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Study design

The KDEP trial: Protocol for a phase II, multicenter, open label, randomized controlled trial to evaluate the efficacy of ketogenic diet for symptomatic improvement of moderate to severe Major Depressive Disorder

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ABSTRACT:

Introduction: Major depressive disorder (MDD) is a disease with a high economic burden across the world, mainly secondary to a decrease in work performance and pill burden. Ketogenic diet is a type of non-pharmacological intervention that is employed in the treatment of refractory epilepsy and has shown promise for the treatment of other psychiatric disorders, including depression. Up to the date, there is a limited number of investigations regarding this topic, making the knowledge very scarce; therefore, our study will assess the clinical efficacy of ketogenic diet, particularly Modified Atkins Diet, as compared to control diet in adults with diagnostic of MDD on standard treatment without resolution of symptoms as a difference in Montgomery-Åsberg Depression Rating Scale (MADRS) from baseline at the third month follow-up visit.

Methods: This is a phase II, multicenter, randomized, controlled, open-label, parallel-group, superiority trial with blinded endpoints. Sample size was calculated as 132 participants (66 participants per arm) to maintain a power of 80% and a two-sided significance level of 0.05. The primary endpoint is the improvement in MDD symptomatology measured by MADRS scale at 3 months from baseline.

Discussion: There is evidence to support the notion that ketogenic diet improves patients symptoms by increasing levels of several molecules resulting in a decrease of neuroinflammation and an increase of neurogenesis, improving mood disorders. We hypothesize that a ketogenic diet will improve depressive symptoms in patients with moderate to severe depression when compared to patients on a control diet.

Keywords: ketogenic diet; Modified Atkins diet; major depressive disorder; Montgomery-Åsberg Depression Rating Scale.

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Introduction

Major Depressive Disorder (MDD) is a psychiatric disorder that is characterized by loss of interest and depressed mood. It is a leading cause of disability worldwide, affecting 35 million adults in the US alone (Ménard, 2016). As the etiology remains unclear, treatments are aimed at symptomatic remission and only half of patients properly respond to available treatments (Brietzke, 2018), making it necessary to study novel interventions.

Ketogenic diet (KD) is a high-fat, low carbohydrate, low protein diet which has been safely used for the treatment of patients with refractory epilepsy for almost a century (Peterman, 1924), and has been investigated in animal and human models of psychiatric disorders only until recently (Bostock, 2017, El-Mallakh, 2001), where beneficial effects at molecular and cellular levels include improvement of neuronal plasticity, stabilization of brain microglia (Huang, 2018), reduction of neurotransmitters and improvement of brain hypometabolism, stimulation of neurogenesis (Yadav, 2013), and inhibition of neuro-inflammatory processes (Yamanashi, 2017). Studies in rats suggest that KD has antidepressant effects (Murphy, 2004) and reduces susceptibility to depression (Sussman, 2015), moreover, humans examples exist showing effectiveness of this intervention, with a case study of a patient with type 2 diabetes mellitus (Cox, 2019) that reduced her depressive symptoms by consuming the diet for 12 weeks and two human trials further demonstrating that those who consumed KD had fewer depressive symptoms as compared to a low-fat diet (McClernon, 2007 & Yancy, 2009).

In MDD, non-pharmacologic strategies such as KD have generated interest due to variable response to standard antidepressants (Papakostas, 2009). One of the challenges of incorporating the classic KD is its reduced compliance owing to its unpalatability and restrictiveness. Modified Atkins Diets (MAD), a modification of classic KD, can counter this problem because carbohydrates may be continued during the induction phase (Sharma, 2014) making the diet more compliant. Additionally, MAD does not differ from classic KD in short-term and long-term efficacy in the treatment of epilepsy in the pediatric population (Rezaei S., 2017). Therefore, MAD is a more pragmatic solution especially in a population suffering from a psychiatric disorder. Although the evidence available of this topic is scarce, studies on the effects of KD on other psychiatric diseases have shown that it is safe, which justifies the need for a phase II trial (Brietzke, 2018).

