magnitude of the problem is poorly understood, as well as greatly under-appreciated. As the incidence of T1DM increases worldwide,[54] the scope of the problem will only rise. To our knowledge, we are the first to identify the temporal relationships between FOH and GV (**see 3.1b**). These findings provide strong justification for an intervention that specifically targets FOH. In this R21, our team proposes to pilot test a CBT and exposure-based therapy intervention that is unique to diabetes care but has been effective in reducing fear and anxiety in other populations with chronic illness. This methodology will provide feedback on progress toward FOH reduction and GV through weekly diary and RT-CGM analysis. We focus on young adults because they have reported higher FOH levels than older adults and young children and they are becoming responsible for their diabetes management in new and challenging roles and situations. Improvement in diabetes self-management in this age group could facilitate the prevention or delay of diabetes complications later in life.

3. Approach

3.1. Preliminary Studies

3.1a. Research Team Expertise. This application brings together an interdisciplinary team with shared (T1DM, FOH, CGM technology for GV measurement, chronic illness, clinical practice) and complementary (CBT, feedback, intervention studies, clinical diabetes education [CDE]) expertise. Collectively, the team's research strengths span conceptual, methodological, clinical, statistical, and research abilities in the areas of self-management and chronic disease.

3.1b. Preliminary Findings. We successfully conducted a study using a prospective repeated measures design, using CGM and a daily fear diary in 30 young adults with T1DM. FOH was linked to GV. (1) Significant temporal relationships emerged in which same-day fear levels were associated with same-day GV (r = .232, p = < .05), and previous-day fear levels were associated with next-day GV (r = .205, p < .05). This between-day relationship was stronger for those who experienced four or more hypoglycemic episodes per week (r = .483, p < .01). (2) FOH was reported by 78% of the sample. (3) During the 6-day CGM recording period, 27% were identified as hyper-responders, indicating that they reported and treated more presumed hypoglycemic episodes (based on daily diary entries) than actual biochemical hypoglycemic episodes measured through CGM recordings. (4) Optimal glycemic control (A1C < 7%) was not consistently associated with low GV. Our data demonstrated that nearly half (45%) of the sample had A1C levels at or below 7.0, yet 57% of those with optimal A1C levels had high GV (> 52 dl glucose standard deviation).

3.2. Design and Methods

3.2a. Overview. Following a 1-week run-in phase, ten young adults aged 18 to 30 years with T1DM (≥ 1 year) and who experience FOH will be randomized to an intervention or attention control group. The intervention group will participate in eight weekly one-hour sessions using a CBT-based approach (FREE), wear a RT-CGM device, and keep a daily diary. The attention control group will also wear a RT-CGM device for 8 weeks but will not participate in weekly sessions and will not keep a diary. Data will be collected: (1) at the beginning of a 1-week run-in period (week 0); (2) at completion of the intervention at the end of 8 weeks (week 8); and (3) post-program at 12 weeks. At completion, FOH, self-management, and A1C will be measured and RT-CGM recordings will be analyzed to determine within-group and between-group differences.

3.2b. Setting and Sample. The study intervention will take place at the University of Illinois at Chicago (UIC) Medical Center and College of Nursing. Inclusion criteria: (1) 18-30 years old, (2) diagnosed with T1DM ≥ 1 year and receive medical care from an endocrinologist, (3) use insulin pump therapy, and (4) have self-reported FOH (screening questionnaire).[55] Exclusionary criteria: (1) pregnant or breastfeeding, (2) actively treated for a mental health condition, (3) have a co-existing chronic illness or taking medications (excluding insulin) that may influence diabetes self-management or GV.

3.2c. Recruitment. Subjects will be recruited through Chicago metropolitan area university medical centers, local diabetes websites, and organizations using flyers, e-announcements, and recruitment letters. At UIC, we will identify potentially eligible subjects through the electronic medical record system and send recruitment letters. The University of Illinois clinics saw over 900 patients with T1DM; thus, there is a sufficient pool from which to recruit. We have been successful in recruiting using these methods for our previous studies.

3.2d. Sample Size Determination. The sample size of 10 subjects (n = 5 intervention group; 5 intention control group) will be sufficient to test the feasibility of the study protocol and to obtain preliminary outcome measures.

