Brief Cognitive Behavioral Therapy for Adherence and Depression in Patients with Type 2 Diabetes in an Urban Primary Care Facility: study protocol for a single-blind parallel-group randomized controlled trial

Statistical Analysis & Data Management Plan

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Clinical Trial Code: D-49-2019

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1 Background

1.1 Study Objectives

Primary objective

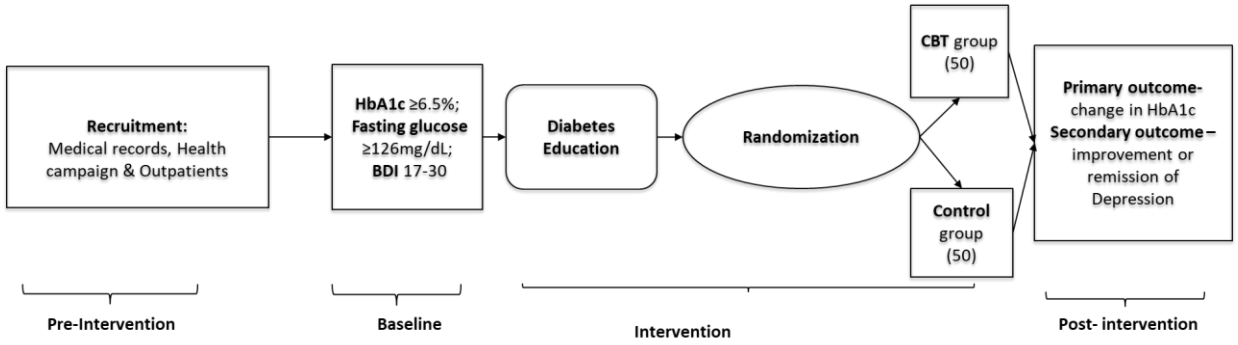
To assess the efficacy of the diabetes-specific Cognitive Behavioral Therapy (CBT) versus control in helping patients with Type 2 diabetes (T2D) and depressive symptoms to achieve glycemic control. Primary endpoint: change of glycated hemoglobin A1c (Hb A1c) level three months after the intervention.

Secondary objective

Estimate the efficacy of CBT in improving depressive symptoms among T2D patients. Secondary endpoint: change of depression score on Beck's Depression Index (BDI).

1.2 Study Design

Prospective, randomized, parallel group, two-arm controlled trial comparing CBT vs control groups after two months of CBT intervention.



2 Analysis Populations

The study population is defined by the following key inclusion and exclusion criteria:

Key inclusion criteria

- Uncontrolled type 2 diabetes mellitus (HbA1c ≥6.5%)
- Mild mood disturbance to Moderate depression (BDI)
- 35 to 80 years of age
- Able to give informed consent and understand given information.

Key exclusion criteria

- Type I diabetes
- Psychiatric disorders other than depression or personality disorders including schizophrenia, bipolar disorder, and substance or alcohol abuse.
- Depressed patients on treatment for depression
- Suicidal patients and those diagnosed with major depressive disorder will be referred to a psychiatrist.

3 Study Centre

Al-Agouza Family Medicine Center (AFMC) is a primary healthcare center in Giza, Egypt. The AFMC patient registry (database) currently has more than 1370 family medical records. It has been maintained since 2011. It has been estimated at 11% of patients in the database are diabetics and between 48-96 new diabetic patients are seen each year.

4 Data Collection Tools

A structured questionnaire will be used to collect data from the study participants. The questionnaire includes the following:

4.1 Demographic (age, residence, gender, marital, status, education level, occupation).

4.2 Diabetes History and Health Behavior Questionnaire

4.3 Measure Treatment Adherence (MTA)

To assess patients' adherence to diabetes medications, the Measure Treatment Adherence (MTA) modified scale will be used (Morisky et al. 1986; Delgado & Lima 2011). Several studies had validated the scale (Lopes et al. 2008; Shams & Barakat 2010). MTA Scale consisted of six questions and allowed answers from "always" to "never," with scores ranging from 1 to 4 points. The highest values indicated the highest level of adherence to treatment. Adherence score will be considered as follows:

- More than 75%- good adherence
- Between 50%-75%- poor/partial adherence
- Less than 50%- non-adherence