Taking all into consideration, our goal is to determine whether MAD improves depressive symptoms measured by MADRS in adult patients aged 18 to 65 years with moderate to severe MDD receiving standard treatment, which may be Selective Serotonin Reuptake Inhibitor (SSRI) or Selective Norepinephrine Reuptake Inhibitor (SNRI) in addition to cognitive behavioral therapy (CBT), when compared to control diet (CD) within a 3-month follow-up period. We hypothesize that MAD will improve depressive symptoms in patients with moderate to severe depression when compared to patients on CD.

Materials and Methods

Trial design

This is a phase II, randomized, controlled, two-arm parallel, multicenter, open-label, superiority trial with blinded endpoints. The primary endpoint is the improvement in MDD symptomatology measured by MADRS at 3 months from baseline and the patients are to be recruited from three psychiatric outpatient clinics.

Randomization

Patients will be randomized in a 1:1 ratio to receive either MAD or CD, stratified by severity of disease at baseline, defined by MADRS (moderate ≥20 points or severe >34 points), and by center (Figure 1). The randomization schedule will be created by a centralized, web-based, random allocation software, with randomly selected blocks sizes of four and six. RedCap software will be employed to ensure allocation concealment, with the physician in charge of enrollment not being informed about the group allocation.

Blinding

The patient, the treating physician and the nutritionist cannot be blinded due to the nature of the intervention. The outcome assessor, data collector and statistician will be blinded to prevent pygmalion effect due to the subjective nature of the outcome. As a result, there is no need for emergency unblinding and under no circumstance should the allocation arm be revealed to the personnel handling the study data.

Eligibility Criteria

Inclusion Criteria

Patients will be included if they have the following criteria: (i) 18-65 years of age, who have been diagnosed with MDD using the DSM-V criteria; (ii) with moderate or severe depression, with Montgomery-Asberg Depression Rating Scale (MADRS) score of ≥ 20 at the moment of enrollment; (iii) currently receiving a SSRI/SNRI and CBT for at least 6 weeks and have residual depressive symptoms; (iv) able to provide informed consent and to complete study procedures.

Exclusion Criteria

Patients will be excluded if they have the following criteria: (i) any primary psychiatric diagnosis according to the DSM-V criteria other than MDD within the last 6 months; (ii) use of antidepressants different from SSRI/SNRI or concurrent alternative therapy or other substances/medications known to produce mood changes; (iii) need of antidepressants dose adjustment throughout the study period; (iv) history of previously receiving KD, previous intolerance, or nonresponse to the KD; (v) history of any suicide attempt or at acute suicidality; (vi) history of alcohol or any substance use disorder within the last year. (Positive urine drug screen at the time of screening); (vii) history of acute or chronic pancreatitis, hypothyroidism, liver failure; (viii) body mass index (BMI ≤ 18.5 kg/m², ≥ 40.0 kg/m²); (ix) women who are currently pregnant or breastfeeding and of childbearing age who are not using recommended methods of contraception; (x) any current medical condition including cardiovascular, pulmonary, gastrointestinal, hepatic insufficiency, severe renal impairment, neurological impairment (dementia), endocrine disorders (hypothyroidism, diabetes mellitus, or Cushing's syndrome) and metabolic disorders (gallbladder disease or removal, disorders of fat metabolism, primary carnitine deficiency, carnitine palmitoyl-transferase deficiency, carnitine translocase deficiency, porphyria, or pyruvate kinase deficiency); (xi) enrolled in a study currently or within 30 days of being eligible.

Recruitment

The present study will recruit patients from 3 high volume psychiatric centers, after a data-based prescreening, potentially eligible subjects will be scheduled for an interview with study staff for further assessment of eligibility and detailed informed consent.

Adherence

Adherence to intervention will be managed by direct evaluation during the trial and employing methods to increase it. The nutritionists will do the diet counseling. Patients will have to maintain a food diary by taking pictures of their meals to prevent nonadherence. Patients and their families will be offered optional weekly online motivational sessions by a nutritionist and a psychologist, obtaining transport expenses and other incentives such as cooking classes, supermarket coupons and subscription to food magazines; this would apply for both intervention and control groups.