3.2e. Procedures. Study staff will screen subjects for inclusion/exclusion criteria. Scores of 3 or 4, indicating that worry occurs *often* or *very often,* on any item on the worry scale (4-point Likert) of the Hypoglycemia Fear Scale (HFS-2)[55] will be used to determine the presence of FOH (personal communication L. Gonder-Frederick, 5/26/15). Those who meet the study criteria will be scheduled for an appointment at the College of Nursing for the start of the 1-week run-in period to: obtain consent and baseline measures (Table 1, Week 0) and apply a RT-CGM device with instructions provided on its care. Following the 1-week run-in period, subjects will be randomized to the FREE intervention or attention control group. During the study period, subjects will continue to receive their usual diabetes care with their health care provider. The subjects will be encouraged to discuss any questions regarding blood glucose management with their diabetes health care provider.

3.2e1. FREE Intervention. Subjects randomized to the FREE intervention group will: (1) attend eight weekly one-hour sessions based on principles of CBT and exposure treatment for specific phobias. The program will consist of 8 weeks of individual sessions (weeks 1-8), in which participants will be taught cognitive restructuring and exposure-based techniques to decrease their FOH. Treatment will target incorrect beliefs about hypoglycemia, hypervigilance to symptoms, fear of symptoms, and maladaptive behavioral responses in response to glucose levels. Participants will create a fear and avoidance hierarchy and be taught to begin approaching previously feared situations (e.g., spending time alone, reducing snacking, allowing glucose readings to reach lower safe levels, etc.) to experience habituation and the resulting decrease in anxiety. To maintain treatment fidelity, sessions will follow a manualized protocol (See Appendix A. Outline of FREE Intervention). Additionally, sessions will be audiotaped and reviewed for fidelity to the treatment protocol. Weekly homework will be assigned to reinforce the program content. (2) FREE intervention subjects will continue to wear a RT-CGM for the 8-week period and complete a daily FOH diary. RT-CGM recordings and daily diaries will serve as cues for glucose and fear levels. At each weekly visit, participants will receive a copy of their RT-CGM recordings for the previous week and (3) have their RT-CGM site changed by a study staff member who is a registered nurse.

3.2e2. Attention Control Group. Subjects randomized to the attention control group will have (1) an initial meeting with study staff (study week 1) to review study purpose and goals, (2) continue to wear a RT-CGM for the 8-week session; and (3) return to have their RT-CGM site changed weekly by study staff (registered nurse). The weekly visits for RT-CGM site changes will facilitate keeping the attention control group engaged

and will assure proper replacement of the glucose sensor (Appendix D).

3.2e3. Subject Retention Strategy. Both the FREE intervention group and the attention control group will (1) wear a RT-CGM; (3) receive reminders of their next appointment; and (4) have weekly visits to change the RT-CGM site. The weekly appointment reminders and RT-CGM site changes will be used to facilitate subject retention. Those in the FREE group will (5) receive additional intervention sessions week 1-8 and (6) weekly CGM downloads with GV analysis when they attend each session. (7) All subjects will be compensated for their time.

3.2f. Measures.

3.2f1. Baseline and Post-Intervention Measures. *Self-report instruments* will be used to obtain demographic and health information, previous history of hypoglycemia, fear of hypoglycemia, self-management behaviors, and related variables (self-efficacy, anxiety, diabetes distress). The scales have strong psychometric properties and have been validated in T1DM populations (Table 1). *Glycemic control* will be measured with a fingerstick for A1C for assessment of longer-term glycemic control using A1C Now® (Chek Diagnostics, Indianapolis, IA).

3.2f2. Ongoing Measures: Diary. A daily diary will be used to measure daily fear levels and perceptions of GV **for FREE participants only**.

Table 1. Measures		
Variables	Measure	Frequency
Aim 1 Feasibility		
Recruitment Retention Acceptability	Number of eligible respondents/Number consented Attendance rate; Completion rate Participant evaluation (Appendix C)	Ongoing Weekly Week 8
Aim 2 Program outcomes		
Previous hypoglycemia	Hypoglycemia Patient Questionnaire[2]	Week 0
FOH	Hypoglycemia Fear Scale (HFS-2[55]) **FREE group only**: Daily FOH Diary: Fear level[57] (Appendix B)	Week 0, Week 8, 12 Daily
Glycemic measures Glycemic control Glycemic variability Perception of glycemic variability	 A1C (A1C Now®) RT-CGM (Dexcom®): Daily glucose standard deviation (GlucSD), continuous net glycemic action (CONGA), coefficient of variation (CV%), interquartile range (IQR) and mean amplitude of glycemic excursions (MAGE) (**see 3.2f3**) **FREE group only**: Daily FOH diary: GV perception[57] (Appendix B)	 Week 0, Week 8, 12 Daily Daily
Diabetes self-management	Diabetes Self-Management Questionnaire[58]	Week 0, Week 8, 12
Other psychological covariates to characterize sample: self-efficacy, anxiety; mood, diabetes distress	Self-Efficacy for Diabetes[59] PROMIS Anxiety and Depressive Mood Scales Diabetes Distress[61]	Week 0, Week 8, 12 Week 0, Week 8, 12 Week 0, Week 8, 12