4.4 Beck's Depression Inventory (BDI)

Moreover, depression will be assessed using BDI (Lustman, Clouse, Griffith, Carney, & Freedland, 1997) as recommended by the research psychiatrist. BDI is a 21-question multiple-choice self-report inventory, used for measuring the severity of depression. A value of 0 to 3 will be assigned for each answer and then the total score will be compared to a key to determine the depression's severity. The standard cut-off scores will be
as follows:

- 1-10 These ups and downs are considered normal
- 11-16 Mild mood disturbance
- 17-20 Borderline clinical depression
- 21-30 Moderate depression
- 31-40 Severe depression
- over 40 Extreme depression

4.5 Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (SCID-IV)

The SCID-IV (Glasofer et al. 2015) will be used to diagnose patients with mood disorders and exclude other psychiatric morbidities.

4.6 Anthropometric and Biochemical Measures

The anthropometric measurements will be performed. The weight in kg and height in cm will be measured using the UGM-200 health scale with barefoot patients, wearing light clothes, and looking at the horizon. The waist circumference in centimeters will be measured on bare skin, mid-distance between the bottom of the rib cage and the top of the iliac crest using an inelastic tape. The BMI will be calculated by dividing the weight by the height squared (BMI= weight in kg/height in cm^2) (Cashin & Oot 2018).
To assess diabetes control, Fasting Plasma Glucose (FPG), 2-hour Plasma Glucose (2-h PG), and HbA1c will be performed at the AFMC clinical laboratory. Subsequently, participants will be randomized to control and treatment groups if they met our inclusion criteria.

5 Intervention

5.1 Diabetes Education Message

All eligible patients will be offered a structured diabetes education by a trained educator as an update to ensure adequate diabetes knowledge in all trial participants. A one-session message for 30-40 minutes and covered the following:

- Pathophysiology of DM

- Early detection of diabetes symptoms

- Risk and predisposing factors

- Recognition of diabetes complications

- Self-care including diabetes-relevant behavior (e.g., nutrition, physical activity, foot care)

- Monitoring and treatment of diabetes

5.2 Cognitive Behavioral Therapy Program

The treatment group will receive four CBT sessions twice a month for two months. The control group will be scheduled the same number of visits as a follow up for DM.

Patients in the CBT intervention group (Safren & Gonzalez 2007) received four educational sessions for 30-45 minutes once every two weeks during patients' regular follow up visits. The visits will be scheduled depending on the patient's availability. The sessions will be delivered by a trained physician. They will be on one to one basis and will be held at the AFMC outpatient clinic. The sessions included:

Session 1: Dealing with thoughts of sadness and depression
Session 2: Dealing with thoughts of anxiety and stress
Session 3: Dealing with anger
Session 4: Enhancement of coping and problem-solving skills

During the sessions, each participant worked with the healthcare provider to:

STEP 1: Identify thoughts and determine their effect on actions and feelings. Some examples include:

a. Thoughts

- "What have I done to deserve this?"
- "This illness is some kind of punishment for bad things I have done"
- "I'll never find anyone who will love me."

b. Feelings

- o "I'm a failure because I have diabetes"
- o "I am unlovable because of this illness and how I am managing it"

c. Actions

- o "There is nothing I can do to stop diabetes complications"
- o "There is no way I can manage everything I need to for diabetes"
- o Not meeting anyone, spending the weekends alone at home

STEP 2: Challenge Thoughts, analyze each thought to work out if it has been realistic or unhelpful. This can be achieved by asking questions such as:

- o What is the evidence for and against this thought?
- o Is thinking this way helping me?
- o Is there really nothing you can do?

STEP 3: Think of an alternative, balanced thought the physician will helpe patients change unhelpful thoughts and behaviors by teaching them some skills during they could apply daily. "I may not be able to control whether I develop complications, but I can feel in control of trying my best to keep healthy"

- o "The research shows that those who test their blood are healthier and less likely to develop long term complications"

Patients will be encouraged to practice these changes in their daily life and discuss how they got on during the next session. This should help patients manage daily life problems and stop them from having a negative impact on their life. Patients will be encouraged to set a diabetes-specific goal in order to improve their glycemic control such as weight loss or HbA1c target values and try to achieve it at the end of the sessions.