As for the evaluation of adherence, this will be done by direct observation and biomarkers. Firstly, patients will have monthly psychiatrist sessions and randomly telephonic follow ups with nutritionists. Secondly, capillary blood ketones levels will be measured by the patient twice per week randomly, forwarding this information to their treating physician via electronic communication; and ketone blood levels measured at their center monthly.

Interventions

The ST will be the administration of an SSRI or SNRI in addition to CBT. All patients will continue receiving CBT and their specific SSRI/SNRI (and dosage) assigned prior to the enrollment, which will remain the same throughout the length of the study. The MAD will be implemented in an outpatient clinic with a 30-60 min education provided by a registered nutritionist. The diet will be initiated without a fast. The nutritionist will emphasize the following recommendations (Kossoff, 2008): (i) restriction of carbohydrate intake to 15 g/day for the first month, which can be increased by 5 g/month to the limit of 30 g/day for the following months; (ii) identifying and encouraging high-fat foods; (iii) no restriction for the intake of protein, calories, and fluids; (iv) administration of low-carbohydrate multivitamin and calcium carbonate supplementation; (v) possible adverse effects; (vi) carbohydrate-counting strategies; (vii) reading food labels.

Patients allocated to the control diet (CD) will receive education regarding the incorporation or maintenance of a healthy diet (information package containing exemplary menus).

Modification/discontinuation

For safety, subjects who develop severe adverse effects, such as kidney stones, severe dyslipidemia, severe hypoglycemia, severe weight loss (BMI ≤ 18.5 kg/m²), severe gastroesophageal reflux, high concentration of blood urea nitrogen and serotonin syndrome will be withdrawn from the intervention. These should be reported as adverse events.

Patients who develop mild side effects, will consult with the medical staff for the investigation of differential diagnosis. These symptoms include

headaches, fatigue, irritability, nausea, difficulty sleeping, constipation, sexual dysfunction, anxiety, insomnia and weight gain. If the symptoms continue (they usually cease in a few weeks), the decision of withdrawing from the intervention will be made by the participant.

Outcomes

Primary outcome: change from baseline at 3 months in depression severity in each treatment group, assessed by the MADRS. The scale will be treated as continuous in order to optimize the power of the study.

Secondary outcomes: (i) differences between baseline Hamilton Depression Rating Scale (HAM-D) and at three months - continuous outcome; (ii) difference between baseline electroencephalography (EEG) and at three months, in order to evaluate any alpha activity over the dorso lateral prefrontal cortex (Bruder et Al, 2008) - categorical outcome; (iii) response rate between groups, defined as a reduction higher or equal to 50% in the MADRS - categorical outcome; (iv) association of blood ketone levels and self-reported adherence to the MAD with a reduction of depressive symptoms as measured by MADRS; (v) side effects measured by the Patient Rated Inventory of Side Effects and laboratory analysis (Hemogram, lipid panel, urea, creatinine, electrolytes, calcium, phosporum, magnesium, liver and pancreatic enzymes, albumin, coagulation profile, glucose and insulin).

Data management

All information regarding clinical records of the participants, source documents, and consent forms will be collected, pseudonymized, and stored electronically in the RedCap database. The online version will be restricted and accessed only through a password system, while solid copies will be stored securely in a closed cabinet in the core center for 10 years post-trial. Access will be restricted to authorized personnel by the principal investigator (PI). Upon inclusion to the trial, each participant will be issued a unique ID number. The document that contains participant details and their IDs will be stored separately and accessed only by PI. Legal Requirements and the trial protocol will be forwarded to the local IRB and the Ethics Committee for approval, and any event labeled as a potential risk by the PI will be reported to IRB.

Given the safety of our intervention shown by previous evidence and the short duration of our trial, we do not expect a high incidence of serious adverse events in our study, making an interim analysis for safety and the implementation of a data monitoring committee unnecessary. In addition, we do not expect a substantial difference between the treatment effect of both groups before 3 months, making an interim analysis for futility or efficacy unjustified. However, we will be registering and analyzing adverse events and laboratory parameters as a secondary outcome throughout the study.