3.2f3.Ongoing Measures: Glycemic Variability. Subcutaneous interstitial glucose levels will be monitored during the run-in phase (over a period of 7 days) and the 8-week intervention (FREE intervention and attention control groups) using a Dexcom G4 Platinum® (San Diego, CA). A glucose sensor and recorder will be placed on the abdomen and changed weekly by a trained study staff member (a registered nurse). All subjects will be able to view their RT-CGM values. At the end of each week, all data will be downloaded to the Dexcom Software and examined for glycemic trends and excursions. The weekly glucose summary will be provided to subjects in the intervention group at each weekly session to provide feedback on their glucose trends. Those in the attention control group **will be able to view** their CGM readings in real-time but **will not** receive weekly summaries. Rather, at the end of the full study (i.e., 12 weeks), they will receive their weekly

summaries.

To analyze GV for study outcomes, the raw data will be downloaded to an EXCEL spreadsheet. The research staff will be trained on data cleaning, confirmation of regular calibration, identification of errors, and review of missing data or time-points. The amount of time spent in hypo- and hyperglycemia will be calculated (% and minutes; < 70 and > 180 mg/dl). GV will be determined by calculating the daily glucose standard deviation (GlucSD), continuous net glycemic action (CONGA), coefficient of variation (CV%), interquartile range (IQR), and mean amplitude of glycemic excursions (MAGE). These are measures that are recommended to obtain a comprehensive evaluation of GV.[62,63]

3.2g. Data Analysis

1. The feasibility of the program will be evaluated by assessment of recruitment, retention, and participant evaluation. Itemized logs of recruitment sites, methods, responses, eligible subjects, and consented subjects will be documented. Retention will be evaluated through documentation of weekly attendance and compliance with RT-CGM site changes. As part of the feasibility assessment, we will also track the number of RT-CGM sensor failures, RT-CGM placement sites, time to failure, and any adverse sensor site problems. Acceptability will be determined through participant evaluation (Appendix C).

2.) We will calculate means and standard deviations of within-group and between-group differences from baseline to program completion (8th week) and post-program (12th week) on the outcomes of FOH, self-management, glycemic control (A1C), and GV.

3.2h. Timeline

Year 1	Mar	Apr	May	June	July	Aug	Sept	Oct	Nov	Dec	Jan	Feb	Mar	Total
Study set up	**X**	**X**	**X**											
FREE subjects				**2**		**2**			**1**					**5**
Control subjects				**2**		**2**			**1**					**5**
Total subjects				**4**		**4**			**2**					**10**

3.2j. Pilot study limitations. One of the limitations is that the small convenience sample may not be representative of the population. This limitation is offset by the fact that this is strictly a feasibility pilot to inform and strengthen a larger study in terms of recruitment, retention and acceptability.