Adherence to CBT has been determined by the number of CBT-sessions attended by participants and will be defined as follows:

- Adherent participation- 3-4 sessions of CBT
- Partially non-adherent participation- 1–2 sessions of CBT
- Non-adherent
- No participation in any session of CBT

6 Post-intervention

In the last visit three months later, all participants will be reassessed for depression using BDI and diabetes compliance using the MTA modified scale. All required labs (FPS, 2-h PG, and HbA1c) will be reperformed.

7 Treatment of Missing Values and Outliers

Appropriate methods will be employed on an individual basis for the missing values and variables normalization. The primary analyses for HbA1c and the BDI scores will be repeated after employing the last observation carried forward method (LOCF). The multiple imputation method will be employed when more than 10% but less than 40% of the values will be missing (Pedersen et al., 2017). If outliers will be apparent to bias the analysis, they will be set to missing.

8 Analysis Variables

8.1 Demographics

The demographics age (35-39/40-45/46-50/51-55/56-60/>60years), gender (male/female), marital status (single/married/divorced/widowed), education level (illiterate/read & write/primary/preparatory/secondary/university), employment status (full time/part time/per diem/unemployed/retired/housewife), and occupation (no work/unskilled worker/manual skilled worker/managerial work/semi-professional(clerk)/professional) will be presented by number and percentage. Exploratory p-values of the Chi-Square test between treatment groups will be displayed.

8.2 Baseline Characteristics

The following variables will be included:

8.2.1 Psychosocial scores

Depressive symptoms using the BDI Scoring will be presented by appropriate descriptive statistics (mean, standard deviation, median, and interquartile range (IQA). Exploratory p-values of the t-test between treatment groups will be calculated.

8.2.2 Anthropometric measurements

Anthropometric measurements including weight [kg], height [cm], BMI [kg/cm^2], and waist circumference [cm] will be presented by appropriate descriptive statistics (mean, standard deviation, median, and interquartile range (IQA). Exploratory p-values of the t-test between treatment groups will be calculated.

8.2.3 Laboratory tests

Laboratory tests including FPG [mg/dl], 2h PG [mg/dl], & HbA1c [%] will be presented by appropriate descriptive statistics (mean, standard deviation, median, and interquartile range (IQA). Exploratory p-values of the t-test between treatment groups will be calculated.

8.2.4 Medical Data

The medical history of DM including age of onset [years], duration of DM [years], & family history of DM (non/father/mother/brothers/sisters/uncles/aunts) will be identified. The number of comorbidities and diabetes side effects will be recorded. The type of comorbidities (hypertension/dyslipidemia/gout/heart disease/others) and the type of diabetes side effects (neuropathy/nephropathy/retinopathy) will be identified. Medical data will be summarized by the appropriate descriptive statistics no, percentage, mean, standard deviation, median, interquartile range (IQA), minimum, and maximum.

8.2.5 Habits and lifestyle

The frequency of blood monitoring (every day/every week/once a month/every other month/few times a year); the mechanism of blood glucose monitoring (home/clinical laboratory); frequency of visiting doctor for follow up (twice a month/every month/every other month/few times a year); diet control (yes/no/sometimes); carbohydrates craving (always/many times/sometimes/never); the pattern of physical activity (yes/no/sometimes) will be identified. The data will be presented by number and percentage. Exploratory p-values of the Chi-Square test between treatment groups will be displayed.

8.2.6 Adherence to treatment

Type of diabetes medication (table/insulin); assessment for adherence based on MTA scale (%); and reasons for non-adherence (ineffective/side effects/forgetful/expensive/better without treatment) will be recorded. Adherence data will be presented by appropriate descriptive statistics (mean, standard deviation, median, and interquartile range (IQA). Exploratory p-values of the t-test and chi-square between treatment groups will be calculated.

The number of study CBT sessions and visited attended by the study groups will be recorded and presented as number and percentage.

9 Statistical Analysis

The analysis will be conducted according to the Consolidated Standards of Reporting Trials guideline (CONSORT). An academic statistician blinded to study groups conducted the study statistical analysis. Quantitative data will be examined for normality distribution using the Shapiro-Wilk's test ($p>0.05$) (Shapiro & Wilk 1965; Razali & Bee Wah 2011) test. Results of $p<0.05$ will be considered significant indicating non-normal distribution. A parametric Levene's test will be used to verify the equality of variances in the samples (homogeneity of variance) ($p>0.05$) (Nordstokke, & Zumbo 2010; Nordstokke et al. 2011).