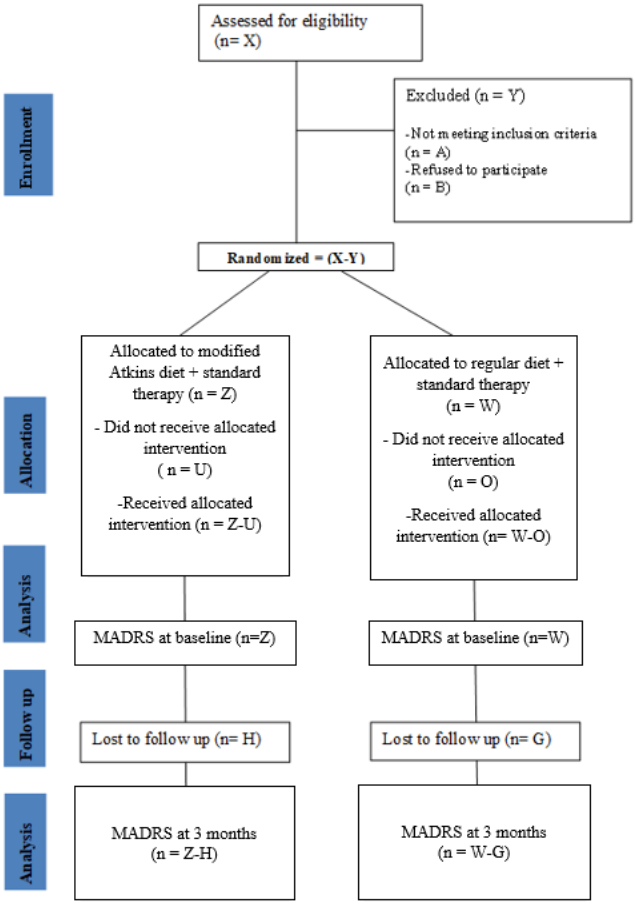

Figure 1. CONSORT flow chart

Sample size calculation

In a recent meta-analysis (Hengartner, 2020), the pooled standardized mean difference (Cohen's d) was 0.3 (95% confidence interval [CI], 0.22 to 0.38) for MADRS for newer antidepressants when compared to placebo. The SMILES trial (Jacka, 2017), a randomised controlled trial designed to evaluate the effect of adjunctive dietary intervention in the treatment of moderate to severe depression, showed an effect size (Cohen's d) of -1.16 (95% CI, -1.73 to -0,59). Since this trial used a similar intervention and the same outcome of our study, we considered it to be the most adequate for our sample size estimation. Nevertheless, this effect is even higher than the one identified for antidepressant drugs. Considering this, we decided to use a conservative approach, choosing the smallest

effect size from the 95% CI for the estimation of our sample size, which is -0.59. This ultimate value is also similar to effect sizes identified with other non-pharmacological approaches, mostly different types of diet (Kascow, 2014; Francis, 2019; Li, 2017). Using the method proposed by Whitley et al. (Whitley, 2002) for the sample size estimation based on the standardized mean difference and taking into account an expected drop-out rate of 40% (Liu, 2018), a final sample size of 132 participants (66 per arm) was obtained, with a power of 0.8 and a two-sided significance level of 0.05.

Statistical Analysis for primary and secondary outcomes

The intervention arm (KD + ST) will be compared against the control arm (CD + ST) for the primary analysis. Continuous data will be reported as mean and standard deviation, ordinal data as median; and first and third quartile and categorical data with frequencies and percentages. Due to the estimated sample size, we assume the central limit theorem applies to our data, allowing the usage of parametric tests. The primary outcome will be assessed by linear regression adjusting by treating center and severity of disease (moderate or severe). In the secondary analysis, linear regression will be used for continuous outcomes and logistic regression for categorical outcomes, including the same covariates. Relative and absolute risk reduction with corresponding 95% confidence intervals will be reported for dichotomous variables, such as the responder's rate. A two-sided alpha of 0.05 for statistical significance will be used. Statistical analysis will be performed by a blinded, independent statistician. The study will employ Up-to-date versions of Stata.