References

1. Davis S, Alonso MD. Hypoglycemia as a barrier to glycemic control. *J Diabetes Complications.* Jan-Feb 2004;18(1):60-68.
2. Seaquist ER, Anderson J, Childs B, et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. *Diabetes Care.* May 2013;36(5):1384-1395.
3. Cryer PE. Death during intensive glycemic therapy of diabetes: mechanisms and implications. *The American journal of medicine.* Nov 2011;124(11):993-996.
4. Lawton J, Rankin D, Cooke DD, Elliott J, Amiel S, Heller S. Self-treating hypoglycaemia: a longitudinal qualitative investigation of the experiences and views of people with Type 1 diabetes. *Diabetic medicine : a journal of the British Diabetic Association.* Feb 2013;30(2):209-215.
5. Polonsky WH, Davis CL, Jacobson AM, Anderson BJ. Correlates of hypoglycemic fear in type I and type II diabetes mellitus. *Health Psychol.* 1992;11(3):199-202.
6. Irvine AA, Cox D, Gonder-Frederick L. Fear of hypoglycemia: relationship to physical and psychological symptoms in patients with insulin-dependent diabetes mellitus. *Health Psychol.* 1992;11(2):135-138.
7. Cox DJ, Gonder-Frederick L, Antoun B, Clarke W, Cryer P. Psychobehavioral metabolic parameters of severe hypoglycemic episodes. *Diabetes Care.* Apr 1990;13(4):458-459.
8. Currie CJ, Morgan CL, Poole CD, Sharplin P, Lammert M, McEwan P. Multivariate models of health-related utility and the fear of hypoglycaemia in people with diabetes. *Current medical research and opinion.* Aug 2006;22(8):1523-1534.
9. Gonder-Frederick L. Fear of hypoglycemia: A review. *Diabetic Hypoglycemia.* 2013;5(3):3-11.
10. Brazeau AS, Rabasa-Lhoret, R., Strychar, I., Mircescu, H. Barriers to physical activity among patients with type 1 diabetes. *Diabetes Care.* 2008;31(11):2108-2109.
11. Richmond J. Effects of hypoglycaemia: patients' perceptions and experiences. *British journal of nursing (Mark Allen Publishing).* Sep 26-Oct 9 1996;5(17):1054-1059.
12. Kilpatrick ES, Rigby AS, Goode K, Atkin SL. Relating mean blood glucose and glucose variability to the risk of multiple episodes of hypoglycaemia in type 1 diabetes. *Diabetologia.* Dec 2007;50(12):2553-2561.
13. Monnier L, Mas, E., Ginet, C. et al. Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. *Jama.* 2006;295(14):1681-1687.
14. Quagliaro L, Piconi L, Assaloni R, Martinelli L, Motz E, Ceriello A. Intermittent high glucose enhances apoptosis related to oxidative stress in human umbilical vein endothelial cells: the role of protein kinase C and NAD(P)H-oxidase activation. *Diabetes.* Nov 2003;52(11):2795-2804.
15. Bohme P, Bertin, E., Cosson, E., Chevalier, N. . Fear of hypoglycaemia in patients with type 1 diabetes: do patients and diabetologists feel the same way? *Diabetes & Metabolism.* 2013;39:63-70.
16. Miller KM, Foster NC, Beck RW, et al. Current State of Type 1 Diabetes Treatment in the U.S.: Updated Data From the T1D Exchange Clinic Registry. *Diabetes Care.* Jun 2015;38(6):971-978.
17. Giorda CB, Ozzello A, Gentile S, et al. Incidence and risk factors for severe and symptomatic hypoglycemia in type 1 diabetes. Results of the HYPOS-1 study. *Acta diabetologica.* Oct 2015;52(5):845-853.
18. Rosaura Polak A, Witteveen AB, Denys D, Olff M. Breathing biofeedback as an adjunct to exposure in cognitive behavioral therapy hastens the reduction of PTSD symptoms: a pilot study. *Applied psychophysiology and biofeedback.* Mar 2015;40(1):25-31.
19. Green L, Feher M, Catalan J. Fears and phobias in people with diabetes. *Diabetes/metabolism research and reviews.* Jul-Aug 2000;16(4):287-293.
20. Davis M, Walker DL, Miles L, Grillon C. Phasic vs sustained fear in rats and humans: role of the extended amygdala in fear vs anxiety. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology.* Jan 2010;35(1):105-135.
21. Adolphs R. The biology of fear. *Current biology : CB.* Jan 21 2013;23(2):R79-93.
22. Boyle S, Allan C, Millar K. Cognitive-behavioural interventions in a patient with an anxiety disorder related to diabetes. *Behaviour research and therapy.* Mar 2004;42(3):357-366.