Simple frequency distribution tables to provide a description for both groups will be generated. Quantitative variables will be summarized using. mean and standard deviation (SD) for normally distributed quantitative variables and median and interquartile ranges (IQR) for not normally distributed quantitative variables. While the number and percentage will be used to summarize qualitative variables.

Exploratory p-values of the student two-tailed independent t-test and Chi-Square test between study groups will be used for baseline quantitative and qualitative variables, respectively. P-values will be reported to three decimal places with p-values less than 0.001 reported as $p < 0.001$. We w used 2-sided p-values with alpha ≤ 0.05 level of significance.

Two sets of analyses will be conducted corresponding to the study outcomes' endpoints: 1) the CBT group demonstrated improvement of HbA1c level at the end of the sessions and 2) the CBT group demonstrated improvement of depression score on BDI versus the control group.

9.1 Software

Pre coded data will be entered on Microsoft office excel program for windows, 2010. Data will be transferred to the Statistical Package for Social Science Version 21 (SPSS-V 21).

9.2 Analysis of Outcomes

9.2.1 primary analysis

The primary variable is the Hb A1c plasma level.

The primary endpoint is the difference between Hb A1c level at baseline and three months later.

The primary outcome is the change of Hb A1c, compared between the different treatment groups using an Analysis of Covariance (ANCOVA), the General Linear Modeling approach to compare the study groups. The HbA1c and BDI at baseline will serve as control variables. HbA1c and BDI values at baseline are the values obtained at

the first visit before the start of the intervention. If the HbA1c value at baseline is missing, the first HbA1c value obtained during the first subsequent visits will be used.

The following hypothesis will be tested:

H0: $\mu_{CBT} = \mu_{control}$ versus H1: $\mu_{CBT} \neq \mu_{control}$

Where μ_{CBT} and $\mu_{control}$ are the expected mean values of the differences in HbA1c values belonging to the CBT and the control groups. The hypothesis will be tested on a 2-sided p-value with alpha ≤ 0.05 level of significance. The results will be displayed by means of the p-value, standard deviation of unadjusted values, and 95%-confidence interval. For that, the assumption of homogeneity of regression slope will be examined by testing the interaction effect of the independent variable and the covariate.

The secondary variable is the BDI score.

The secondary endpoint is the difference between BDI at baseline and three months later.

The secondary outcome is the change of BDI compared between the different study groups using an Analysis of Covariance (ANCOVA), the General Linear Modeling approach to compare the study groups. The HbA1c and BDI at baseline will serve as control variables. HbA1c and BDI values at baseline are the values obtained at the first visit before the start of the intervention. For that, the assumption of homogeneity of regression slope will be examined by testing the interaction effect of the independent variable and the covariate.

The following hypothesis will be tested:

H0: $\mu_{CBT} = \mu_{control}$ versus H1: $\mu_{CBT} \neq \mu_{control}$

Where μ_{CBT} and $\mu_{control}$ are the expected mean values of the differences in the BDI score belonging to the CBT and the control groups. The hypothesis will be tested on a 2-sided p-value with alpha ≤ 0.05 level of significance. The results will be displayed by means of the p-value, standard deviation of unadjusted values, and 95%-confidence interval. For that, the assumption of homogeneity of regression slope will be examined by testing the interaction effect of the independent variable and the covariate.

9.2.2 Secondary analysis

The primary outcome change of glycemic control after adjustment for potential confounders will be further analyzed by ANCOVA with additional control variables. A correlation analysis will be performed with the age, sex, comorbidities, and diabetes side effects as potential control variables.

The resulting p-values will be checked. If Pearson's correlation coefficient has a p-value <.05, the control variable will be used to conduct further ANCOVA. The additional

ANCOVA will include the study groups, HbA1c baseline, and the selected control variables.

The secondary outcome change of depression symptoms after adjustment for potential confounders will be further analyzed by ANCOVA with additional control variables. A correlation analysis will be performed with the age, sex, comorbidities, and diabetes side effects as potential control variables.

The resulting p-values will be checked. If Pearson's correlation coefficient has a p-value <.05, the control variable will be used to conduct further ANCOVA. The additional ANCOVA will include the study groups, BDI baseline, and the selected control variables.

9.2.3 Subgroup analysis

A subgroup analysis of the type of diabetes treatment will be conducted for the primary outcome. This will be done by including diabetes treatment type and study groups variables in the ANCOVA.