Missing data

For the primary outcome MADRS, any missing data will be dealt with using Intention-to-treat analysis (ITT) and per-protocol analysis (PP) as primary and secondary analysis, respectively. Efforts will be made to account for the reason of the nature of the missing data and will be properly accounted for in the results section. When encountering missing data, Multiple imputation methods (MI) will be used. Sensitivity analysis with a "best-worst-case" analysis will be performed in order to assess the possible impact of the missing data of the primary outcome on the findings. As the primary outcome will be treated as a continuous variable, a "best-worst-case" dataset will be generated assuming that all patients lost to follow up in the intervention arm have a beneficial outcome, by imputation of a value of plus 2 SD from the mean, and that all patients in control arm have a harmful outcome, by imputation of a value of minus 2 SD from the mean.

Discussion

This is the first randomized clinical trial assessing the efficacy and safety of a KD in an adult psychiatric population. Eligible patients are those diagnosed with moderate to severe MDD with MADRS > 20 points, under treatment with SSRIs/SNRIs and CBT for at least 6 weeks. Stratified randomization in random sized blocks will be done to balance the groups with a target of 66 participants in each arm.

KD will be introduced to patients and followed up by a multidisciplinary team for 3 months. Control group will receive a CD, represented by their usual diet plus nutritional education. Both groups will continue to receive their standard pharmacological and psychological treatment. Primary outcome change in MADRS will be assessed after 3 months of treatment. Secondary outcomes are change in the HAM-D17 scale after 3, response rate between groups, association of blood ketone levels, changes in the EEG after 3 months and self-reported adherence to the KD. Authors should discuss the results and how they can be interpreted from the perspective of previous studies and of the working hypotheses. The findings and their implications should be discussed in the broadest context possible. Future research directions may also be highlighted.

Strengths, limitations & controversial decisions

Because there are no previous studies assessing this intervention within humans or the population of interest, the main strength of our study is novelty. The results will be of interest for the future management of MDD due to the relatively high prevalence and burden worldwide, which facilitates the recruitment process.

Our study has several limitations. First, it is an open label trial. However, we must consider the impracticality of blinding the participants about the diet they would be receiving and the safety of patients; although the probability of a life-threatening situation is low, the concern for the wellbeing and security of subjects must be addressed. Nevertheless, to maintain the objectivity and validity of the study, it was decided to blind the rest of the personnel involved.

The study population, considering that this is a phase II trial, consisted of moderate and severe MDD patients to ensure homogeneity and enhance internal validity, which could limit generalizability.

Another limitation is adherence, which could be affected by the severity of the disease and the nature of the intervention. Lack of adherence can reduce the apparent effect on the primary outcome, which can

introduce bias, so it was decided to use an ITT analysis and to estimate its amount in the sample size calculation, to decrease its impact as much as possible. Also, the main outcome will be analyzed as a continuous variable, which could lead to difficulties in the interpretation especially in translating the numerical difference in MADRS into a clinically relevant effect.

Furthermore, high dropout rate is another challenge, estimated at 40% based on previous studies, however we have reinforced the importance of the adherence strategies and multidisciplinary follow up to prevent it.

Alternative results

There is a likelihood that we might not be able to show a significant difference between KD and CD in terms of improving depressive symptoms, considering the limitations. If the ITT analysis and the PP analysis differ significantly, the results must be interpreted carefully as the ITT may shift the result towards the null hypothesis. If the study does not yield statistically significant results, our findings could still be valuable for other studies regarding this population or intervention.

Conclusions

Due to the novelty of our proposal, irrespective of the results, the knowledge our trial might provide to science will outweigh the difficulties. This may lead to a new modality of treatment for a highly prevalent disease.

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Data Availability Statement: In this section, please provide details regarding where data supporting reported results can be found, including links to publicly archived datasets analyzed or generated during the study.

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Conflicts of Interest: The authors declare no conflict of interest.

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