23. Maxmen J W, N. Kilgus, M. . *Essential psychopathology and its treatment.* New York, NY: W.W. Norton 2009.
24. Leiter LA, Yale, J. F., Chiasson, J. L., Harris, S., Kleinstiver, P. & Sauriol, L. Assessment of the impact of fear of hypoglycemic episodes on glycemic and hypoglycemic management. *Canadian Journal of Diabetes.* 2005;29(3):1-7.
25. Goebel-Fabbri AE, Fikkan J, Franko DL, Pearson K, Anderson BJ, Weinger K. Insulin restriction and associated morbidity and mortality in women with type 1 diabetes. *Diabetes Care.* Mar 2008;31(3):415-419.
26. Hanna KM, Weaver MT, Stump TE, Slaven JE, Fortenberry JD, DiMeglio LA. Readiness for living independently among emerging adults with type 1 diabetes. *The Diabetes educator.* Jan-Feb 2013;39(1):92-99.
27. Weiner MF, Skipper FP, Jr. Euglycemia: a psychological study. *International journal of psychiatry in medicine.* 1978;9(3-4):281-287.
28. Zander H, Beneke J, Veagedes D, Muller A, Zwaan M. Type 1 diabetes mellitus and bulimia nervosa: insulin restriction does not always represent purging of unwanted calories. *Practical Diabetes International.* 2014;31(4):161-163a.
29. Anderbro T, Amsberg S, Adamson U, et al. Fear of hypoglycaemia in adults with Type 1 diabetes. *Diabetic medicine : a journal of the British Diabetic Association.* Oct 2010;27(10):1151-1158.
30. Desjardins K, Brazeau AS, Strychar I, Rabasa-Lhoret R. Are bedtime nutritional strategies effective in preventing nocturnal hypoglycaemia in patients with type 1 diabetes? *Diabetes, obesity & metabolism.* Jul 2014;16(7):577-587.
31. Barnard KD, Parkin C, Young A, Ashraf M. Use of an automated bolus calculator reduces fear of hypoglycemia and improves confidence in dosage accuracy in patients with type 1 diabetes mellitus treated with multiple daily insulin injections. *Journal of diabetes science and technology.* Jan 2012;6(1):144-149.
32. Barnard KD, Skinner TC. Cross-sectional study into quality of life issues surrounding insulin pump use in type 1 diabetes. *Practical Diabetes International.* 2008;25(5):194-200.
33. Davey RJ, Stevens K, Jones TW, Fournier PA. The effect of short-term use of the Guardian RT continuous glucose monitoring system on fear of hypoglycaemia in patients with type 1 diabetes mellitus. *Primary care diabetes.* Apr 2012;6(1):35-39.
34. Hermanides J, Norgaard K, Bruttomesso D, et al. Sensor-augmented pump therapy lowers HbA(1c) in suboptimally controlled Type 1 diabetes; a randomized controlled trial. *Diabetic medicine : a journal of the British Diabetic Association.* Oct 2011;28(10):1158-1167.
35. Nicolucci A, Maione A, Franciosi M, et al. Quality of life and treatment satisfaction in adults with Type 1 diabetes: a comparison between continuous subcutaneous insulin infusion and multiple daily injections. *Diabetic medicine : a journal of the British Diabetic Association.* Feb 2008;25(2):213-220.
36. Rubin RR, Peyrot M. Health-related quality of life and treatment satisfaction in the Sensor-Augmented Pump Therapy for A1C Reduction 3 (STAR 3) trial. *Diabetes technology & therapeutics.* Feb 2012;14(2):143-151.
37. Schmitz KH, Jacobs, D. R., Hong, C-P., Steinberger, J., Moran, A., Sinaikko, A. R. Association of physical activity with insulin sensitivity in children. *International Journal of Obesity and Related Metabolic Disorders.* 2002;26(10):1310-1316.
38. Amsberg S, Anderbro T, Wredling R, et al. A cognitive behavior therapy-based intervention among poorly controlled adult type 1 diabetes patients--a randomized controlled trial. *Patient Educ Couns.* Oct 2009;77(1):72-80.
39. Cox DJ, Ritterband L, Magee J, Clarke W, Gonder-Frederick L. Blood glucose awareness training delivered over the internet. *Diabetes Care.* Aug 2008;31(8):1527-1528.
40. Ismail K, Thomas SM, Maissi E, et al. Motivational enhancement therapy with and without cognitive behavior therapy to treat type 1 diabetes: a randomized trial. *Annals of internal medicine.* Nov 18 2008;149(10):708-719.
41. Costea M, Ionescu-Tirgoviste C, Cheta D, Mincu I. Fear of hypoglycemia in type 1 (insulin-dependent) diabetic patients. *Romanian journal of internal medicine = Revue roumaine de medecine interne.* Oct-Dec 1993;31(4):291-295.
42. Cox D, Gonder-Frederick L, Polonsky W, Schlundt D, Julian D, Clarke W. A multicenter evaluation of