The HbA1c values for the subgroup analysis will be displayed by descriptive statistics (n, mean, standard deviation, median, and interquartile-range (IQA)) and they will be compared by p-values of t-test.

Descriptive statistics of demographic and baseline medical and psychosocial characteristics will be displayed by type of diabetes treatment. Exploratory p-values of t-test and chi-square tests will be presented to examine differences between both subgroups.

10 Monitoring

10.1 Data Monitoring

The trial has a calculated sample size of 80. The intervention duration is short for two months. Accordingly, the study is expected to bear no to minimal risk. Thus, no data monitoring committee (DMC) will be needed.

10.2 Harms

An adverse event is defined by this study as any unfavorable medical occurrence in a subject that has a temporal relationship to the study intervention (CBT). All adverse events will be collected and recorded after the patients will be enrolled in the study. However, only serious adverse events that result in severe or permanent disability or prolonged hospitalization will be reported to the Research Ethical Committee (REC).

There are no to minimal risks associated with the CBT program. The program targets depressive symptoms. However, like any medical treatment, the program may bear the risk that it will not work. In this case, patients may feel disappointed that their depression will deteriorate. However, such clinical deterioration is rare. (Morisky et al. 1986; Delgado & Lima 2011).

Potential side effects may include risks associated with blood withdrawal. There may be some minor discomfort or pain associated with collecting blood. Some participants may experience minor local bruising or brief lightheadedness. For that, blood specimens will be collected by trained and experienced lab technicians. Some patients might be slightly distressed by the rating scales. Thus, we will keep the collected information as minimal as possible and will be part of the clinical care.

Possible benefits of the program include reduced depressive symptoms, distress, and impairment, and clinically significant remission of depressive symptoms.

10.3 Auditing

Regular team meetings will be conducted to address any difficulties experienced during the study especially those participants may be having difficulties and ways of best dealing with them. Serious adverse events will be reported to the REC at the Faculty of Medicine, Cairo University.

11 Ethics and dissemination

11.1 Research Ethics Approval

The study protocol, consent form, participant education, and recruitment materials both in local language and English versions have been reviewed and approved on December 2018 before study implementation by the department of public health and community medicine; department of psychiatry; department of internal medicine at Elkasr Eleini Medical School, the REC at Cairo University; and the administrative office at Alagouza health district.

11.2 Protocol Amendment

Any modifications to the protocol which may impact the study conduct or may cause potential benefits or harm to the patient including changes of study objectives, design, procedure, target population, sample size, or significant administrative matters will require a formal amendment to the protocol. Such amendment will be agreed upon by the REC at Cairo University prior to implementation. Minor administrative changes of the protocol that have no effect on the study will only need the approval of the department of public health and community medicine and will be documented in a memorandum. The REC may be notified of such changes.

11.3 Confidentiality

All participant and study-related information including consents and questionnaires will be stored in a locked file cabinet in an area with limited access to the study site. All reports and administrative forms will be recognized by an identification (ID) number. Records that link participant ID numbers to other identifying information will be stored in a separate locked file in an area with limited access to keep participant confidentiality.

All electronic databases will be password protected and stored on the AFMC computer and will be accessible to only study investigators approved by the REC. Data analysis will be performed at Cairo University.

11.4 Access to Data

The Project Principal Investigator will have access to all data set. the final data set will be available to the other team members at the end of the study. The final set will not include any identifier information to ensure participants' confidentiality.

11.5 Ancillary and Post-Trial Care

Enrolled patients will be protected against negligent harm based on the standard of REC at Cairo University.

12 Dissemination policy

12.1 An Interim Period of Analysis and Documentation of Study Results

Every effort will be made to reduce the period between data collection and the release of the study results. We assume that around six to ten months will be needed to make a complete manuscript ready for publication.

12.2 Reporting of Study Results

We will disseminate the study results to the study team members, patients, the public, and the medical and scientific community.

Data will be shared no later than two years after one year of data collection. We will provide a complete data set via an appropriate data archive for dissemination purposes.

12.3 Status of the Trial

Currently, the trial is in the data analysis phase. Recruitment started in April 2019. We were able to screen 394 participants. Around 100 met our inclusion criteria and accepted to participate. We anticipate final follow-up data and publication to be ready by February 2021.

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