blood glucose awareness training-II. *Diabetes Care.* Apr 1995;18(4):523-528.
43. Cox DJ, Gonder-Frederick L, Polonsky W, Schlundt D, Kovatchev B, Clarke W. Blood glucose awareness training (BGAT-2): long-term benefits. *Diabetes Care.* Apr 2001;24(4):637-642.
44. George JT, Valdovinos AP, Russell I, et al. Clinical effectiveness of a brief educational intervention in Type 1 diabetes: results from the BITES (Brief Intervention in Type 1 diabetes, Education for Self-efficacy) trial. *Diabetic medicine : a journal of the British Diabetic Association.* Dec 2008;25(12):1447-1453.
45. Schachinger H, Hegar K, Hermanns N, et al. Randomized controlled clinical trial of Blood Glucose Awareness Training (BGAT III) in Switzerland and Germany. *Journal of behavioral medicine.* Dec 2005;28(6):587-594.
46. Vallis M, Jones A, Pouwer F. Managing hypoglycemia in diabetes may be more fear management than glucose management: a practical guide for diabetes care providers. *Current diabetes reviews.* 2014;10(6):364-370.
47. Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *New England Journal of Medicine.* 1993;329(14):977-986.
48. Ceriello A, Novials A, Ortega E, et al. Evidence that hyperglycemia after recovery from hypoglycemia worsens endothelial function and increases oxidative stress and inflammation in healthy control subjects and subjects with type 1 diabetes. *Diabetes.* Nov 2012;61(11):2993-2997.
49. Soupal J, Skrha J, Jr., Fajmon M, et al. Glycemic variability is higher in type 1 diabetes patients with microvascular complications irrespective of glycemic control. *Diabetes technology & therapeutics.* Apr 2014;16(4):198-203.
50. Kildegaard J, Christensen TF, Hejlesen OK. Sources of glycemic variability--what type of technology is needed? *Journal of diabetes science and technology.* Jul 2009;3(4):986-991.
51. Hartley CA, Phelps EA. Changing fear: the neurocircuitry of emotion regulation. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology.* Jan 2010;35(1):136-146.
52. Wolitzky-Taylor KB, Horowitz JD, Powers MB, Telch MJ. Psychological approaches in the treatment of specific phobias: a meta-analysis. *Clinical psychology review.* Jul 2008;28(6):1021-1037.
53. Karen RL. *An Introduction to Behavior Therapy and its Applications.* New York: Harper & Row; 1974.
54. Soltesz G, Patterson CC, Dahlquist G, Group ES. Worldwide childhood type 1 diabetes incidence--what can we learn from epidemiology? *Pediatric diabetes.* Oct 2007;8 Suppl 6:6-14.
55. Gonder-Frederick LA, Schmidt KM, Vajda KA, et al. Psychometric properties of the hypoglycemia fear survey-ii for adults with type 1 diabetes. *Diabetes Care.* Apr 2011;34(4):801-806.
56. Hofmann SG, Smits JA. Cognitive-behavioral therapy for adult anxiety disorders: a meta-analysis of randomized placebo-controlled trials. *The Journal of clinical psychiatry.* Apr 2008;69(4):621-632.
57. Penckofer SM, Ferrans C, Mumby P, et al. A psychoeducational intervention (SWEEP) for depressed women with diabetes. *Annals of behavioral medicine : a publication of the Society of Behavioral Medicine.* Oct 2012;44(2):192-206.
58. Schmitt A, Gahr A, Hermanns N, Kulzer B, Huber J, Haak T. The Diabetes Self-Management Questionnaire (DSMQ): development and evaluation of an instrument to assess diabetes self-care activities associated with glycaemic control. *Health and quality of life outcomes.* 2013;11:138.
59. Lorig K. Self-Efficacy for Diabetes. http://patienteducation.stanford.edu/research/sediabetes.html. Accessed October 1, 2015, 2015.
60. Spielberger CD, Sydeman SJ. State-Trait Anxiety Inventory and State-Trait Anger Expression Inventory. *The use of psychological testing for treatment planning and outcome assessment*. Hillsdale, NJ, England: Lawrence Erlbaum Associates, Inc; 1994:292-321.
61. Polonsky WH, Fisher L, Earles J, et al. Assessing psychosocial distress in diabetes: development of the diabetes distress scale. *Diabetes Care.* Mar 2005;28(3):626-631.
62. Rodbard D. New and improved methods to characterize glycemic variability using continuous glucose monitoring. *Diabetes technology & therapeutics.* Sep 2009;11(9):551-565.
63. Bergenstal RM, Ahmann AJ, Bailey T, et al. Recommendations for standardizing glucose reporting and analysis to optimize clinical decision making in diabetes: the Ambulatory Glucose Profile (AGP).

Diabetes technology & therapeutics. Mar 2013;15(3):198-211.